Evolving strategies to diagnose and manage autoimmune liver disease

by

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A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF MEDICINE

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October 2022

"The journey of a thousand miles must begin with one step" (Lao Tzu)

Leave of Absence & Covid-19 Statement

My research was conducted September 2015-2018 while working as a Clinical Research Fellow at the Queen Elizabeth Hospital Birmingham (QEHB). This was on a part time basis while simultaneously fulfilling clinical duties. I returned to full time clinical training in Gastroenterology and General Internal Medicine in September 2018, while writing up my thesis. This was followed by maternity leave and an approved leave of absence from research.

The SARS-CoV-19 (Covid-19) pandemic hit the UK in early 2020, with the first national lockdown occurring in April 2020, during my maternity leave. The resulting isolation and lack of the social and family support a new family would normally experience made those months especially challenging and I delayed my return to work until December 2020. This was swiftly followed by further lockdowns; my hospital was badly hit and emergency medical rotas impacted negatively on training and research time. The pandemic has also made childcare difficult, we have experienced nursery closures and my son has been required to self-isolate over a dozen times to date, meaning further disruption to thesis writing. As a result of this extreme disruption, I successfully applied for a further extension to my thesis deadline in January 2021, initially extending to December 2021 and then once further to April 2022.

The events of the past twelve months have changed the world in ways we do not yet fully understand. Attitudes of patients towards their healthcare will undoubtedly have been affected and the pandemic has changed the way patients access healthcare, likely forever, with a steep acceleration in the use of digital consultations. Patient attitudes to this concept may well now be different to when I investigated them; the impact of Covid-19 on the research findings is described within the thesis discussion chapter.

Abstract

Background

Primary Sclerosing Cholangitis (PSC) is a rare immune-meditated liver disease characterised by progressive destruction of bile ducts. This leads to cholestasis, biliary strictures, cirrhosis and hepatobiliary malignancy. PSC has an unpredictable prognosis, no proven treatment and overall poor long-term outcomes. While rare, the impact of PSC is high, with a large symptom burden and the need for management in specialist centres for most patients.

Aims

This thesis aims to improve the understanding of PSC, from the perspective of patients, clinicians and healthcare providers. It aims to identify the barriers that PSC patients experience to their optimal medical management and explore the potential utility of two evolving technologies to improve patient experiences of their healthcare. These technologies are telemedicine and quantitative multiparametric MRI imaging.

Methods

Four complementary studies were designed, using both quantitative and qualitative research methods. These studies included a 10-year retrospective cohort study into PSC at a large tertiary centre, semi-structured qualitative interviews with PSC patients recruited nationally, a questionnaire into the personal burden of medical intervention for PSC and attitudes to telemedicine, and a large observational trial of the utility of quantitative MRI techniques in PSC and related autoimmune disorders. These studies are initially discussed individually and are then combined in the final discussion chapter to provide an overall view of PSC patient and healthcare experiences.

Results

All studies confirmed the large burden that PSC poses to patients and healthcare providers, along with the need for advances in new treatments and risk stratification methods. Particular challenges highlighted by patients were difficulties accessing knowledgeable medical care and how to overcome the uncertainties that PSC presented to them, both in terms of daily life but also long-term prognosis. Interest in telemedicine as one method to bypass traditional geographic barriers in accessing specialist care was high. However, hidden complexities within chronic illness behaviour, especially a particularly fragile doctor-patient relationship identified in this thesis, meant that telemedicine would not be universally accepted. Investigation into the utility of quantitative MRI technology observed correlations with existing markers of disease activity and severity, and demonstrated the ability to predict some clinically significant events. Although this was no better than existing serum biochemistry, the potential of this technology for future risk-stratification is confirmed.

Conclusions

This thesis adds to the published literature of the ongoing high burden of PSC with particular added value from in-depth discussions with patients themselves. This has identified multiple areas of concern that should become priorities for further work, including the need for improved risk stratification tools to allow individualised management and prognostication, as well as improving access to specialist care. While telemedicine and new imaging technology may have future utility for patient benefit, both need further research in order to better understand their impact and utility in real-life clinical situations. PSC continues to present a challenge to patients and clinicians alike.

Acknowledgements

Authors contributions

Katherine Arndtz (KA) was supervised throughout by Professors Gideon Hirschfield (GMH), Jayne Parry (JP) and Sheila Greenfield (SG). All were involved in the conception, study design, analysis and write up of this study. KA performed all ethical approval, recruitment, investigation, initial analysis and write up. James Hodson (JH, a professional statistician at QEHB) supported KA with the advanced statistical analysis of both the cohort and MRI studies. Trained MRI technicians at QEHB performed the MRI scanning sequences. KA supplied Perspectum Diagnostics technicians with anonymised MRI images and novel MRI metrics were returned to KA for analysis.

Conflict of interest statement

KA has no conflicts of interest to declare. The MRI study was an academic collaboration with Perspectum Ltd; a privately funded commercial enterprise that develops medical devices to address unmet clinical needs, including Liver*MultiScan*®.

Financial support statement

This thesis presents independent research supported by the Birmingham NIHR BRC based at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Personal Reflection & Dedication

In truth, completing this research and thesis write-up has been the single hardest thing I have ever done. It has taken over six calendar years to complete; three to prepare and complete the data collection, then another three years of write up, all on a part-time basis. This has been interspersed with maternity leave, continuing my medical training, and raising a feisty toddler through a rather terrifying world-wide pandemic. I am hopeful now that the countless late nights working on this are coming to an end; I have done all I can.

While immensely challenging, this time has also been some of the most interesting and educational of my studies to date. Never before have I had the time, access and support to investigate such a fascinating topic, of my own choosing no less, and to develop such an array of different investigative techniques. I hope this thesis might act as a building block in the further understanding of what life is like for patients with PSC and other chronic diseases, and how we as clinicians might work towards alleviating some of the struggles faced by our patients. This is the core of why I wanted to be a doctor, to help people, cliched as it sounds.

Forgetting the results for a moment, the process of planning, executing and analysing these studies has been invaluable to me, as a person and a clinician. My understanding of the legal and ethical processes involved in research has grown exponentially, as has my previously poor statistical acumen. I feel far more able to critically appraise other research now I understand the processes involved. In particular, being able to spend time developing skills in qualitative research methods has been different, interesting and useful for the future. I am now far more aware of the hidden struggle patients face, how the language I use can affect patients' experiences so significantly, and how little changes can be made that can make a real difference to patients. In addition to this, the organisation, forward planning, multi-tasking

and determination I have needed to complete this body of work will be of much value going forward.

Discovering the magic bullet for PSC was always going to be way beyond my capabilities; much cleverer people than I with much fancier toys are working on it and I wish them well. Instead, I have focussed on the more achievable goals of advancing the understanding of PSC from a patient point of view, and looking at two methods of potentially improving their management, via telemedicine or improving risk stratification using MRI.

While my findings are not earth-shattering, I hope they will lend weight to the cries of patients wanting and desperately needing change. Change is hard; it is not possible to please everyone and with the resource constraints within today's NHS, it is important that any changes give the most benefit to the most people. Equally, patients with rare diseases have additional battles on top of the disease itself, given their struggle to access knowledgeable medical care and the immense uncertainty "PSCers" face is almost unique. The judicious organisation of appropriate telemedicine strategies and advances in MRI technology will impact on not just those with PSC, but potentially improve and equalise access to care across the UK for all patients with chronic diseases.

I conclude this reflection by wanting to send heartfelt thanks to a lot of people:

Foremost to the patients who took part in this research, whether it be a quick questionnaire in clinic, an hour spilling their life stories to me over a cup of tea, or those poor souls I convinced to spend their free time having repeated MRI scans and extra blood tests. You are appreciated more than you know. I remember what you told me and I will help carry your torch.

To my supervisors and everyone else who has helped me academically along the way; thank you for putting up with me, especially for so long. Thank you for reading the countless drafts, re-drafts and re-re-drafts. Thank you for scheduling meetings around baby naptimes, working commitments and international time zones. Thank you for your absolutely invaluable insights, suggestions and advice. This thesis would not exist without you.

And finally, to my longsuffering family; thank you for giving me the time and space to complete this challenge. Especially to my husband James and my son Thomas, thank you for putting up with my grouchiness and my absent bedtimes. This is for you.

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5 List of Abbreviations

Acronym	Definition
AASLD	American Association for the Study of the Liver
AIH	Autoimmune hepatitis
AILD	Autoimmune liver disease
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
CARMS	QEHB Clinical Audit Registration and Management System
Covid-19	SARS CoV-19 (coronavirus 19)
DILI	Drug induced liver injury
ELF	Enhanced liver fibrosis
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FDA	Food and Drug Agency
FIB-4	Fibrosis-4
HCV	Hepatitis C Virus
HES	Hospital episode statistics
HIV	Human Immunodeficiency virus
IAIHG	International AIH group
IBD	Inflammatory bowel disease
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
INR	International Normalised Ratio

JLA	James Lind Alliance
KA	Katherine Arndtz, student
LMS	Liver*Multiscan*™
MRCP	Magnetic resonance cholangeopancreatography
MRI	Magnetic Resonance Imaging
mpMRI	Multiparametric MRI
MRE	Magnetic resonance elastography
NAFLD	Non-alcoholic fatty liver disease
NIHR	National Institute for Health Research
PBC	Primary Biliary Cholangitis
PIS	Patient Information Sheet
PPI	Patient & Public Involvement
PSC	Primary Sclerosing Cholangitis
QEHB	Queen Elizabeth Hospital Birmingham
RCT	Randomised controlled trial
TE	Transient elastography
UDCA	Ursodeoxycholic acid
UHB	University Hospitals Birmingham NHS Trust
ULN	Upper limit of normal range

CHAPTER 1: Introduction

Rationale, objectives, thesis structure and background

6 CHAPTER 1: INTRODUCTION

6.1 Summary of Thesis Structure and Rationale

This section will describe the rationale for the thesis topics and the objectives of the work. It will also explain the use of mixed methods research and demonstrate the overall thesis structure. This is followed by a detailed review of auto-immune liver disease focussing in particular on primary sclerosing cholangitis (PSC) as well as describing the background to the use of telemedicine and non-invasive imaging techniques in these cohorts of patients.

6.1.1 Rationale

As a gastroenterology specialist registrar and clinical research fellow, I have gained first-hand clinical experience managing complex patients with auto-immune liver disease (AILD) at Queen Elizabeth Hospital Birmingham (QEHB). It became clear to me how this cohort represent a great unmet need in research and how they experience significant barriers to receiving optimal medical management; thus, the initial ideas for this thesis were formed.

Of the main forms of AILD, PSC stood out to me as being of particular interest. PSC is a rare chronic fibro-inflammatory liver disease characterised by progressive destruction of the bile ducts and a long-term poor prognosis, with high risks of liver failure requiring liver transplantation and death within 15-20 years of diagnosis. Uniquely amongst the spectrum of AILD, PSC has no effective treatment and at the same time has an especially unpredictable prognosis. A full evidence-based review of PSC is included later on within this chapter. These challenges are faced by patients and clinicians alike and are unusual in the current era of

modern medicine. Therefore, my investigation was tailored to focus in more detail towards PSC, within the spectrum of other AILDs.

6.1.2 Thesis Objectives

The overriding questions for this thesis were to investigate what the burden of PSC is from a patient and healthcare point of view, to identify challenges to its optimum management, and to investigate how evolving technologies may provide solutions to these challenges.

The broad objectives for this thesis were to describe:

1) The medical journey and healthcare resource use of patients with PSC
2) The personal experiences of patients with PSC, both of their disease and their healthcare
3) How telemedicine might impact upon healthcare experience for patients with PSC and other AILDs
4) How advances in MRI technology might improve risk stratification in PSC and other AILDs

6.1.3 Structure of PSC services at Queen Elizabeth Hospitals Birmingham

Before explaining the thesis structure in more detail, it is important to understand the environment that this research was conducted within.

University Hospitals Birmingham NHS Foundation Trust (UHB) serves over a million patients a year including patients local to the West Midlands area, but also providing specialist services both nationally and internationally[1]. QEHB is the largest acute hospital of the Trust and is one of the largest liver transplant units in the UK, performing upwards of 240 liver transplant a year and with more patients on the liver transplant waiting list than any other unit in the UK[2].

QEHB performs 10% of liver transplants on patients with PSC[2] and looks after one of the UK's largest PSC cohorts in dedicated weekly specialist clinics in the newly built Centre for Rare Diseases. This clinic is run by QEHB clinicians with a specialist interest in this condition and whom are also involved with clinical research, thus providing patients with state-of-the art treatments and access to emerging therapies. There is often a gastroenterologist with an interest in Inflammatory Bowel Disease (IBD) present; this allows simultaneous management of both conditions which are closely linked, as will be explained in later sections. Blood sampling can be performed immediately within the Centre for Rare Diseases and it is common practise to combine clinic appointments with other investigations on the same day, with results available in time for the PSC clinic appointment itself. As a result of this infrastructure, the PSC clinic at QEHB provides a "one-stop-shop" approach for many of its patients.

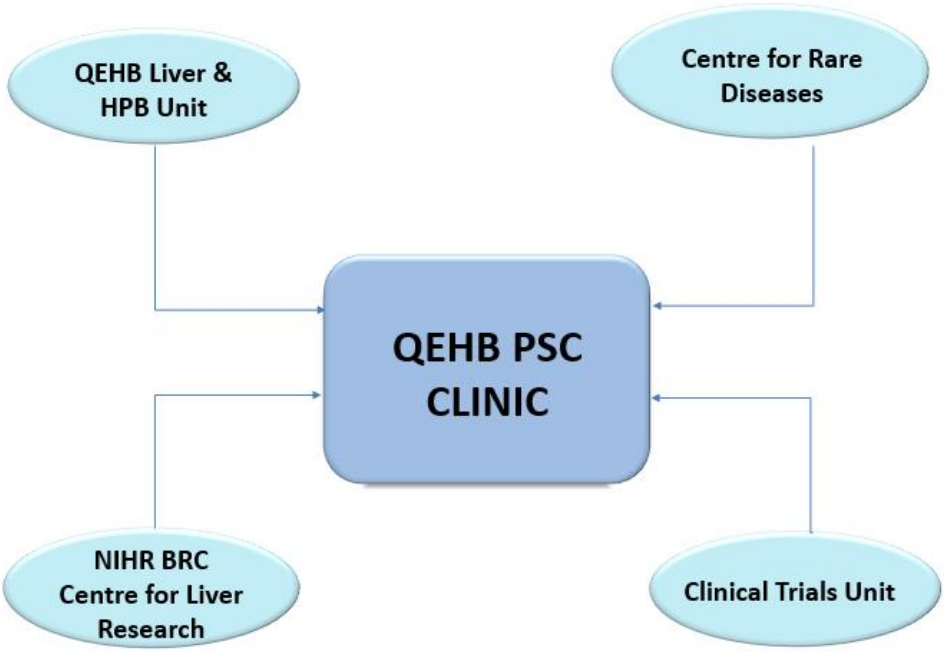
The QEHB Liver and Hepatobiliary (HPB) Unit has close links with the nearby National Health Institute for Health Research (NIHR) funded Birmingham Biomedical Research Centre (BRC), and especially the Centre for Liver Research. Clinical trial Chief Investigators and Research Fellows frequently support NHS clinics at QEHB, both to provide routine clinical care, and to

promote access to the multiple clinical trials running within the nearby University-run Clinical Trials Unit.

QEHB manages a large proportion of the UK's PSC population and its additional advanced clinical computer systems means this site provides a good resource in which to study the current management of PSC in the UK. At the time this research was undertaken, QEHB was in the final stages of creating an online platform for the introduction of Virtual Clinics; this was a video conferencing system to allow for remote clinical consultations, i.e. video clinics, whereby patients could stay at home yet still access and consult with their clinicians. At the time this research was commenced, this virtual clinic was in the final stages of preparation and was planned to commence in the weekly PSC clinic.

The overall organisation of QEHB liver services can be seen in Figure 1.

Figure 1. The organisation of QEHB PSC services 2015-2018



6.1.4 The use of multiple methods

The objectives for this thesis are broad, with many individual research questions identified. Therefore, multiple research methods were employed in order to best answer each of the four objectives. This also maximised educational opportunities for the researcher, who then had the opportunity to explore different methods of investigation, both qualitative and quantitative. These methods are described below.

6.1.4.1 Quantitative Research

Traditional medical training focusses on critical appraisal of quantitative research in order to practise evidence-based medicine. Quantitative data is that of objective facts and figures, for example, the incidence of a disease or the risk of a specific endpoint, such as death or liver transplantation. Randomised-controlled studies, cohort and observational studies generate quantitative data which is then mathematically analysed using statistical techniques. A major weakness of quantitative data is that it is unable to incorporate the context or personal element to the situation being investigated or consider social or cultural influences[3]. The author of this thesis can relate to this in their personal experience as a clinician and can recall many encounters where a patient's concerns were not of their numerical results, but of how to cope with living with their PSC without any certainty of if and when it might progress.

Medical research is also traditionally quantitative, asking questions which can "overlook the shared interests of patients, carers and clinicians" and thus the results can "fail to provide answers that are useful in practice"[4]. This creates a mismatch between the research being conducted and what questions patients or healthcare professionals need answering to impact

positively on real-life important scenarios. Attempts are being made to ameliorate these research mismatches by work from the UK's James Lind Alliance (JLA), particularly in the arena of chronic liver disease. Within the JLA 2015 Priority Setting Partnership on chronic liver disease, four of the top ten priorities were regarding AILD and two were specifically focussed on PSC[5]. These priorities are set after consultation with patients, carers and clinicians alike and further corroborate the need for more patient-centred research in AILD.

6.1.4.2 Qualitative Research

Qualitative research, in contrast, uses more open-ended data gathered from personal interactions, such as in interviews or focus groups. This is subsequently collated to present the "richness" of ideas or opinions, rather than the summative amount of each idea identified[6]. While this reduces the above-mentioned quantitative data mismatch between stakeholder priorities and research being implemented, qualitative data often includes just a very small sample of the overall study population. The individuals included will inevitably have their own biases, as do the researchers themselves, and this can affect the interpretation of the results[6]. It is therefore vital to ensure this small sample is representative of the wider subject population when drawing conclusions and to have independent corroboration of the analysis in order to reduce bias.

6.1.4.3 The approach taken in this thesis

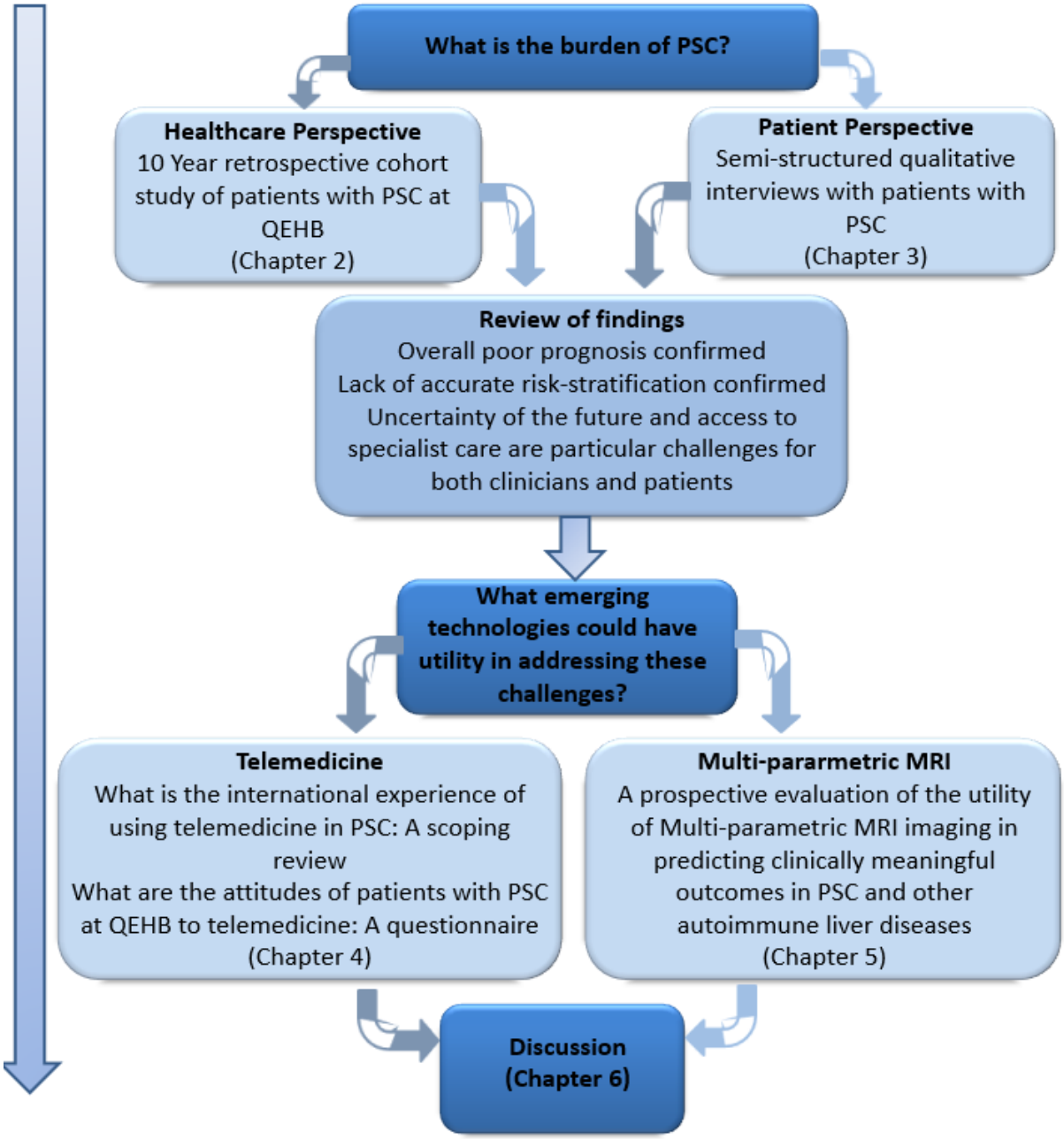
Given the advantages and disadvantages of both methods of research, there has been increasing interest in combining these within one study, or a series of related studies. The rationale for using both qualitative and quantitative research methods is that the combination provides a more comprehensive understanding on a subject and can answer a number of interrelated questions which could not be answered by one approach alone[6]. This form of mixed methods investigation has been increasing in popularity over recent decades, especially in health and social sciences, with increasing importance placed on patient-led research[7].

This thesis incorporates a number of separate studies of varying quantitative and qualitative methodology, the results of which are then finally discussed together to create a wider picture than each of the studies could have done alone. Thus, this thesis cannot be viewed as a formal mixed method piece of work as the required "integration of approaches at the design, analysis or presentation stage"[6] has not been completed. The questions asked in each study can be viewed instead as separate stepping stones contributing towards the overall understanding of PSC experiences.

6.1.5 Summary of thesis structure

This thesis consists of four studies which together provide a body of evidence to answer the research objectives. This structure is summarised in Figure 2.

Figure 2: Overall Thesis structure



Chapter 1 introduces the thesis structure and provides a state-of-the-art summary of AILD, with particular reference to PSC.

Chapter 2 describes a ten-year retrospective cohort study of PSC patient management at QEHB. This investigation aims to bridge a gap in the scientific knowledge of real-life PSC clinical management and to start understanding the burden of PSC on patients and healthcare providers. This study also provides baseline evidence for the standard management of PSC at QEHB, with the potential for future comparison once the virtual clinic has been formally introduced, as this may change the current pathways of care.

Chapter 3 presents a series of qualitative semi-structured interviews with PSC patient participants. Little is known about the burden of disease in these patients, what it is like to live with PSC, and what patients feel is most important. Without knowledge of the patient perspective, healthcare services cannot hope to improve ways of managing these individuals. This study presents discussions regarding patient experiences of illness, their healthcare and explores their priorities for the future. Given the incoming QEHB virtual clinic, these interviews also included specific discussion of attitudes towards telemedicine techniques.

The results of these two studies raised a number of opportunities for further research, particularly into areas where the experiences of PSC patients could be improved and where barriers to their diagnosis and treatment could be broken down. The research therefore progressed to investigate the potential utility of these technologies in more detail:

Chapter 4 describes a scoping review exercise into the utility of telemedicine in chronic liver disease and then presents an anonymous questionnaire to the QEHB PSC cohort on this topic. The use of virtual consultations may improve access to specialist care across the UK and given

the incoming QEHB Virtual clinic, it was timely to explore the potential utility of this intervention in this cohort of patients.

Chapter 5 presents a large risk-stratification study investigating the utility of novel quantitative-MRI technology in patients with PSC and other AILDs. As described in more detail in later sections, all patients with AILD have a need for improved methods of risk stratification to predict clinically useful outcomes and direct the highest risk patients towards new treatments.

Chapter 6 is the final discussion chapter. Each of the aforementioned studies serves to answer a different facet within exploring the entire burden of PSC. However, the studies combine to produce a wider picture of PSC and are inevitably interrelated (Figure 3). The final chapter presents the combined results for the four studies, comparing and contrasting these, and aiming to increase the overall breadth of understanding of the problems PSC creates for patients and healthcare providers as well as the impact telemedicine and new MRI techniques could make on these.

Figure 3: How the different studies within the thesis integrate to answer the overall thesis objectives

6.2 Introduction to Auto-immune Liver Disease

This next section provides an overview of AILD and the challenges encountered by patients and clinicians alike in managing these rare chronic diseases. Particular attention is paid to describing PSC, given this is the main focus of this thesis. This is followed by an introduction to telemedicine and subsequently to the role of MRI imaging in liver disease, as these relate directly to the studies described in the following chapters.

6.2.1 Overview

There are three main forms of auto-immune liver disease, Primary Sclerosing Cholangitis (PSC), Auto-Immune Hepatitis (AIH) and Primary Biliary Cholangitis (PBC). These conditions are all rare, yet with increasing incidence globally and with a disproportionately high burden of disease for the number of patients directly affected[8]. Patients experience challenges in accessing life-long specialist hepatology management for their disease and the best methods of phenotyping or risk stratifying patients with AILD are poorly understood. PSC is a particular challenge for patients and physicians and was thus chosen as the main focus of this thesis; the evidence for this is described below.

6.2.2 Primary Sclerosing Cholangitis

PSC is a rare immune-mediated liver disease characterised by relentless and progressive inflammation affecting intra-hepatic and/or extra-hepatic bile ducts[9]. This leads to cholestasis, advancing liver fibrosis and high risks of biliary malignancy. There is no proven disease-modifying therapy.

6.2.2.1 Epidemiology

Unlike traditional auto-immune conditions, PSC demonstrates a male preference (male: female ratio of 2:1[10]) and has no clinically useful auto-antibody profile, except to aid with the exclusion of other related conditions. Typical onset is in the 4th decade of life[9]. PSC has an annual incidence of 0.1-1.3 per 100,000 population per year, with recent increasing disease incidence observed in Northern European and American populations[11]. Despite this, PSC remains rare, with an incidence far below the accepted 50 per 100,000 population per year standard for inclusion as a rare disease[12]. PSC is closely associated with inflammatory bowel disease (IBD); this is observed in up to 83% of patients of Northern European origin[13]. Given the strength of this association, all patients diagnosed with PSC are recommended to have an index screening colonoscopy[9].

6.2.2.2 Diagnosis

The diagnosis of PSC is made in the presence of chronic cholestasis (usually defined as raised serum alkaline phosphatase, ALP) along with compatible imaging/histological features[9]. Such features include stricturing of the biliary system on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Most presentations of PSC are visible on imaging and are thus labelled as "large duct"; around 5% present with only histological changes and are thus labelled "small duct PSC"[9]. Small duct PSC has a better long-term prognosis, but progresses to large duct PSC in 23% of cases[14]. MRI is the recommended modality used for the diagnosis of PSC; ERCP should be reserved for specific scenarios where biliary decompression or sampling is required[9]. One typical feature of PSC on liver histology is periductal "onion-skin" fibrosis, however, invasive liver biopsy is now recommended only when MRCP is normal in the presence of chronic cholestasis (looking for small duct PSC), where there is diagnostic uncertainty or if there is concern about the presence of an overlap syndrome (such as with AIH)[9].

The above features are enough for a diagnosis of PSC, but must be in the absence of a secondary cause such as chronic cholecystitis, Human Immunodeficiency Virus (HIV) or Immunoglobulin G4 (IgG4) disease. These alternative diagnoses must be excluded as targeted treatments for these exist, unlike in PSC. In addition to ALP, liver enzymes (aspartate transaminase, AST and/or alanine aminotransferase, ALT) are often mildly raised in PSC. A raised bilirubin or derangement of other markers of synthetic liver function, including measures of blood clotting such as the International Normalised Ratio (INR), serum albumin and platelet count, are associated with cirrhosis, portal hypertension and a poorer long-term prognosis[15].

6.2.2.3 Clinical Features

Common symptoms of PSC include abdominal pain, fatigue and pruritus; half of patients have symptoms at diagnosis however more will develop these overtime[16]. Asymptomatic patients have better prognosis, hypothesised to be due to earlier diagnosis creating a lead-time delay[9]. Results from a national patient survey completed by PSC Support (the UK's national charitably funded disease-specific support group) showed that 80% of sufferers regularly experienced significant symptoms[16]. Patients with PSC also have high rates of social isolation, depression and anxiety, with poorer health-related quality of life scores than healthy controls[17].

6.2.2.4 Prognosis

The progressive inflammation of bile ducts observed PSC leads to advancing fibrosis, recurrent bacterial cholangitis and liver cirrhosis. Up to half of PSC patients develop a dominant biliary stricture leading to worsening cholestasis, biliary obstruction and risks of cholangiocarcinoma[9]. Patients who develop a dominant stricture experience a poorer prognosis regardless of subsequent management, such as with biliary balloon dilatation via ERCP along with histology taken to exclude cancer[18]. Over a median 15-year period from diagnosis, 37% of patients progress to liver failure and experience either liver transplantation or death[19]. In the UK, 11% of all liver transplants are currently performed for PSC and this proportion is climbing annually[2].

PSC has an 11% lifetime risk of hepatobiliary cancer, including hepatocellular carcinoma, gallbladder cancer and cholangiocarcinoma[8]; the latter now accounts for 58% of all deaths in PSC[20]. The risk of cholangiocarcinoma is highest in those with large duct PSC, especially those

with dominant strictures[20]. Up to half of cholangiocarcinoma diagnoses are made within the first two years of PSC diagnosis[21], with no evidence that a longer duration of PSC is associated with increased cholangiocarcinoma risk[22]. The combination of PSC with IBD has additional associated increased risks of colorectal cancer (up to 15% lifetime incidence[8]), cholangiocarcinoma (hazard ratio 28.4[23]) as well as increasing patient morbidity.

6.2.2.5 Medical Management

Amongst the spectrum of AILD, PSC is of particular interest due to there being no evidence-based disease-modifying therapy available, and thus nothing to ameliorate the often-relentless progression towards liver transplantation. In the era of modern medicine this is a rare occurrence and thus poses particular challenges to both patients and clinicians. Ursodeoxycholic Acid (UDCA), a synthetic bile acid, has been trialled in PSC; although some small studies showed improvements in liver biochemistry, none have demonstrated improvement in outcomes such as liver transplantation, cholangiocarcinoma or death[24,25,26,27]. One study into the use of high-dose UDCA was halted early due to a high rate of adverse events[28]. Thus, current guidance does not recommend the routine use of UDCA in PSC, nor the use of corticosteroids or other immunosuppressive agents as these also lack efficacy[9]. Despite this, UDCA continues to be commonly prescribed in PSC[29].

The search for new treatments is ongoing and there are a number of UK-based interventional therapeutic trials in progress. These use serum ALP measurements as a surrogate marker for higher risk disease, usually an ALP of above 1.5-2 times the upper limit of normal (ULN)[30,31]. Reducing ALP levels may be associated with improved prognosis in PSC[32]. However, it is widely

accepted that ALP is a suboptimal marker of disease risk and that new, more accurate markers need to be developed[33].

Measures must also be taken to address the remaining symptomology of PSC. No specific treatments exist to ameliorate fatigue; it is recommended that alternative causes for fatigue (such as depression) should be actively explored and treated if found[9]. Pruritus can be successfully managed with bile acid sequestrants such as cholestyramine in the first instance, with second line agents also available for use if required. However, these agents do not work for everyone and chronic itch remains a significant problem for some patients[16].

6.2.2.6 Monitoring

Given the lack of disease-modifying therapy, current clinical management of PSC instead looks towards symptomatic management and monitoring for complications, such as the development of cirrhosis, cholangiocarcinoma or liver failure. Timely referral for liver transplantation, should this be required, is important given the unpredictable nature and fast progression of PSC in some individuals. Advanced PSC is a widely accepted indication for liver transplantation and has a good long-term post-transplant prognosis[34]. Due to the risks of cholangiocarcinoma development, which is an absolute contraindication to transplant in the UK[35], it could be argued to transplant patients with PSC early. However, the risk of recurrent PSC in the transplanted liver in up to 40% of cases thus further complicates the optimum timing of transplantation[36].

Surveillance for malignancy is important in PSC. International guidelines advises screening via yearly colonoscopy for those with PSC-IBD and annual ultrasound to exclude gallbladder

neoplasia in all PSC patients[9]. However, the evidence base is weak in how to best survey for cholangiocarcinoma; it is recommended to use non-invasive imaging (such as MRCP) for patients with new symptoms or a sudden worsening of liver biochemistry[9]. However, challenges remain in quantifying any changes seen and how these changes relate to future adverse outcomes.

6.2.2.7 Recurrent bacterial cholangitis

Recurrent bacterial cholangitis in PSC typically presents with fever, abdominal pain, pruritus and jaundice, but may be more insidious in nature; this can make the diagnosis challenging for non-specialists. Cholangitis commonly requires antibiotics and may necessitate repeated acute hospital admissions. These episodes can dramatically affect the same liver biochemistry which also serves as surrogate biochemical markers of disease severity; thus it becomes even more challenging to stage the disease[37]. Multiple courses of antibiotics are often required, leading to potentially multi-resistant organisms and increasingly difficult-to-treat infections[9].

6.2.2.8 Risk Stratification

Monitoring for disease progression and predicting high risk disease remains problematic in PSC. Rates of progression are unpredictable with some patients advancing quickly, and others remaining asymptomatic for many decades. Accurate prediction at individual level has implications for clinical practice as well as in the much-needed interventional clinical trials. Given the uncertain prognosis in PSC, the development of improved risk stratification methods is vital to assess patients with PSC in order to more fully inform the patient and clinical team of clinical progression. This is of key concern to patients, with uncertainty ranking as high as physical symptoms on direct questioning of UK patient cohorts[16,38].

The usual biochemical means of staging advanced liver failure to better time transplantation may overestimate disease severity in PSC due to chronic cholestasis or intermittent cholangitis. For example, bilirubin levels score highly within the in the Modified End-stage Liver Disease scoring system (MELD[39]) or the UK equivalent (UKELD) score[40] which is used to inform the appropriateness of transplantation. However, in PSC, these can be raised in the presence of a dominant stricture causing biliary obstruction, in which case ERCP for biliary decompression alongside brushings of the biliary epithelium (to rule out cholangiocarcinoma) might be a more appropriate initial treatment than referral for transplantation.

A number of prognostic models using patient factors and biochemical markers for high risk disease have been developed. This includes the revised Mayo natural history model for PSC[41] which, while remaining useful within the research arena, uses data derived from tertiary hepatology units with a likely higher disease burden and this score is rarely used in clinical practice in the UK[9]. The UK-PSC risk score is also validated for prognosis in PSC in small cohorts

however predicts outcomes from the date of diagnosis, which can vary and may not reflect the actual onset of disease[42].

Ultrasound-based transient elastography and the serological test Enhanced Liver Fibrosis (ELF) have both been shown to correlate strongly with histological fibrosis staging and with transplant-free survival in PSC populations[43,44]. Evolving MRI-based techniques have also shown promise and are undergoing further investigation, but are not yet validated in PSC[45]. Due to these limitations and the lack of external validation between cohorts, international guidance does not currently recommend any single method of non-invasive risk stratification method in PSC[9].

6.2.2.9 Accessing specialist care

Given the abovementioned complexities in optimum PSC management, it is recommended that all symptomatic patients are managed by hepatology units with particular expertise in PSC[9]. Clinical trials are usually based in such centres and patients not referred may not otherwise have the opportunity to partake. Specialist centres are likely to be better able to manage patients with more complex disease, dominant strictures or with intractable symptoms, although this is anecdotal. Patients with early or asymptomatic disease may be well served by more local general gastroenterology or community follow up, however the popularity of this with patients themselves is uncertain.

Despite the recommendations for specialist management, hepatology services are not equally spread throughout the UK. The 2017 Liver Atlas states that 64% of qualified hepatologists were based in specialist regional centres or transplant units, rather than in local district general

hospitals, yet this report also states that many patients with liver disease need local hospital care as well as onward referral to tertiary units[46]. The locations of liver units are not geographically evenly spread, nor do they accurately reflect the underlying local prevalence of liver disease or liver disease-related hospital admissions[46]. Thus, patients may find themselves in a "postcode lottery" of access to specialist liver services. The use of new technology, such as telephone or video clinics, may bypass these geographical barriers and allow patients better access to the care they need.

In conclusion, PSC has marked consequences for both quality and quantity of life and with considerable associated morbidity. Optimum clinical management is difficult given the need for effective disease-modifying therapy, better risk stratification tools and inequality of access to specialist PSC services across the country. Overcoming these barriers would undoubtedly improve experiences for patients and clinicians alike. Given the above-mentioned unique needs of PSC patients, this cohort were chosen as the main focus for investigation within this thesis. However, due to the unmet needs of other AILD cohorts, both AIH and PBC patient cohorts were included within the Questionnaire and MRI studies (Chapters 4 & 5). These conditions are therefore discussed further below.

6.2.3 Autoimmune Hepatitis

AIH is characterised by liver parenchymal inflammation, the presence of serum auto-antibodies, raised immunoglobulins and of response to immunosuppression, all unlike PSC[47]. Diagnosis is based on a combination of these and characteristic histological findings at liver biopsy such as interface hepatitis and the formation of rosettes[49]; histological findings feed into the commonly used modified AIH diagnostic score from the International Autoimmune Hepatitis Group (IAIHG)[48]. Unlike in PSC, liver biopsy is important at diagnosis to confirm AIH, but also to exclude alternative or co-morbid potential aetiologies such as non-alcoholic fatty liver disease (NAFLD), drug-induced liver injury (DILI) or indeed biliary pathology (such as PSC or PBC).

6.2.3.1 Clinical Features

While remaining a rare disease, AIH is over 10 times more common than PSC; AIH has an incidence of 16-18 per 100,000 population per year[49] and this is increasing over time[50]. In contrast to PSC, AIH presents as a more traditional immune-mediated disorder. AIH has a strong female preference (male: female ratio between 1:4 and 1:6), with typical onset in the 6th decade of life and with other manifestations of auto-immune diseases present in up to half of all patients[49]. Type 1 AIH is the classical form, affecting over 90% of adults and typically involving the presence of serum anti-nuclear antibodies (ANA) or anti-smooth muscle antibody (ASMA)[49]. Patients with Type 2 AIH run a more severe disease course and anti-liver kidney microsomal antibodies (anti-LKM) are observed; additional antibodies such as anti-soluble liver antigen (anti-SLA) can also predict more severe disease[51].

AIH is a heterogenous disease; it can present acutely as a severe hepatitis with jaundice or liver failure (25% of cases[52]) or more insidiously, either with asymptomatic abnormal liver enzymes or with non-specific symptoms such as fatigue, anorexia or right upper quadrant pain[49]. At diagnosis, 30% of patients have features of cirrhosis and these have associated poorer outcomes compared to those with early disease[52].

Untreated, AIH usually runs a relapsing and remitting course, with almost inevitable progression to liver fibrosis and cirrhosis[53]. The aim of treatment is complete biochemical and histological resolution of hepatic inflammation. The proportion of patients achieving complete response varies between studies (38-93%)[54] and treatment is often life-long, given the high risk of relapse if treatment is withdrawn. With successful maintenance of remission long-term, fibrosis or even cirrhosis may regress[55]. Current treatment is however imperfect, with up to 50% of non-cirrhotic patients developing cirrhosis over time, despite therapeutic intervention[52]. Failure to normalise liver tests within 12 months of therapy or experiencing more than four ALT flares per decade are associated with increased risks of liver-related death or transplant[54]. Liver transplant, if needed for AIH, has an over 90% 10-year transplant survival rate[52].

6.2.3.2 Medical management

The treatment of AIH is with non-specific immunosuppression; corticosteroids are the mainstay of remission induction swiftly followed by additional maintenance therapy, usually with azathioprine as first line. Patients not tolerating this standard management algorithm may be tried on budesonide (as a better tolerated non-systemically absorbed corticosteroid), mycophenolate mofetil, tacrolimus or biological therapies as second- and third-line treatment options. Corticosteroids are usually continued at low doses of 5-7.5mg for 12-18 months after

complete resolution of liver biochemistry, at which point a second liver biopsy is sometimes performed to assess for ongoing inflammation and to guide further therapeutic decision making.[56]

In tandem with the need to swiftly resolve hepatic inflammation and maintain long term remission, is the need to keep medication dosages to a minimum given the high side effect burden and the long-term risks involved in lifelong immunosuppression. Long term use of prednisolone predisposes to weight gain, hair loss, diabetes, osteoporosis, glaucoma and higher doses can also cause psychological effects including psychosis[57]. The use of corticosteroids can themselves reduce health-related quality of life, independently of AIH disease remission and the presence of cirrhosis[58]. Other immunosuppressive agents also have side effects as well as predisposing to sepsis and malignancies including skin cancers and lymphomas. There is therefore a balance to be sought between finding the medication dosages required to completely suppress hepatic inflammation, while also minimising the side effects of such medication, and promoting patient compliance[59].

6.2.3.3 Monitoring

AIH activity is monitored clinically on serum bloods tests with particular reference to the liver enzymes (ALT and AST) and Immunoglobulin G (IgG); these form surrogate markers of hepatic inflammatory activity. Successful resolution of hepatic inflammation in AIH leads to improved long-term clinical outcomes however normalisation of serum liver tests does not exclude underlying residual inflammation[60]. Ongoing histological inflammation occurs in up to 45% of patients with complete normalisation of liver tests, and this continues to infer a higher risk of disease progression[61]. Conversely, persistently raised transaminases can be due to co-morbid

fatty liver disease or an idiosyncratic reaction to immunosuppression (as can be observed with azathioprine), rather than ongoing hepatic inflammation[62].

Overall, serum liver tests are poor markers of the activity and severity of liver disease, with levels sometimes normal despite advancing cirrhosis[63] and with additional controversy over what the normal limits of ALT should be[64]. The role of an isolated rise in IgG without a simultaneous rise in liver enzymes remains unclear, but may predict relapse if immunosuppression is withdrawn[65,66]. Overall, up to half of patients experience a relapse, despite ongoing therapy[52], further demonstrating the need for improved clinical management.

6.2.3.4 Risk stratification

As a result of these difficulties in non-invasive monitoring of AIH activity, guidelines traditionally recommended repeat histological assessment via percutaneous liver biopsy 18-24 months after resolution of serum biochemistry,[67]. This would aim to assess for complete histological resolution of inflammation and to aid in long term therapeutic management considerations such as immunosuppression reduction regimes. However, while giving access to real liver tissue without the need for imperfect surrogate markers, liver biopsy has limitations; risks remain of complications from the procedure itself and inter-observer variation between reporting the pathology results has been frequently described[68]. Sampling error is also a problem; the assessment of such a small proportion of liver tissue risks significantly over or underestimating the whole liver burden of disease. Biopsy is also often uncomfortable and is in generally unpopular with patients, who are keen to explore non-invasive alternatives[69].

Repeated liver biopsies are thus being performed less frequently[70]. Anecdotally, a more pragmatic approach is increasingly used instead, using non-invasive markers of inflammatory

activity (such as liver biochemistry and IgG) and the experience of the individual specialist, to guide therapeutic decisions. However, this remains imperfect and improved methods of non-invasive monitoring for AIH activity are needed. UK-AIH is a national research collaboration funded by the NIHR and aims to improve the understanding and treatment of AIH. UK-AIH currently has a prospective study ongoing including the development of risk stratification criteria for high and low-risk patient cohorts, based on non-invasive clinical data[71].

Recent developments in non-invasive methods of liver imaging, such as MRI, have the potential for more accurate assessment of underlying liver inflammation; this is described in more detail in below sections. These imaging techniques have potential utility for informing evidence-based decision making in AIH, to promote faster reduction of immunosuppression in patients with complete resolution of inflammation or conversely, to predict patients at high risk of deterioration; the latter may allow clinicians to intervene even before the liver biochemistry deteriorates.

Additionally, variation has been observed in the clinical management and outcomes of AIH patients across UK centres[72,73]. With AIH remaining a rare disease, experience amongst clinicians varies and patients can travel long distances to access appropriate specialist clinical care. This introduces geographical challenges for patients and clinicians alike, similar to those described previously in PSC.

Overall, there are many unknowns in the long-term management of patients with AIH and these patients represent a great unmet need for better non-invasive markers of disease activity and improvement in access to knowledgeable medical care. Thus, like those with PSC, they represent an interesting and worthy group of patients to assess further, thus justifying their inclusion within the questionnaire and quantitative MRI studies (Chapters 4 & 5).

6.2.4 Primary Biliary Cholangitis

PBC is a chronic cholestatic liver disease affecting primarily the intrahepatic bile ducts; it is described best as a chronic non-suppurative lymphocytic cholangitis. Like PSC and AIH, PBC is a rare disease, with an incidence of 2-3 per 100,00 population per year[74]. There is a strong female predominance (female to male ratio of around 10:1) and a median onset at 65 years of age[75].

6.2.4.1 Clinical features

The initial presentation of PBC is often asymptomatic and up to 90% of patients have no liver fibrosis at presentation[76]. However, in the decade following diagnosis, over half of asymptomatic patients subsequently progress to developing symptoms; those who do remain asymptomatic longer term do still have reduced survival compared to healthy controls[77,78].

Like other AILDs, the symptoms of PBC are non-specific and include fatigue and pruritus. Symptom severity does not correlate with commonly used clinical markers of disease severity[79]. Patients may thus experience a significant symptom burden but with only mildly raised liver tests; this may predispose to a wider than usual divide between patient and clinician priorities. Pruritus is treated medically in a similar fashion to that described for PSC, however may be intractable and an indication in its own right for transplantation[80]. As before, fatigue has no specific treatment. Like with AIH, over half of PBC patients have other co-morbid autoimmune conditions such as sicca complex, coeliac disease or thyroid disease, all of which add to the symptom burden for these patients[81].

6.2.4.2 Diagnosis

Diagnosis of PBC is made in the context of chronic cholestasis and the presence of serum anti-mitochondrial antibodies (AMA) at a titre of >1:40, often accompanied by a rise in Immunoglobulin M concentrations[81]. AMA-negative PBC occurs in 5% of patients; in this case the diagnosis maybe confirmed using alternative auto-antibodies such as anti-Sp100 or anti-Gp210[82] and/or histological assessment, with the presence of florid bile duct lesions being very suggestive of PBC[81]. Historically, liver biopsy was often undertaken in the diagnosis of PBC however, more recently the diagnosis is usually made clinically, with biopsy reserved for instances where AMA is negative or where there are specific concerns about alternative aetiologies or overlap syndromes. Like with other AILDs, liver biopsy is problematic in heterogenous diseases such as PBC, and sampling error may further confound the diagnosis[83].

6.2.4.3 Medical Management

Like in PSC, immunosuppression in PBC has no accepted role, except where true overlap with AIH might be present. The management of PBC includes the long-term use of oral UDCA at a recommended dose of 13-15mg/kg; this treatment is lifelong if successful and well tolerated[81]. If treatment is commenced while the PBC is in its early stages and providing a good response is seen, the risks of future liver transplantation and death are markedly reduced[84,85]. Due to the efficacy of UDCA, the incidence of transplantation for this cohort is relatively low with 6% of liver transplants completed annually for this indication in the UK[86,2].

A number of definitions of UDCA response have been proposed. The Toronto stratification criteria define response as an ALP reduction to under 1.67 xULN, or complete normalisation,

within 24 months of therapy[87]. Other response criteria include Paris (bilirubin ⩽17 µmol/L, ALP ⩽3× ULN, and AST ⩽2× ULN) and Barcelona (decrease in ALP by >40% of pre-treatment levels or normalization at one year) criteria which also confers excellent long-term outcomes[88,89]. Guidelines thus advise the assessment of UDCA biochemical response in all patients after one year of optimum UDCA therapy[81]. Younger, and especially male patients with PBC are less likely to respond to UDCA and overall have a poorer prognosis[75,8].

6.2.4.4 Risk stratification

Markers of synthetic liver function impairment, especially bilirubin levels are known to correlate with poorer outcomes in PBC, indeed it is recommended that liver transplantation is considered once the bilirubin reaches a modest 50umol/L[81]. Earlier predictors of risk include the Globe and the UK-PBC risk scores, both of which have been developed from the study of large national cohorts and allow prediction of survival over time[90,91]. Some studies have also shown an association between the non-invasive AST to Platelet Ratio Index (APRI) and fibrosis[92] or transplant-free survival[93]. These non-invasive risk stratification methods to individualise care for patients are not in routine clinical use yet have potential utility, whether to identify higher risk patients for second line therapies or to guide management in primary care for those at lower risk. As with PSC, patient attitudes to primary care management for their PBC are uncertain. Quantitative MRI may have an emerging role in staging the entire liver burden of disease in PBC, however is yet to be formally validated in this patient cohort.

Some patients do not tolerate adequate doses of UDCA due to side effects, in particular gastrointestinal disturbance and worsening itch[94]. Adequate response does occur in around 60-70% of those who tolerate an adequate dosing regimen[95], indicating an unmet need for

second line treatments which are more effective and/or are better tolerated. Trials are ongoing for such treatments[96]. In 2017, Obeticholic acid (OCA) was licensed as second line therapy in the UK, although phase 4 studies are ongoing and long-term efficacy with survival benefit is not yet proven[97]. Additionally, morbidity in PBC remains high, particularly due to symptoms such as fatigue and itch; the latter may be worsened by OCA in up to 10% of patients[97].

Like in PSC and AIH, there is variation in PBC patient management observed between centres and individual clinicians[98]. Access to second line therapy or clinical trials may not be easily available for all patients and therefore, telemedicine may have a role in equalising such access across the UK, similar to that observed in PSC.

In conclusion, many questions in PBC management remain including geographical difficulties faced by patients in accessing specialist care and in effective risk stratification for higher risk disease. Therefore, including these patients within the MRI and questionnaire investigations within this thesis, along with AIH and PSC, was justified.

The background to telemedicine and quantitative MRI assessment in liver disease will now be discussed below:

6.3 Improving access to care

As described above, AILDs are rare chronic liver diseases requiring long term management, often by specialist hepatology services. Given the unequal distribution of such services across the UK, these patients can struggle accessing the care they need[46].

6.3.1 Telemedicine

One proposed method of improving access to medical services is the use of telemedicine, i.e. the "use of telecommunication systems to deliver healthcare at a distance"[99]. This is an umbrella term that includes interventions from real-time video conferencing to digital remote monitoring of clinical parameters such as blood glucose. The 2016 Cochrane review into the utility of telemedicine reviewed 93 randomised controlled trials (RCTs) published globally up until June 2013[99]; this study concluded that telemedicine use in some circumstances led to similar or improved outcomes when compared to standard face-to-face care and that this could be cost-effective. However, this review also concluded that more evidence was needed to establish the full effects of this, including the acceptability to patients.

Chronic liver disease currently poses a great burden on current resources, and this is projected to increase massively in the decades to come; liver disease currently kills over 16,000 people per year in the UK, with prevalence and mortality increasing annually, at a time when most other chronic conditions are seeing mortality improvements[100]. However, of the studies included in the Cochrane review, none specifically looked at participants with liver disease[99]. Therefore, evidence for the efficacy and acceptability in this patient population, and especially to those with AILD, is lacking.

As well as potentially being more cost efficient, telemedicine can reduce the patient burden of physically attending their healthcare provider, who may be many hours travel away. This is especially true for patients with AILD who can travel long distances to access disease-specific medical care, given the geographical inequality of the distribution of such services[46]. Telemedicine may have utility in improving medical access for many patients with chronic diseases requiring lifelong care and for those with complex or rare diseases requiring specialist management in tertiary centres, as seen in AILD. Using telemedicine techniques, the patient can access medical care from anywhere in the world, reducing the personal impact of physically attending hospitals including travel costs, loss of earnings and general disruption to the patient's schedule.

6.3.2 QEHB Virtual Clinic

At the time this research was being undertaken, QEHB was introducing video link virtual clinics into their outpatient liver services, with the PSC clinic included within the pilot scheme. The PSC cohort were chosen for the pilot for logistical reasons rather than there being overt evidence that this cohort of patients wanted or needed this change, although both seem likely to be true. Additionally, the Cochrane review concluded that the healthcare resource usage, cost and acceptability to both patients and healthcare professionals of the use of telemedicine, was still unknown and just one third of the studies included focussed on real-time video-conferencing[99]; these studies included patients with conditions such as heart failure, diabetes, mental health problems and stroke rehabilitation; none had liver disease. Only six studies were performing specialist consultations. This all indicates an ongoing paucity of data for telemedicine in AILD[99]. Investigation into the international experience of

telemedicine in PSC and the attitudes of the QEHB PSC clinic cohort to this technology are discussed further in Chapter 4.

Overall, virtual clinics could be of benefit to not just PSC patients, but those with other chronic diseases that have a need to develop more patient-centred care. Telemedicine is potentially both widely generalizable to other centres and transferable to other disease groups, and could be used as a model for how any chronic disease might be managed across a network. The ongoing coronavirus pandemic has exponentially accelerated the use of telemedicine techniques across the world. However, this arose from necessity rather than because the evidence behind its efficacy was proven. Close monitoring is needed over coming years to assess the impact this sudden change might have had on patient experience, clinical efficacy and healthcare resource usage. The effects of Covid-19 will be discussed in more detail in the final discussion (Chapter 6).

While improving access to disease-specific care is important for patients with PSC, and other AILDs, this is not the only intervention needed to improve experiences for patients and clinicians. As described earlier, AILD patients have an unmet need for improved risk stratification that can be used to improve and personalise care pathways; this is discussed further below.

6.4 Non-invasive assessment of liver disease

The inability to accurately risk stratify patients with AILD is of concern to both patients and clinicians. Given the aforementioned limitations of invasive liver biopsy, there has been great international interest in recent years in developing improved non-invasive techniques to accurately measure liver fibrosis and to better predict outcomes in chronic liver disease; these are discussed below:

6.4.1 Serum markers

A variety of serum composite scores and markers have been shown to have merit in the non-invasive assessment of chronic liver disease, however, many studies included mainly NAFLD or viral hepatitis cohorts[101]. These markers include the AST:ALT ratio[102], APRI[103], and Fibrosis-4 (FIB-4) tests[104]; these use easily available serum blood tests however a major pitfall is the inability to identify intermediate risk patients. The serum ELF test is also easy to obtain via standard venepuncture and has a sensitivity of 90% for the presence of fibrosis overall, yet a specificity of only 41% for severe fibrosis[105,106]. None of these markers give information as to the heterogeneity or aetiology of the underlying liver disease

6.4.2 Transient Elastography

As an alternative to using blood markers, other tests have been developed to more directly assess liver stiffness, as a surrogate for inflammation or fibrosis. Transient Elastography (TE) is an ultrasound-based technique that assesses liver stiffness, with higher readings indicating higher liver stiffness levels reflective of worsening fibrosis. This test has good diagnostic accuracy in ruling out significant fibrosis[107], however requires specialist equipment, is

operator dependant and significant intra and inter-observer variability has been identified when repeat readings are taken, especially in the context of larger body habitus and ascites[108,109]. Additionally, active liver inflammation (as seen in AIH), biliary obstruction (such as a dominant stricture in PSC), hepatic venous outflow obstruction, or having recently ingested a large meal can all increase liver stiffness[110]. Thus Elastography readings are a composite of fibrosis, inflammation, cholestasis and hepatic congestion, and must be interpreted with this in mind.

6.4.3 Non-invasive assessment in PSC

When looking at PSC specifically, the utility of these non-invasive methods remains understudied. The modified disease-specific Mayo score uses age, bilirubin, albumin, AST and variceal bleeding to give a categorical result of low, intermediate and high risk of survival[111]. However, this has been criticised for failing to predict other adverse events and is now potentially outdated given changes to the management of varices[112]. TE correlates well with the severity of liver fibrosis however was best at discriminating between no/mild and severe fibrosis, with the intermediate ranges again less well served[113]. Changes in liver stiffness measurements over time may be more predictive of disease-specific events[113], however this finding needs validating in larger cohorts. ELF testing has been shown to correlate closely with transplant-free survival and with elastography, however it is not clear how the normal variation seen in PSC activity over time may affect these single readings[114].

6.4.4 The role of MRI

With recent advances in non-invasive imaging technology, there is the desire to pursue these modalities in AILD to improve risk stratification, facilitate appropriate clinical management, prioritise entry into clinical trials or access to new treatments and to avoid painful invasive procedures (such as liver biopsy) where possible. Magnetic resonance imaging (MRI) is of particular interest given the detailed images of the entire liver and biliary tree that can be obtained, along with an excellent safety profile, especially when no intravenous contrast is required. MRI scanning sequences can also be standardised and regularly calibrated across scanners/centres, to ensure little or no variability in the image acquisition techniques.

Conventional MRI uses magnetic fields to excite protons and measures the resulting relaxation signals to create T1 and T2-weighted images of tissue. MRI has potential benefits over biopsy and TE as it samples the entire liver via a standard scanning technique, thus limiting potential for sampling errors, and it allows patients with larger body habitus and ascites to be scanned. MR-based Elastography (MRE) works on similar principles to TE, however can be adversely affected by liver-iron content, which can often be found in chronic liver diseases of any aetiology[115]. While MRE can accurately diagnose the presence of liver fibrosis, it is unclear if this is accurate enough to reliably monitor progression or regression of liver disease over time[115].

In general, most non-invasive risk stratification techniques perform more poorly when differentiating early fibrosis from normal tissue and overall there remains an unmet need in this area for more accessible and reliable methods of non-invasively quantifying hepatic inflammation and fibrosis.

6.4.5 Quantitative MRI techniques

Multi-parametric MRI (mpMRI) combines functional imaging (spectroscopy) with standard structural T1 and T2-weighted views in order to create a composite picture of the underlying tissue structure and function[116]. This has utility in the non-invasive quantitative assessment of many body organs, including prostate, breast and cardiac disease, as well as in cirrhosis assessment[117,118,119]. Quantitative mpMRI can standardise an otherwise complex system of reporting which traditionally uses radiologists to create semi-qualitative reports that have potential for inter and intra-observer variation, similar to that described previously with liver histology. Using standardised quantitative analysis excludes any operator dependant variation, potentially improving reliability and transferability.

One example mpMRI protocol in liver disease is the Liver*Multiscan*™ (LMS, Perspectum Diagnostics, Oxford, UK). This is a proprietary Food and Drug Agency (FDA) approved algorithm that uses post-processing of MRI images to combine the assessment of liver fat (via proton density fat fraction, PDFF), iron (via T2*image acquisition) and fibrosis/inflammation (via T1 scores, with higher T1 indicating higher amounts of inflammation and fibrosis)[120]. Performing this combined assessment leads to a corrected T1 score (cT1) that is the mainstay for the LMS reporting structure. The whole liver tissue volume is assessed resulting in metrics such as whole liver cT1 (via mode, mean and median values) as well as assessment of tissue heterogeneity (via the interquartile range, IQR). The scanning algorithm technique is discussed more fully in the literature[121]. LMS has been shown to correlate with histological fibrosis, to predict clinical outcomes and to potentially be of cost-benefit in some models of liver disease management[121,122,123]. However, this has mainly been studied in the NAFLD cohort and this technology has not previously been investigated in auto-immune liver disease.

Therefore, there is an unmet need and research opportunity to investigate quantitative multi-parametric MRI technology in the AILD cohort; this was met in this thesis via the completion of an observational clinic trial, discussed further in Chapter 5.

6.5 Summary of the Introduction Chapter

Patients with AILD represent a great unmet need in research and they experience substantial barriers to receiving optimal medical management. PSC is an especially interesting and unique cohort of patients with difficulties accessing specialist care and in managing their disease course, given the lack of effective risk stratification and treatment. Novel technologies can potentially overcome some of these barriers; MRI techniques may be able to predict clinical useful outcomes and potentially risk stratify patients. Additionally, telemedicine may be able to provide the same quality of specialist care but at a distance, thus reducing travel burden on patients and improving access to care. However patient experiences, attitudes to new changes and their priorities for their own care remain unknown.

Due to the multiple methods and studies included within this thesis, the approach has been taken to analyse the separate studies individually in the first instance (described within the individual study chapters with presentation of the results) and then amalgamate and interpret the collective findings together in the Discussion chapter.

CHAPTER 2:

A ten-year retrospective cohort study of patients with Primary Sclerosing Cholangitis managed at Queen Elizabeth Hospitals Birmingham

7 CHAPTER 2: A TEN-YEAR RETROSPECTIVE COHORT STUDY OF PATIENTS WITH PSC MANAGED AT QEHB

7.1 Introduction

As mentioned in Chapter 1, PSC is a rare cholestatic liver disease with significant risks of patient morbidity and mortality. This rarity, along with a lack of disease modifying therapy, makes PSC a challenge for clinicians and patients. In order to assess the impact of proposed new methods of managing PSC, it is important to explore what the current standard management pathways are for these patients; such pathways are currently unknown for PSC, exacerbated by the lack of disease-modifying therapy or optimum monitoring strategies.

QEHB has a large PSC cohort seen in dedicated clinics and with close links with other local academic and research institutions. QEHB also has advanced computer systems which can be easily interrogated to amass large amounts of clinically useful patient information. The QEHB PSC cohort attend from all over the UK; this cohort is therefore not typical of those seen at a single site serving mainly a local population.

To more fully understand the impact of PSC on the wider NHS, healthcare data from local hospitals as well as QEHB is needed. Hospital Episode Statistics (HES) is an NHS database covering details of all hospital attendances including patient demographics, diagnoses, procedures, admissions and outpatient appointments in England[124]. The primary aim of this system is to allow hospitals to be paid correctly for the services they administer but secondary uses include assessment of the effective delivery of care, to support local service planning and to determine fair access to healthcare. It is possible to interrogate this database to gather national information on the activity of a specific group of patients, such as those diagnosed

with PSC and seen at QEHB, thus gaining a national view of the healthcare burden of this cohort.

This chapter describes a retrospective cohort study of QEHB patients with a diagnosis of PSC, with additional national data provided via the HES system.

7.2 Aims

The aim of this study was to investigate describe the patient characteristics and management of a hospital-based pre-transplant cohort of PSC patients, based at QEHB.

The objectives were to describe the:

1) characteristics of PSC patients including demographics and disease features.
2) referral pathways into QEHB.
3) clinical management and how this reflects current international guidance.
4) clinical outcomes experienced by patients including liver transplantation or death.
5) healthcare resource use, both within the QEHB and nationally.

7.3 Methods

A retrospective ten-year cohort study of patients with PSC managed via the outpatient clinic service at QEHB between 1/11/2005 and 31/10/2015 was performed. Data was collected from QEHB by reviewing electronic case notes. National healthcare activity data was collected via the HES system.

7.3.1 Data collection

The data collection proforma was designed to capture clinically important aspects of PSC. The variables collected were those commonly used in the PSC clinic, according to the experience of the Lead Investigator (KA) and after discussion with senior colleagues. National PSC guidelines were consulted to ensure all relevant information was included[9]. Discussions with the QEHB Informatics team and experience of the Investigator revealed that electronic records were likely to be incomplete prior to 2005, thus it was decided not to collect data from earlier than this date.

The proforma was created using Microsoft Excel; a copy of this can be seen as Appendix A along with detailed descriptions of how each variable was calculated. In all metrics, where the data was not available, this was coded as unknown.

7.3.2 Identification of the study population

The study population was defined as patients who had attended QEHB for their first liver outpatient clinic appointment between 1/11/2005 and 31/10/2015 and who had a diagnosis of PSC. The QEHB informatics team searched for first QEHB outpatient clinic activity during these dates and using the HES code for Primary Sclerosing Cholangitis (Patient Diagnosis: Liver Cirrhosis cause type: Primary Sclerosing Cholangitis, 07[125]).

The full Inclusion Criteria were as follows:

1) Patients with an ever diagnosis of PSC (based on a six-month history of cholestasis AND consistent imaging/biopsy findings AND treated as PSC by the QEHB liver team)
2) And who had attended their first QEHB outpatient clinic appointment for their liver disease between 1/11/2005 and 31/10/2015.

The Exclusion Criteria were: -

1) Patients without a confirmed diagnosis of PSC.
2) Patients with additional liver disease aetiologies present which could have been contributing to the clinical picture (e.g. viral hepatitis or biopsy proven non-alcoholic steatohepatitis); other co-morbid autoimmune liver disease diagnoses were included given the potential for overlap with PSC.
3) Patients first seen at QEHB for their liver disease prior to 1/11/2005.
4) Patients who did not attend the QEHB outpatient's clinic for their liver disease during the study period (e.g. patients with only inpatient admissions).
5) Patients who had received a liver transplant from another NHS Trust prior to first QEHB clinic attendance

7.3.3 End-points for data collection

The inclusion period finished on 31/10/2015 and follow up was capped on 31/12/2016; this was to ensure a minimum 12-month clinical follow up period for every subject. Data collection was ceased either at the time of death, liver transplantation, or on the 31/12/2016 (whichever was the earlier), in order to ensure a fixed end point for the study. For patients undergoing liver transplantation during the study period, no further information was collected after this date except the final outcome as of 31/12/2016, for example if the patient had subsequently died or been discharged from QEHB follow up.

7.3.4 Hospital Episode Statistics Data

Data for PSC patients already known to QEHB and identified by the above described search was extracted using HES. PSC patients who had never been seen at QEHB were not able to be extracted by this search without additional national applications, as per HES regulations. The data extracted needed to be anonymised prior to transfer to the study team and was therefore unable to be linked at patient level with the QEHB dataset. Blood test or imaging results and prescription data are not recorded by the HES system. HES contains inpatient data from 01/01/2001 and outpatient data from 01/01/2006. The data extracted thus contains information from these dates (or later depending on first PSC coding), until 31/12/2017. It was not possible to differentiate activity occurring before or after transplantation via this HES dataset.

7.3.5 Data Management & Ethical Considerations

The study was registered with the QEHB Clinical Audit Registration and Management System (CARMS, registration 12973). All principles identified in the 1975 Declaration of Helsinki[126] and Good Clinical Practice (GCP)[127] were observed throughout the study. Patient confidentiality was strictly adhered to; the investigator was part of the clinical team and was the only individual directly accessing patient records, which were subsequently anonymised using a secure code known only to the investigator. Therefore, written consent for individual participants for this cohort study was not required. Information governance was maintained, with an encrypted database being created and stored on the secure hospital server. No patient identifiable data was taken offsite.

7.3.6 Pilot study

To confirm the timeframes and data quality, a 100 patient pilot study was completed before full data acquisition went ahead. 100 patients were randomly selected, ten from each of the ten years of recruitment between 1/11/2005-31/10/2015. These were assessed according to the dataset (described below) and the results were discussed for quality acceptability within the study team.

In total, 115 records were assessed as 15 were excluded to due not meeting the inclusion criteria (six did not have a PSC diagnosis, two duplicates were found, six had no clinical information at all available and one was not a new patient during the study time frame). Of the 100 patients in the pilot study, the dataset was >80% complete in all patients. The most common missing metrics were body mass index and the date of PSC diagnosis. Subjects in the first two years of the pilot study (i.e. 1/11/2005-31/10/2007) were observed to have more missing data, however, after discussion with the study team regarding the large amount of remaining information available from these early subjects, it was felt the early data was complete enough to make some conclusions. Therefore the whole cohort was subsequently interrogated in full.

7.3.7 Statistical Methods

The patient demographics, disease variables, referral information and outcomes were reported according to data type. Continuous variables were reported as medians and range. Categorical variables were reported as frequency and percentage.

For the three main outcomes (liver transplant, hepatobiliary cancer and death), comparisons were made between the outcome groups based on their features at first QEHB clinic visit. Comparisons between these outcome groups were made using Mann-Whitney tests, with Fisher's exact test used for nominal variables.

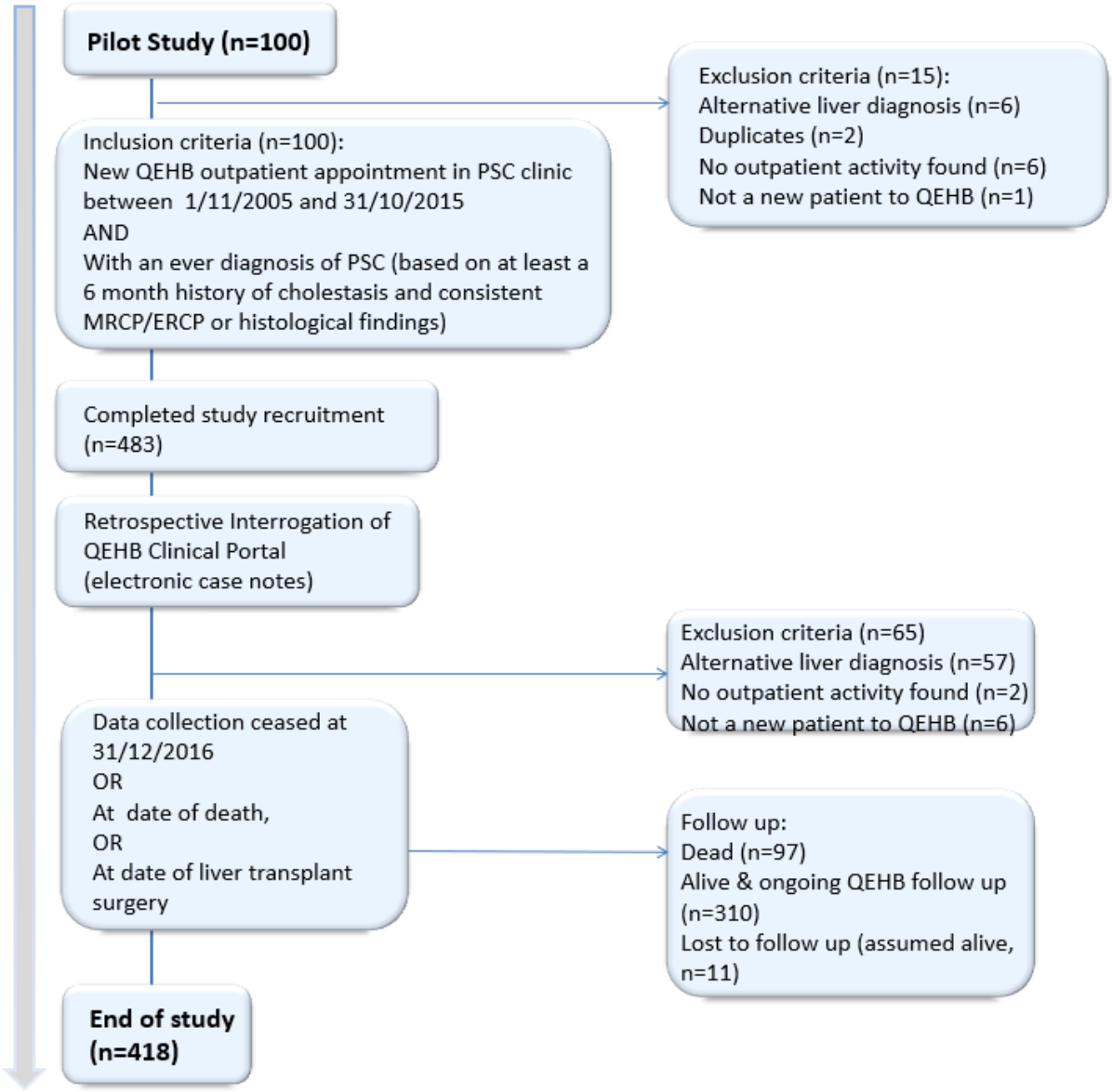
The prognostic accuracies of serum markers at first QEHB clinic visit to future outcomes were assessed using ROC curve analyses. While there are no absolute cut offs for the usefulness of a ROC curve analysis, convention dictates that a score of 0.5-0.7 is considered poor discrimination, 0.7-0.8 denotes acceptable discrimination, and above 0.8 excellent discrimination[128]. For the best serum marker for each outcome, Youdon's J statistical analysis was used to find the best cut-off for these variables.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), unless stated otherwise, with $p<0.05$ deemed to be indicative of statistical significance throughout.

7.4 Results

In total, 483 individuals were identified in the data extract performed via the QEHB informatics team. All electronic patient records via the QEHB Portal system were reviewed with 65 patients subsequently excluded. Reasons for these exclusions were not having a confirmed diagnosis of PSC (n=57), not having any outpatient clinic activity (n=2) and not being seen for the first time during the study period (n=6). A flow chart for this study can be seen in Figure 4; in total 418 subjects were left to be fully analysed.

Figure 4. Flow chart of recruitment to the PSC Cohort Study



7.4.1 Patient Demographics

Median age was 40 years (range 18-84years), with over half of patients diagnosed under 40 years. Two thirds of patients were male (65%) and 360 (88%) were of White ethnicity; 206 patients (59%) were in full time work. The full demographics of the cohort are seen in Table 1.

Table 1: PSC Cohort Patient Demographics

Patient Characteristics	***Whole Cohort (n=418)***
Age at diagnosis (Years, n=349)	40 (range 18-84)
Age distribution at diagnosis (Years, n=349)	
<18	38 (10.9%)
19-25	55 (15.8%)
26-40	90 (25.8%)
41-60	115 (33.0%)
61-80	47 (13.5%)
81+	4 (1.1%)
Male Gender (%)	270 (64.6%)
Body Mass Index (kg/m^2, n=362)	24.0 (range 12.6-43.1)
Ethnicity (n=409)	
White	360 (88.0%)
Asian/Asian British	30 (7.3%)
Black/ African/Caribbean/Black British	4 (1.0%)
Other	6 (1.5%)
Mixed	9 (2.2%)
Employment type (n=352)	
Full time	206 (58.5%)
Part Time	7 (2.0%)
Retired	83 (23.6%)
Student	40 (11.4%)
Unemployed	16 (4.5%)

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified.

7.4.2 Disease Demographics & symptoms

The majority of the cohort had large duct PSC (86%) and over two thirds also had a diagnosis of IBD (67%). A minority (30 patients, 7%) also had a diagnosis of an overlap with AIH. Many were prescribed UDCA during the study period (60%), however, the dose of this varied with 144 (63%) patients receiving under the standard recommended dose for PBC of 13-15mg/kg[129]. There was no evidence found for the presence of symptoms for 66 patients (16%) however the remaining patients commonly described jaundice (43%), pruritus (37%), and fatigue (37%). Overall, three quarters of patients (76%) described more than one symptom during their disease course. The disease phenotype and symptoms documented of the QEHB PSC cohort are seen in Table 2.

Table 2: PSC Cohort Disease Phenotype & Symptoms

Factor	Whole Cohort (n=418)
Disease characteristics	
Co-morbid IBD diagnosis (n=413)	276 (66.8%)
Large duct PSC (n=396)	339 (85.6)
AIH overlap	30 (7.1%)
Taking UDCA (n=410)	245 (59.8%)
UDCA dose if taking (mg/kg, n=228)	11.7 (2.8-32.5)
Clinical Features (n=410)	
Asymptomatic	66 (16.1%)
Jaundice	175 (42.7%)
Pruritus	152 (37.1%)
Fatigue	151 (36.8%)
Cholangitis	133 (32.4%)
Abdominal pain	61 (14.9%)
Ascites/oedema	47 (11.5%)
Weight loss/sarcopenia	30 (7.3%)
Encephalopathy	19 (4.6%)
Variceal bleeding	13 (3.2%)
Other (nausea/joint pain/dry mouth)	5 (1.2%)
More than one symptom	311 (75.9%)

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified.

7.4.3 Diagnosis & Referral to Specialist Centres

Table 3 shows the cohort in terms of their referral pathway, timescales and the severity of disease at the time of referral to QEHB. Over half of the QEHB cohort (55%) had home postcodes outside the “B” area, and QEHB was the likely natural primary treatment centre for 58 patients, under 15% of the entire cohort.

The reasons for referral to the QEHB clinic included for initial diagnosis (n=119, 30%), ongoing routine management (n=104, 26%), liver transplant assessment (n=87, 22%) and cholangiocarcinoma concerns (n=44, 11%). At the time of referral to QEHB, half of patients had evidence of advanced disease in the form of cirrhosis (51%), with the majority of these of these having additional portal hypertension (84%). It was not possible from the data available to extrapolate accurately how long the patients had been experiencing symptoms or abnormal liver tests before the PSC diagnosis was made. However, for those diagnoses made outside QEHB and referred in at a later date, the median time from diagnosis to QEHB clinic was 5 years (range 1 month to 25 years).

Table 3: PSC Cohort Diagnosis & Referral Pathway

Factor	Whole Cohort (n=418)
Patient home postcode	
Within "B" postcode area	182 (43.5%)
Diagnosis	
Diagnosis made by QEHB (n=353)	130 (36.8%)
Time from non-QEHB diagnosis to QEHB clinic (years, n=223)	5 (range 0.1-25)
Age at first QEHB clinic (Years)	45 (Range 16-84)
Source of QEHB referral (n=409)	
External Gastroenterologist	218 (53.3%)
External Hepatologist	80 (19.6%)
External surgeon	7 (1.7%)
QEHB internal referral	26 (6.4%)
Adolescent transition referral	15 (3.7%)
GP	61 (14.9%)
Patient request	2 (0.5%)
Reason for referral (n=405)	
Diagnosis	119 (29.4%)
Second Opinion	12 (3.0%)
Ongoing management	104 (25.7%)
Transplant/TIPSS assessment	87 (21.5%)
Cholangiocarcinoma assessment	44 (10.9%)
Trials	5 (1.2%)
Patient request	10 (2.5%)
ERCP	8 (2.0%)
Adolescent transition	16 (4.0%)
Disease assessment at first QEHB clinic	
Cirrhosis (clinical diagnosis, n=413)	209 (50.6%)
Portal hypertension (n=413)	176 (42.6%)
Relevant blood tests (n=415)	
Bilirubin	20 (3-608)
UKELD	48 (40-73)
ALP (median)	471 (28-5051)
ALP xULN (130U/L)	2.22 (0.22-38.85)

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified. TIPSS – transjugular intrahepatic portosystemic shunt. ULN – upper limit of normal.

7.4.4 Prognosis & Outcomes

The prognosis and clinical outcomes of the full cohort can be seen in (Table 4). The majority of patients continued with QEHB follow up (64%); a small number were discharged (10%) however, in all cases this was to other hepatology specialist closer to the patient's base location. No patient was discharged from QEHB follow up to a non-speciality centre. In total, 178 patients were assessed for potential liver transplant surgery during the study period; 155 were accepted for listing (87%) and 127 of these went on to receive a liver graft (82%).

Overall, 97 patients died during the study period (23%); 29 of deaths were due to liver or graft failure (30%) and due to either hepatobiliary or colorectal cancer (30%). However, 22 of causes of death remained unknown (23%). 20 deaths were post-liver transplant (21%), of which 40% was due to multi-organ failure, usually in the first few weeks after transplant surgery. Of the 77 patients who died without undergoing liver transplantation, 50 (65%) were confirmed as due to liver failure or PSC-related cancers. Cholangiocarcinoma accounted for 24% of all deaths (n=25), with an additional two patients having had curative surgery and one patient being end of life at the end of the study period.

Table 4: PSC Cohort Prognosis & Outcomes

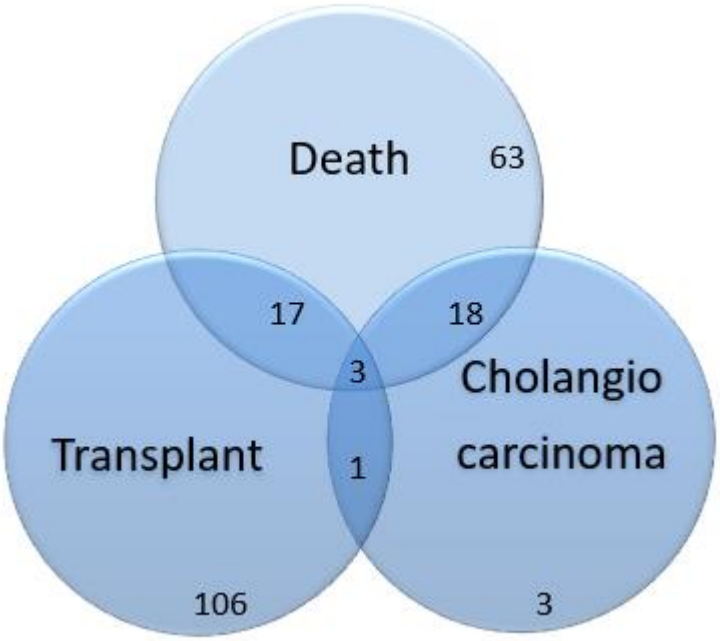
Factor	Whole Cohort (n=418)
Follow-up	
Lost to follow up	11 (2.6%)
Ongoing follow up	310 (74.2%)
Follow-up locally *QEHB follow up*	43 (10.3%) 267 (63.9%)
Mortality	
Total	97 (23.2%)
Pre-transplant*	77 (18.4% of whole cohort)
Unknown	20 (26.0%)
Liver failure	28 (36.4%)
Cancer (18 Cholangiocarcinoma, 1 Hepatocellular carcinoma, 2 Colorectal carcinoma, 1 Neuroendocrine tumour)	22 (28.6%)
Dementia	1 (1.3%)
Sepsis/MOF	6 (7.8%)
Post-transplant**	20 (4.8% of whole cohort)
Unknown	2 (10%)
Graft failure (chronic)	1 (5%)
Cancer (Cholangiocarcinoma 3, oesophageal 2, pancreatic 2)	7 (35%)
Heart failure	1 (5%)
Sepsis with Multiple organ failure	8 (40%)
Intracranial haemorrhage	1 (5%)
Liver Transplantation	
Assessed for transplant	178 (42.6%)
Listed for Transplant	155 (37.1%)
Transplanted	127 (30.4%)
Overall Cancer diagnosis	
Total	32 (7.7%)
Cholangiocarcinoma	25 (6.0%)
Hepatocellular carcinoma	3 (0.7%)
Colorectal carcinoma	2 (0.5%)
Other (oesophageal/pancreatic)	2 (0.5%)

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified.
**Subsequently of those who died pre-transplant. **subsequently of those who died post-transplant.*

7.4.5 Outcomes & Risk Stratification

The initial QEHB clinic appointment was usually a comprehensive disease assessment and was thus a good timepoint at which to investigate how future outcomes might potentially be predicted. The outcomes assessed were future transplant surgery, hepatobiliary cancer (in particular cholangiocarcinoma), diagnosis and mortality. The outcomes and relationship with each other can be seen in Figure 5.

Figure 5. The relationship between the outcomes of death, transplant and hepatobiliary (HPB) cancers in the QEHB PSC cohort.



7.4.5.1 Liver Transplant

Overall, 127 of the cohort underwent liver transplantation during the study period (30.4%) with a median age at transplant of 46 years (range 17-72 years). Those undergoing liver transplant were diagnosed significantly younger than those who did not (p=0.011) however gender, BMI, ethnicity and co-morbid IBD were not associated with this outcome (see table 5). Large duct PSC was more likely to result in liver transplantation than small duct PSC (34% vs 12%, p<0.001) and having cirrhosis at the first QEHB clinic was strongly associated with future transplantation (53% vs 7%, p<0.001). Being prescribed UDCA was associated with higher risks of future transplantation (22% vs 37%, p=0.002) and having an initial ALP of >2xULN at first QEHB clinic doubled the risk of future transplantation from 20% to 40% (p<0.001).

Patients in whom QEHB was not their natural primary treatment centres were more likely to undergo future transplantation (33% vs 16%, p=0.008). Patients diagnosed external to QEHB also had higher risks of future transplant compared to those diagnosed by the QEHB (38% vs 15%, p<0.001). Of 104 patients with known year of diagnosis who went on to require liver transplant surgery, the median time from diagnosis of PSC to transplant surgery was 5.3 years (range 0.03-29.00 years).

Table 5: PSC Cohort Liver Transplant outcomes and patient/disease factors

Factor	No Liver Transplant (n=291)	Liver Transplant (n=127)	p-value
Patient characteristics			
Age at PSC diagnosis (Years, n=349))	41.0 (8-84)	38.5 (11-70)	**0.011**
Male Gender	180 (62.1%)	90 (70.9%)	0.095
Body Mass Index (kg/m^2, n=362)	25.2 (12.7-43.1)	25.0 (15.6-38.6)	0.446
Ethnicity (n=409)			0.423
White *Asian/Asian British* *Black/ African/Caribbean/Black British* *Mixed*	252 (86.6%) 21 (7.1%) 5 (1.7%) 4 (1.4%)	114 (89.8%) 11 (8.7%) 0 (0%) 2 (1.6%)	
Patient local to QEHB	49 (16.9%)	9 (7.1%)	**0.008**
Disease characteristics			
Co-morbid IBD diagnosis (n=413)	193 (66.6%)	83 (65.4%)	0.651
Large duct PSC (n=396)	222 (76.6%)	116 (91.3%)	**<0.001**
Taking UDCA (n=410)	155 (53.4%)	89 (70.1%)	**0.002**
UDCA dose if taking (mg/kg, n=228)	11.7 (2.8-25.1)	13.3 (5.7-32.5)	0.078
Diagnosis made at QEHB (n=372)	113 (39.0%)	17 (13.4%)	**<0.001**
Severity of disease at first QEHB clinic			
Cirrhosis (clinical diagnosis, n=413)	98 (33.8%)	110 (86.6%)	**<0.001**
Portal hypertension (n=413)	95 (32.1%)	108 (85%)	**<0.001**
Relevant blood tests (n=415)			
Bilirubin	39.2 (3-608)	88 (5-508)	**<0.001**
UKELD	48 (45-73)	52 (41-72)	0.242
ALP (median)	579 (28-3752)	757 (114-5051)	0.299
Outcome			
Death	77 (26.5%)	20 (15.7%)	**0.017**

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified. Significance was based at the 0.05 level and highlighted in bold.

7.4.5.2 Cholangiocarcinoma

Cholangiocarcinoma was diagnosed in 25 patients, (16%). It was always not possible to ascertain the timing of cholangiocarcinoma diagnosis (n=3) or a time of PSC diagnosis (n=8). Of the remaining 14 patients, the time from PSC diagnosis to cholangiocarcinoma diagnosis ranged from 9 months to 24 years (median 3 years); six cases of cholangiocarcinoma were diagnosed within the first year after the PSC diagnosis (43%). Of the 22 patients where diagnosis of cholangiocarcinoma was known, median age at cholangiocarcinoma diagnosis was 60 years (range 30-72 years).

The outcomes of those who were diagnosed with cholangiocarcinoma were poor; 21 (84%) died during follow up, all with cholangiocarcinoma being implicated as primary cause of death. All that survived either underwent local surgical resection (n=2) or the cholangiocarcinoma was found incidentally on explant post-transplantation (n=1). In one further case, the patient was end of life when follow up ceased. The time from cholangiocarcinoma diagnosis to death ranged from 1-21 months (median 4 months).

Gender was not associated with future cholangiocarcinoma (p=0.900), neither was ethnicity (p=1.000), living local to QEHB (p=0.550), having PSC diagnosed at QEHB (p=0.126), having co-morbid IBD (p=0.824), being cirrhotic at first appointment at our centre (p=0.216) or taking UDCA (p=0.392, table 6). No cholangiocarcinoma was observed in small duct PSC (p=0.056).

None of the 66 asymptomatic patients developed cholangiocarcinoma, a significantly lower rate than for those who were symptomatic (p=0.037). Being symptomatic in this cohort therefore increased the future cholangiocarcinoma risk from 0% to 7.1% compared to those

without symptoms. Older age at PSC diagnosis was also risk factor (mean: 46.2 years vs 40.1 years, p=0.017) and patients diagnosed with PSC over 35 years of age had a seven-fold increased risk of future cholangiocarcinoma development (1.3% vs 7.1%, p=0.010); this cut-off was used as it provided the largest risk difference between those with future cholangiocarcinoma diagnoses and those without. Similar results were also seen for age at first appointment at the QEHB (mean: 56 years vs 44 years, p=0.010), with patients seen under 40 years of age having a much lower risk (0.5% vs 10%, p<0.001).

Table 6: PSC cohort Cholangiocarcinoma and patient/disease factors

Factor (n=of those known)	No cholangiocarcinoma (n=393)	Cholangiocarcinoma (n=25)	p-value
Patient characteristics			
Age at PSC diagnosis (Years, n=349)	40 (8-84)	46 (25-63)	**0.017**
Male Gender	254 (64.6%)	16 (64.0%)	1.000
Body Mass Index (kg/m^2, n=362)	25.2 (12.7-43.1)	23.9 (18.8-34.4)	0.647
Ethnicity (n=409)			1.000
White	344 (87.5%)	23 (92.0%)	
Asian/Asian British	32 (8.1%)	0 (0%)	
Black/ African/Caribbean/Black British	3 (0.8%)	1 (4.0%)	
Mixed	5 (1.3%)	1 (4.0%)	
Patient local to QEHB	56 (14.2%)	2 (8.0%)	0.554
Disease characteristics			
Co-morbid IBD diagnosis (n=413)	259 (65.9%)	17 (68.0%)	0.824
Taking UDCA (n=410)	233 (59.3%)	12 (48.0%)	0.298
UDCA dose if taking (mg/kg, n=228)	12.3 (2.8-32.5)	12.3 (3.5-24.0)	0.812
Diagnosis made at QEHB (n=372)	127 (32.3%)	3 (12.0%)	**0.043**
Severity of disease at first QEHB clinic			
Cirrhosis (clinical diagnosis, n=413)	193 (49.1%)	16 (64.0%)	0.215
Portal hypertension (n=413)	190 (48.3%)	14 (56%)	0.286
Relevant blood tests (n=415)			
Bilirubin	49 (3-508)	131 (5-608)	**<0.001**
UKELD	49 (45-73)	52 (43-72)	**0.037**
ALP (median)	611 (28-5051)	1001 (169-3752)	0.278
Outcome			
Death	76 (19.3%)	21 (84%)	**<0.001**

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified. Significance was based at the 0.05 level and highlighted in bold.

7.4.5.3 Mortality

Overall, there was a 23.2% risk of death for the QEHB cohort (n=97) with a median age of 61 years (range 20-85 years). Gender was not associated (p=0.140), nor was ethnicity (p=0.869), co-morbid IBD (p=0.082), or UDCA use (p=0.336, see Table 7). Those living local to QEHB had lower risk (12% vs 25 %, p=0.030).

Patients with large duct disease had significantly higher risk of death than those with small duct disease (7% vs 24 %, p=0.003), as did symptomatic patients (8% vs 26%, p=0.011) and those with established cirrhosis at first QEHB clinic (12% vs34 %, p<0.001). Older age at diagnosis of PSC was associated with increased overall mortality (mean: 52 years vs 37 years, p<0.001) as was older age, with patients first seen over the age of 45 having a 37% future mortality compared to 9.2% of younger patients (p=004).

Of those who died and whose date of diagnosis of PSC was known (n=74), the time ranged from 3.4 months to 25.3 years (median 5.4 years) from diagnosis.

Table 7: PSC Cohort Mortality and patient/disease factors

Factor	Alive (n=321)	Dead (n=97)	p-value
Patient characteristics			
Age at PSC diagnosis (Years, n=349))	37.4 (8-84)	52.2 (16-80)	**<0.001**
Male Gender	206 (64.2%)	64 (66.0%)	0.140
Body Mass Index (kg/m^2, n=362)	25.2 (15.6-38.6)	25.0 (12.7-43.1)	0.341
Ethnicity (n=409)			0.869
White	279 (86.9%)	88 (90.7%)	
Asian/Asian British	29 (9.0%)	4 (4.1%)	
Black/ African/Caribbean/Black British	2 (0.6%)	2 (2.1%)	
Mixed	4 (1.2%)	1 (1.0%)	
Patient local to QEHB	51 (15.9%)	7 (7.2%)	**0.030**
Disease characteristics			
Co-morbid IBD diagnosis (n=413)	220 (68.5%)	56 (58.9%)	0.082
Large duct PSC (n=396)	257 (80.1%)	82 (84.5%)	**0.003**
Taking UDCA (n=410)	185 (57.6%)	60 (61.9%)	0.336
UDCA dose if taking (mg/kg, n=228)	12.3 (2.8-32.5)	12.6 (3.5-24.0)	0.915
Diagnosis made at QEHB (n=372)	113 (35.2%)	17 (17.5%)	**0.011**
Severity of disease at first QEHB clinic			
Cirrhosis (clinical diagnosis, n=413)	137 (42.7%)	72 (74.2%)	**<0.001**
Portal hypertension (n=413)	135 (42.1%)	69 (71.1%)	**<0.001**
Relevant blood tests (n=415)			
Bilirubin	45 (3-508)	84 (4-608)	**<0.001**
UKELD	48 (45-70)	52 (42-73)	0.141
ALP (median)	585 (28-5051)	796 (114-3752)	0.509
Pre-death Outcomes			
Liver transplant	107 (33.3%)	20 (20.6%)	**0.017**
Cholangiocarcinoma	4 (1.2%)	21 (21.6%)	**<0.001**

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified. Significance was based at the 0.05 level and highlighted in bold.

7.4.5.4 Risk stratification

The predictive value of common clinically available blood tests available at the first QEHB visit in predicting future important patient outcomes was assessed (Table 8). Markers of poor synthetic liver function were associated with future need for liver transplant, mortality and cancer. Bilirubin, ALP and albumin were the best predictive markers for transplant, cholangiocarcinoma and death respectively (Table 8) and cut offs were created using the Youdon's J statistical method to predict the future risk of adverse outcomes (Table 9).

Table 8: Predicting clinically significant outcomes of the PSC cohort using serum markers available as first QEHB clinic.

	Future Transplant		**Future cholangiocarcinoma**		**Future mortality**	
	AUROC (SE)	***p-Value***	***AUROC (SE)***	***p-Value***	***AUROC (SE)***	***p-Value***
Serum markers of disease activity & severity (n=412)						
ALP	0.629 (0.028)	**<0.001**	**0.722 (0.046)**	**<0.001**	0.661 (0.030)	**<0.001**
Bilirubin	**0.780 (0.024)**	**<0.001**	0.684 (0.066)	**0.003**	0.675 (0.030)	**<0.001**
ALT**	0.570 (0.029)	**0.024**	0.607 (0.058)	0.074	0.517* (0.034)	0.608
Alb	0.705* (0.027)	**<0.001**	0.659* (0.068)	**0.009**	**0.706* (0.028)**	**<0.001**
INR	0.639 (0.030)	**<0.001**	0.524 (0.064)	0.696	0.618 (0.033)	**<0.001**
Platelets	0.632* (0.032)	**<0.001**	0.521 (0.066)	0.736	0.502* (0.035)	0.954
Creatinine	0.538* (0.031)	0.222	0.502 (0.068)	0.975	0.533 (0.037)	0.329
Na	0.536* (0.031)	0.240	0.571* (0.067)	0.246	0.621* (0.034)	**<0.001**
UKELD	0.756 (0.024)	**<0.001**	0.645 (0.068)	**0.017**	0.696 (0.030)	**<0.001**

*Six patients had no blood tests on the system so were excluded from this analysis, leaving 412 to be analysed unless otherwise specified. ALT n=406. *=reversed. Significance was held at the 0.05 level and highlighted in bold.*

Table 9: Risk of future outcomes by the best serum markers at first QEHB clinic visit

Outcome and lifetime risk	*Best serum predictive marker at first QEHB clinic*	*p value*
Liver transplant	Bilirubin	**0.005**
53%	>22umol/L	
12%	<22umol/L	
Cholangiocarcinoma	ALP	**<0.001**
1%	<470 IU/L	
12%	>471 IU/L	
Death	Albumin	**<0.001**
10%	<43g/dl	
35%	>43g/dl	

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified. Significance was based at the 0.05 level and highlighted in bold.

7.4.6 Hospital Episode Statistics Data

7.4.6.1 Results

Of the 418 strong PSC cohort, 65 were found to have no national hospital admissions (16%). Of those that were admitted, the median number was six admissions (range 1-176); further breakdown was not possible. Of the hospital admissions, 44% were at QEHB, 30% of which were emergency admissions and 37% overall were coded as being primarily due to PSC. However, 43% of admissions were not under a primary gastrointestinal speciality. The proportion of elective vs emergency admissions was statistically not different between QEHB and elsewhere (p=0.974, Table 10). Fewer non-attendances were recorded at QEHB compared to external sites (5.5% vs 9.1%, p<0.001).

Table 10: HES data for Inpatient & Outpatient PSC cohort activity

Factor	Whole Cohort (n=418)
Inpatient data	
No admissions	65 (15.6%)
Hospital admissions (n=4546)	6 (1-176)
Location QEHB	1995 (43.9%)
Type of admission	
Emergency admissions (n= 1358)	
QEHB	595 (43.8%)
Elsewhere	763 (56.2%)
Non-emergency admissions (n=3188)	
QEHB	1400 (43.9%)
Elsewhere	1788 (56.1%)
Length of stay (13041 total bed days)	6 (0-383)
PSC coded as reason for admission	1701 (37.4%)
Admission Specialty	
Colorectal Surgery	130 (2.9%)
Liver Surgery	125 (2.7%)
Upper GI Surgery	8 (0.2%)
Gastroenterology	1493 (32.8%)
Liver	830 (18.3%)
Other specialty	1960 (43.1%)
Outpatient data	
Outpatient appointments (n=28552)	50 (0-272)
QEHB	13927 (48.8%)
Elsewhere	14625 (51.2%)
Non-attendances (n=2103)	
QEHB	767 (5.5% QEHB OPAs)
Elsewhere	1336 (9.1% elsewhere OPAs)

Data are reported as median (range) or as N (%) and are based on n=418, unless otherwise specified.

7.4.6.2 Estimating costs of care

The HES data allows a national estimation of costs encountered by the NHS for patients with PSC. This data does not consider any direct patient costs and does not include prescriptions or blood tests.

In terms of inpatient admissions, 65 patients (15.6%) were not coded as having any inpatient hospital stays. The remaining patients encountered a total of 4546 hospital admissions including 13041 hospital bed days. At a conservative estimate of a cost/tariff of £400 per day of inpatient stay (anecdotal cost), this amounts to a £5.2 million cost to the NHS, or £14,777 per patient with at least one admission. Over a third (37.4%) of admissions were for a primary PSC diagnosis, at a cost of £1.95 million.

Outpatient tariffs vary by speciality and if they are new or follow up sessions; this was not differentiated by the HES data for this cohort. To provide a conservative estimate of outpatient costs, the 2019-2020 tariff for a follow up hepatology appointment was £146[130]; the study cohort thus had an approximate outpatient cost to the NHS of £3.98 million, or £9560 per PSC patient. £294,420 of this cost was in missed appointments, 63.5% of which was in local hospitals rather than at QEHB.

Certain imaging and interventional procedures also have individual tariffs. These are shown below (Table 11) along with the frequency seen in the study cohort and associated calculated costs to the NHS.

Table 11: HES data for the QEHB PSC cohort Inpatient & Outpatient activity

Procedure (2019-2020 Tariff)	*Total number of procedures via HES (£)*	*Total number of procedures via QEHB data (£)*
Liver biopsy (£726)	252 (£182,952)	87 (£63,162)
Colonoscopy (£517)	1060 (£548,020)	254 (£269,240)
MRI – (£213)	73 (£15,549)	676 (£143,988)
CT – (£124)	217 (£29,608)	(data not collected)
Ultrasound (£49)	21 (£1029)	1181 (£57,869)
Diagnostic ERCP (£822)	47 (£38,634)	1 (£822)
Therapeutic ERCP (£3006)	85 (£255,510)	38 (£114,228)
EUS – (£612)	65 (£39, 780)	72 (£44,064)
Total cost of above procedures	**£1,282,212**	**£693,373 (incomplete data)**
Cost per patient with PSC	**£3072**	**£1663 (incomplete data)**

Adding the inpatient, outpatient and imaging costs together suggests an overall cost to the NHS of £10.6 million, or £25,519 per patient, during the study period.

7.5 Discussion

This ten-year retrospective cohort study aimed to describe the patient characteristics and management of a hospital-based pre-transplant cohort of patients with PSC; this was based at QEHB.

7.5.1 Study Findings

These results lend weight to the challenges faced by patients and their medical team in managing PSC. This includes ongoing poor long-term outcomes (demonstrated by high rates of transplantation, cancer and death) in the context of no proven disease-modifying therapy.

While UDCA is not recommended for use in the European guidelines given the lack of proven efficacy in PSC[129], the majority of patients were taking the drug at QEHB and these were more likely to have very abnormal liver tests, especially ALP. This indicates an uncertainty amongst clinicians about the evidence behind UDCA and potentially a preference from the clinicians, and/or patients, to try something, even if it is unproven, and especially in more severe disease.

Of those taking UDCA, there was a wide range of dosages observed. Many were not taking the 13-15mg/kg that is recommended for Primary Biliary Cholangitis (a likely target dose in PSC if UDCA was to be recommended). This may reflect patient intolerance to the side effects of UDCA, which are commonly itch, gastrointestinal disturbance and weight gain, or a lack of medical confidence in the drug's efficacy in PSC, meaning the full dose is not being encouraged. This all adds to the challenges of managing PSC and demonstrates the unmet need for new efficacious and tolerable treatments for this disease.

Despite limitations within the HES dataset, these proof of concept results indicate that a significant amount of both inpatient and outpatient PSC activity is still occurring outside the large tertiary centres, in this case QEHB. Patients are often managed by more than one NHS Trust and can require intervention by either site, or at multiple sites simultaneously. These complex patterns of care need to be considered when evaluating changes in patient management at a single site, such as the introduction of telemedicine at QEHB, as this change may impact local demand for services as well as those at the central site.

The results suggest variation in referral practices from outside centres (who may not be confident in managing PSC at different stages or who may have different local guidance on who to refer and when) as well as the wide heterogeneity of PSC presentations and disease severity. Patient preference may also be important as community support groups spread the knowledge of QEHB being a particular centre of excellence for PSC. It seems probable that the very sick patients would be referred to specialist sites earlier than those with a slower progression, however, this was not possible to assess from the dataset.

Half of patients were cirrhotic at their first QEHB clinic, further evidence of the severity of disease being seen at QEHB with the resulting increased morbidity and mortality risks for patients. Liver transplant and mortality was more common in those referred into QEHB rather than the local population; this likely reflects referral bias and the resulting increased severity of disease seen at QEHB as a transplant centre covering a large part of England and Wales, This remains, however, an important observation that maybe clinically relevant when assessing an externally referred patient for the first time.

ALP levels are traditionally used to identify higher risk patients and in assessing the efficacy of new treatment within clinical trials; however, ALP level was not the best predictor of future transplantation or death in this study whereas other serum tests such as bilirubin did predict these outcomes. The best use of these easily accessible variables in clinical practice remains unknown, but may allow for some improved identification of higher risk individuals or direct cancer surveillance strategies. This may be most important at the initial specialist clinic appointment as the results from PSC patient interviews (to be discussed in Chapter 2) suggested patients had often waited a long time for their specialist referral appointment and they had significant anxiety about their prognosis. Overall however, no non-invasive marker had an area under the curve (AUROC) >0.780 in this study, again indicating a need for better prognostic tools in PSC.

This cohort study demonstrates the costs of PSC, both from a patient and a healthcare perspective. The majority of patients were of working age and many worked full time; thus, the progression of their illness over time has economic effects if they become unable to work due to ill health. There is an additional burden on patients and workplaces to enable patients to attend long term hospital follow up. The HES data confirmed nationally that few patients with PSC escape hospital admission, with a wide range of numbers of admissions per patient, again suggesting the heterogeneity and spectrum of PSC as a disease.

While a small number of patients were discharged from QEHB follow up back to their local hepatology service, the majority were not; this indicates a lack of facilities or confidence within local services to manage the patient safety and provides supportive evidence for the ongoing inequality of hepatology care across the country. This may explain the enthusiasm the

interviewees expressed for exploring new techniques of accessing specialist PSC care, such as virtual clinics, that may be used to improve access to these services and reduce any geographical barriers. The issue of virtual clinics will be discussed in more detail in later chapters.

7.5.2 Comparison to existing literature

The findings of this large cohort study are congruent with what is already known about PSC; the disease tends to affect young, slim people of Caucasian ethnicity and many patients also suffer from co-morbid inflammatory bowel disease. Few of the QEHB cohort remained asymptomatic throughout their disease course, with the majority of patients describing multiple symptoms over time; this is reflected within the published PSC Support questionnaire[16] and supported by the findings of qualitative interviews with PSC patients (Chapter 2).

The outcomes of the QEHB cohort were comparable to those reported in the literature; The high morbidity (represented by high rates of liver transplant requirement and cancer) and mortality of PSC is confirmed, thus providing further evidence of the unmet needs of patients with PSC. The QEHB PSC cohort had high rates of cancer, both pre and post-liver transplantation, as is also described in the literature[8]. Receiving a diagnosis of cholangiocarcinoma is a complete contra-indication to liver transplantation in the UK[35] and has am extremely poor prognosis; this was seen as a median survival of 4 months in the QEHB cohort. As such, this is an important condition to diagnosis and risk stratify for, the latter being something not currently possible given the unpredictability of cholangiocarcinoma to affect

people with PSC at any stage in their disease process, rather than just those with advanced liver damage[15].

Of the QEHB cohort, older age at diagnosis was significantly associated with future cholangiocarcinoma although referral bias may again be relevant in the QEHB data as some patients were referred specifically due to concerns over cancer development. Additionally, younger patients may be more able to access transplantation compared to older recipients, and thus not have time to develop malignant complications.

7.5.3 Strengths and limitations

This study was focussed on describing the largest UK cohort of PSC patients over a long follow up period, ten years. QEHB have advanced information technology systems and the electronic case notes are well established, thus the salient data for describing this cohort of patients was almost intact. Given the rarity of PSC overall as a disease, this study included a large proportion of the total UK cohort of PSC patients and is thus a useful addition to the published literature. The addition of the HES data provides a snapshot of the national burden of PSC and allows comparison of the resource usage of this cohort of patients in local hospitals as well as a specialist centre.

However, this does remain a single centre study and thus management techniques may differ from those seen elsewhere. While no direct comparisons can be made with other centres, the proportion of liver transplant activity at QEHB performed for PSC (10% of all elective liver transplants) lies in the midrange of that seen at other transplant centres in the UK (6-17%)[2]

and this may suggest any differences in management observed nationally are not resulting in changes to outcomes. While the study findings may not be entirely generalizable, being derived from retrospective data from a single-centre, the results of this study have identified areas which may benefit from further investigation. QEHB is a large receiving centre for new referrals and even if these findings do only have internal merit, this could still aid in the management of a considerable number of new PSC referrals each year. White overall data completeness was good, a limitation to this study is that it is based on incomplete and retrospective data. Attempts were made to cross-check details directly from the source (i.e. using histology and imaging reports rather than just clinic letter free text), however, assumptions were made which could have been erroneous. For example, there being no mention within the clinic letters of any symptoms might not have meant the patient was asymptomatic.

Additionally, some discrepancies were noted between the HES and QEHB datasets. HES data identified that over half of activity lies outside QEHB so the HES data for PSC-related procedures should be higher than at QEHB. However, ultrasound and MRI activity identified in the HES dataset are remarkably low compared to the QEHB data. HES data only included activity from England which is likely of relevance as QEHB covers a large part of Wales for tertiary and transplant specialist liver services. A further confounder to the HES data is that hepatology services can be coded under different specialities in differing Trusts, for example some Trusts have their liver services under a surgical umbrella and some under medical gastroenterology.

7.5.4 Implications for future practice and research

This cohort study has confirmed the unmet need for research for patients with PSC. Given the ongoing poor outcomes of PSC patients, research into new disease-modifying treatments to improve prognosis are vital. Additionally, further work is needed to risk stratify a patient's individual risk of these poor outcomes. By developing such improved risk stratification techniques, not only could patients be better prioritised and surveyed for the onset of complications, but also their mental anguish may be reduced by knowing more about how their personal risks compare to the PSC population as a whole. One method of providing this might be the use of quantitative MRI techniques, as discussed previously within the Introduction chapter and discussed further in Chapter 5.

This study confirms that the burden of PSC to both patients and healthcare providers remains considerable and changes to the management of patients should be considered now, while scientists research new disease-modifying therapies which are likely to take decades to reach patients. Calculating the costs of these interventions will be complex and will need to include the impact on multiple NHS Trusts nationally, rather than just the impact in one centre. In order to more fully understand the impact of PSC and its related healthcare on patients, it is important to involve the patients themselves. Chapter 3 therefore describes a series of qualitative interviews with PSC patients exploring their experiences of their disease and of their healthcare.

CHAPTER 3:

Understanding the experiences of people diagnosed with PSC using semi-structured qualitative interviews

8 CHAPTER 3: UNDERSTANDING THE EXPERIENCES OF PEOPLE DIAGNOSED WITH PSC USING SEMI-STRUCTURED QUALITATIVE INTERVIEWS

8.1 Introduction

Chapter 1 has confirmed the high morbidity and mortality on PSC. In addition, the unpredictable prognosis and lack of disease-modifying therapy of PSC produces an almost unique set of circumstances which those affected must negotiate and learn to live with.

8.1.1 Rationale

This chapter incorporates a series of semi-structured qualitative interviews with patients diagnosed with PSC, exploring their experience of their disease, their healthcare management, and how these experiences might be improved. Comparison has been made to existing models of chronic illness, allowing conclusions to be made regarding the generalisability of these interview findings to other chronic illnesses, other healthcare settings and to be of interest to general physicians as well as PSC specialists. This comparison has identified areas where PSC patients' experience differs from accepted models of care and thus where specific intervention may be needed to help this particular cohort of patients.

The interviews also provided a forum for discussion about the incoming QEHB virtual clinic (Chapter 1) and what opinions might be to this potential change in management. The results described within this chapter pre-date the current Covid-19 pandemic and are thus untainted by recent world events; rather than now being less relevant, these results reflect true background patient opinion, which is likely to resurface over time. This is important to acknowledge when planning what outpatient clinic management will look like going forward

and how much telemedicine to retain in the longer term. The impact of Covid-19 on this thesis' results is discussed in more detail in Chapter 6.

8.1.2 Existing literature

Attempts have been made previously to assess the quality of life in PSC using existing quantitative generic disease-scoring questionnaires[131,132,133], with one 2016 study using additional free-text responses for more detailed analysis[134]. These studies found that patients with PSC have lower health-related quality of life than healthy controls as well as experiencing a significant psychological burden including social isolation and existential anxieties on top of a heavy symptom burden. However, these studies primarily used quantitative questionnaire-based scoring systems rather than formal qualitative research methods. Patients with PSC remain an understudied cohort, with likely interesting experiences of healthcare given their rare, untreatable and unpredictable disease.

8.1.3 Qualitative Research

To more fully understand the patient perspective of PSC and its associated healthcare, qualitative research methods can be used to allow deeper investigation into patient perspectives, for example, to ascertain what the patient experience of PSC truly is and what questions need answering to be useful to patients in the real world. Qualitative research uses open-ended data gathered from personal interactions, such as in interviews, which is subsequently collated to present the richness of ideas or opinions, rather than the amount of each type[135]. The results can be used to complement more traditional quantitative methods,

such as those described in the Cohort study (Chapter 2), to better understand patient experiences.

Qualitative research methods provide the best means of investigating the broadness of patient experience and semi-structured interviews of a purposively selected group of PSC patients would provide an evidence base to said experience and other aspects of PSC patient healthcare. This study will identify areas where PSC patient care could be improved which may also be beneficial to other patient cohorts and of interest to non-liver specialist clinicians.

8.2 Aims

This study aimed to explore the experiences of PSC patients of their disease and of their PSC-related healthcare in the UK. Specific objectives were to explore: -

1) How the diagnosis was reached and its impact on the individual
2) What the patient personal experience is of living with PSC
3) What the patient experience is like of their PSC-related healthcare needs and how this might differ from established models of chronic disease
4) What opinions are of potential changes to their medical care, including discussion of telemedicine.

8.3 Methods

8.3.1 Study design

The study is a series of qualitative interviews[136]. These were semi-structured to allow discussion of a number of pre-determined topics within all interviews, such as regarding telemedicine, thus allowing all subjects the opportunity to comment upon these. These topics are documented within the Topic Guide" (Appendix C). Open questioning was used throughout to promote deeper discussions on topics the interviewee felt most relevant to them; this allowed the introduction of new topics of relevance to the patients.

The sole interviewer (KA) was a female doctor of White British ethnicity with experience working in the PSC clinic at QEHB and who had undergone training in qualitative research. Interviews were face-to-face where possible, however, telephone interviews were permitted to ensure to include a broad spectrum of participants from across the UK.

8.3.2 Study population

The study population was adults with PSC who were receiving healthcare input for their PSC in the UK.

The inclusion criteria for the study were:

1) Patients over the age of 18 who were able and willing to give informed consent
2) Who self-reported they had a formal diagnosis of PSC
3) Who were currently under the care of a UK doctor for their PSC

Exclusion criteria were:

1) Participants with a previous liver transplant
2) Non-English speakers requiring an interpreter for the interview to be completed.

Pre-transplant patients with PSC were chosen for this investigation, both to match the QEHB PSC clinic cohort (Chapter 2) and to allow for more detailed exploration of early PSC, which remains understudied in comparison to post-transplant literature.

8.3.3 Sampling & data saturation

Unlike quantitative research where the sample size is maximised to reflect the whole target population, the aim of qualitative research is not to exhaust the data but instead to gather the breadth or range of experiences or opinions; this is known as "conceptual saturation"[137]. Accepted qualitative methodology suggests this saturation point is likely to be reached within 15-20 interviews[138], provided the sample is selected to give maximum variability, aiming to collect the breadth of potential experiences. This is known as "purposive sampling" and usually includes using subject demographics and disease status[138]. For this study, therefore a sample size of 15-20 patients was aimed for.

8.3.4 Recruitment

The study was advertised through PSC Support's Facebook page, website and newsletter in February 2018 (Appendix D). Interested parties were asked to contact the researcher (KA), whereby further information about the study was sent including the Participant Information Sheet (PIS) and the study consent form (Appendix E).

The researcher than conducted a telephone call with the potential participant for further discussion. It was explained that a purposive sampling technique[137] would be employed to gather as broad an experience of PSC as possible and thus, not every respondent would undergo the full interview process. To inform this sampling method, a small dataset was created for all respondents including geographic, demographic and disease severity data (Table 12). Once ten potential participants had been identified, the researcher commenced selection of interviewees, after reflection with experts within the study supervisory team.

Patients were selected to include a spread of geographical regions, age, gender, different managing hospitals and the spectrum of PSC severity.

In total, 26 potential participants volunteered for the study; 25 answered the screening questions and all said they were happy to proceed (Table 12). Limited demographic information is given due this being a rare disease with the potential risk of the participants being identifiable if more detail is published. Thus, patient age was categorised into decades and individual hospitals have been given a numerical code known only to the investigator.

Table 12. Pre-screening table of interested candidates for the interview study

Screening number	*Study Number*	*Gender*	*Age (years)*	*Time since diagnosis (years)*	*Location of PSC treatment*	*Assessment of disease severity*	*Symptoms Present*	*IBD present*
1	011	Female	20-30	5	1	Cirrhosis	Yes	Yes
2	010	Male	50-60	2	1	Transplant assessment	Yes	Yes
3*	021	Female	50-60	2	6	Early disease	Yes	No
4	n/a	Female	50-60	3	1	Early disease	No	Yes
5	027	Male	70-80	15	1	Recurrent Cholangitis	Yes	Yes
6	013	Male	70-80	3	1	Recurrent Cholangitis	Yes	No
7	026	Male	50-60	4	11	Recurrent Cholangitis	Yes	Yes
8	020	Male	40-50	6	5	Early disease	No	Yes
9	014	Female	60-70	4	1	Early disease	Yes	No
10	015	Female	50-60	3	1	Early disease	Yes	No
11	n/a	Female	50-60	15	1	Transplanted	Yes	Yes
12	012	Male	30-40	5	1	Transplant assessment	Yes	Yes
13	n/a	Male	40-50	13	1	Transplanted	Yes	Yes
14	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
15	017	Female	60-70	14	3	Early disease	No	No
16	n/a	Female	30-40	5	1	Transplant assessment	Yes	No
17*	023	Male	50-60	25	8	Listed for transplant	Yes	No
18	n/a	Male	30-40	10	1	Transplanted	Yes	Yes
19	025	Male	60-70	2	10	Early disease	Yes	Yes
20*	022	Male	30-40	5	7	Early disease	No	Yes
21	n/a	Female	50-60	14	11	Transplanted	Yes	Yes
22	019	Female	50-60	9	4	Early disease	Yes	Yes
23	016	Male	30-40	12	2	Transplant assessment	Yes	Yes
24	018	Female	50-60	16	3	Early disease	Yes	No
25*	024	Female	30-40	6	9	Early disease	Yes	Yes

Grey indicates those not subsequently included within the interview study; Screening number 14 had no experience of UK healthcare, four were post-liver transplant (11, 13, 18, 21) and thus excluded, and two (4, 16) were asked to remain as reserves, however were subsequently not interviewed required as data saturation[137] had been reached. *phone interview

8.3.5 Data Collection

8.3.5.1 Interview technique

Interviews occurred between 15/12/2017 and 21/5/2018; each interview was anticipated to take around 60-90 minutes. Interviews were completed within the participants' home or place of work, according to their preference. Phone interviews were conducted when the travel distance was prohibitive; four interviews were conducted via phone (study numbers 021-024 in Table 12). All work undertaken adhered to guidelines set out in the University of Birmingham's Code of practice for the safety of social researchers[139].

Throughout the interviews, open questioning was used; subjects were encouraged to tell their "stories", to explore their experiences of being diagnosed, of living with their PSC, and of their medical management. The Topic Guide was used to ensure a minimum dataset for each interview, however, the interviewer allowed the participant to 'shape' the interview themselves and to introduce topics they felt to be most relevant. This allowed new topics to emerge. The semi-structured approach with concurrent analysis also allowed the interviewer to explore previously identified themes and specific hypotheses in subsequent interviews.

8.3.5.2 Interview recording

Each interview was recorded and transcribed verbatim prior to analysis; the transcription was done via an approved professional transcription service with a confidentiality agreement in place. Each tape was anonymised prior to transcription using an alphanumeric code known only to the researcher.

8.3.5.3 Interview analysis

Thematic analysis was used throughout the data collection period; this is a widely accepted method within qualitative research of "identifying, analysing and reporting patterns within data" and of interpreting these[140]. This method of analysis involves reading the data, underlining initial ideas, known as codes, and then re-reading the data to refine these ideas into common ideas, known as themes[137,140].

Data collection was simultaneous with this analysis, known as the constant-comparative method[141]. This allows the analysis to continuously evolve as the dataset expands; as more interviews are conducted and new themes are detected, these themes can be deliberately explored in subsequent interviews and previously completed interviews can be re-analysed for the existence of the newly identified themes. The data continues to be refined until no new themes are identified; this is when the saturation point has been reached and data collection can cease[137].

Using accepted thematic analysis theory in this study, the first three transcripts were analysed for an overview of the data and parts of the transcripts of relevance to the research questions were highlighted, known as “open coding”. These interviews were then read through again in more detail, with recurring or otherwise seemingly important ideas across the interviews then recorded in a separate table; known as “temporary constructs”[137]. These initial transcripts were reviewed with the research supervisory team, along with the Investigator’s preliminary analysis of emerging themes; feedback was given to the researcher regarding interview technique and analysis before further interviewing commenced. Using the constant comparative method[141], the interviewer was able to constantly re-analyse the new and existing data to identify newly emerging “themes” and “subthemes” throughout the interviewing stage. [137]

An example transcript analysis can be seen as Appendix F. The study supervisory team reviewed the transcripts and initial analysis independently to validate the Investigator’s analysis and to confirm that saturation had indeed been achieved.

8.3.5.4 Data Saturation

After 15 interviews, few new themes were observed to be emerging. However, on investigation of the subject demographics (Table 12), a high proportion of the interviewees were based in Central England, despite the previously employed purposive sampling intention. Thus, a further three interviews were planned with particular efforts to recruit patients from further afield, to reduce geographical bias and to ensure that data saturation[137] had truly been reached. At 18 interviews it was confirmed that data saturation had been achieved after

reflection with the supervisory team and that the sample was as broad as possible from the list of interested parties; data collection therefore ceased.

8.3.6 Ethical Considerations & Funding

Ethical approval was via the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (ERN_16-0130). As participants were being recruited through community channels and being interviewed by a researcher from the University of Birmingham, NHS ethical approval was not required. Funding for participant travel expenses (where applicable) and the interview transcripts was achieved via the QEHB patient charity.

Patient confidentiality was maintained at all times. The full identity of the participant was known to the interviewer only. Participants were identified only by their unique study number on all documentation. All documents and transcripts were kept anonymously in a password protected Excel file, on a secure university sever, with the code known only to the researcher. All physical data was kept onsite in a locked filing cabinet behind swipe card access doors. All data will be stored for up to 10 years and will then be destroyed, as per the University of Birmingham's Code of Conduct for Research[142].

Informed written consent was gained from all interviewees. For interviewees seen in person, written consent was gained after all questions had been answered and before starting the interview. For telephone interviews, written consent was gained via post or email in advance of the interview, with verbal re-confirmation of consent completed immediately before the interview commenced. It was explained to participants that recruitment was entirely

voluntary and that complete withdrawal could be made up to two weeks after the interview date.

8.3.7 Patient & Public Involvement

The study proposal was discussed with the Chair of PSC Support; they agreed that this investigation would be useful and of interest to patients. The documents for the study were similarly reviewed and agreement gained to the study design and wording. The interview Topic Guide was created from these discussions to ensure a relevant minimal dataset was achieved in every interview.

8.3.8 Reduction of bias

A disadvantage of qualitative research is that the results can be interpreted in different ways. It is acknowledged that the personal biases, experiences and beliefs of the interviewer can affect the interviewees answers, as can the environment or timing on the day[143]. This may be especially true if the researcher has personal experiences similar to those they are studying or if they otherwise have a vested interest in the results, such as a clinician interviewing patients similar to those they see in their clinical practice.

To reduce this, open questions and the Topic Guide were used to reduce the impact of the interviewer on the interview. The interviewer aimed to only listen and to prompt when needed, rather than actively participate verbally during the interview, and to reflect the participants words, rather than paraphrase. Closed questioning was used only to clarify a

detail if this was unclear to the interviewer or to gain specific information as per the Topic Guide. Analysis was independently verified by the research supervisory team.

Recruitment was via community channels to reduce biases that could have been introduced if the study was performed solely through the QEHB PSC clinic and to allow participants from all over the UK to partake. The interviewer introduced themselves as a researcher from the University of Birmingham, rather than as a clinician. This aimed to reduce bias and aid impartiality of the interview process. That the interviewer was also doctor working with the liver team at QEHB was not actively hidden from interviewees and was discussed if relevant or if asked directly by interviewees.

8.4 Study Results

8.4.1 Subject demographics

In total, 18 interviews were completed. 14 were conducted in person; four were via telephone. Ten interviewees were male and the ages represented were 20-80 years of age; the most common age bracket interviewed was 50-60 years. Interviewees were between 2 and 16 years after their PSC diagnosis; 11 described co-morbid IBD. Three of the participants stated their PSC was currently asymptomatic, the remainder reported regular symptoms. All interviewees were white British or European; no interest was received from individuals of other ethnic groups.

The interviewer made a brief assessment of the severity of the participants' PSC using information gleaned from the interview. For the purpose of this study, the absence of cirrhosis, hospital admissions for PSC and no previous liver transplant assessment was considered early disease; ten participants were in this category. The remainder had more advanced disease; one was cirrhotic, three were experiencing recurrent bacterial cholangitis requiring hospital admissions, three were undergoing liver transplantation assessment, and one was active on the transplant waiting list.

Seven participants received their medical care from the same trust (QEHB) with the remaining managed elsewhere across the UK. Twelve English counties were represented by the interview cohort plus interviewees from Scotland and Wales; no interest was received from participants in Northern Ireland.

Three participants in the study were on the PSC Support committee.

8.4.2 Analysis

As previously described in the methods section, a thematic analysis was then completed using the transcribed interview data. A number of themes and sub-themes were identified within the data. A summary of the themes identified within the interview transcripts is seen as Table 13, along with transcript numbers identifying the frequency of which themes were seen in which interview transcripts.

Table 13. Summary of themes identified from PSC patient interviews

Theme	*Subtheme*	*Interview Numbers*
Before PSC	Background health	11, 12, 15, 16, 17, 21
	IBD diagnosis	10, 11, 12, 16, 18, 19, 21, 22, 25, 26, 27
PSC Symptoms	Pain	11, 12, 13, 14, 18, 21, 23, 24, 26, 27
	Itch	12, 13, 16, 18, 19, 20, 21, 24, 26, 27
	Fatigue	10-16, 18, 19, 20, 21, 23, 24, 25, 26, 27
	Cholangitis	10, 11, 12,13, 14, 16, 18, 21, 23, 24, 25, 26
	Weight loss	10, 11, 12, 14, 16, 20, 22, 23, 27
	"Brain Fog"	12, 13, 14, 16, 19, 20, 21, 23, 24, 25, 26, 27
Diagnostic Process	Complex/long process	10, 11, 12, 13, 14, 15, 20, 21, 23, 24, 25, 27
	Multiple hospitals	10, 12, 14, 18, 22, 23, 24, 25, 26, 27
	Incorrect initial diagnosis	10, 11, 13, 14, 15, 21, 23, 25, 27
	Diagnosis event itself	10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 25, 26
	Effect on patient	11, 12, 13, 15, 16, 19, 20, 21, 23, 24, 25, 26, 27
PSC medical management	Treatment	All
	Hospital admissions	10, 11, 12, 13, 16, 23, 26
	Research	10, 12, 15, 16, 17, 18, 19, 20, 21, 24, 26, 27
	Monitoring	10, 15, 16, 17, 18, 22, 23, 24, 25, 26, 27
Outcomes	Liver Transplant	All
	Cancer	10, 13, 17, 18, 19, 21, 23, 25, 27
	Death	10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26
Patient experience of healthcare	System failings	10, 11, 14, 16, 18, 20, 21, 23, 24, 25, 26
	Access	10, 11, 12, 14, 16, 17, 20, 23, 24, 25, 26, 27
	Importance of the specialist	10, 13, 14, 15, 16, 17, 18, 21, 24, 26, 27
	Doctor/Patient relationship	10,11, 12, 13, 14, 15, 16, 17, 22, 24, 25, 26, 27
Personal impact of disease	Disrupted narrative	All
	Stigma/Isolation	10, 12, 13, 14, 15, 17, 18, 20, 22, 24, 25, 26
	Family/peers	10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27
	Lucky	14, 15, 17, 18, 19, 20, 23, 24, 26, 27
	Low mood	11, 12, 16, 17, 19, 21, 23, 24, 26, 27
Importance of information	Patients seeking knowledge	All
	Peer support/self-advocating	10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27
	Who knows more? Dr/patient?	10, 11, 12, 14, 15, 16, 18, 21, 22, 23, 25, 26, 27
	Exchange between providers	12, 13, 14, 16, 17, 18, 24, 25, 26, 27
Uncertainty	Prognosis	All
	Day-to-day	10, 13, 14, 19, 20, 21, 23, 24, 26, 27
	Treatment	13, 17, 18, 19, 22

Once the thematic analysis was completed and reflected upon by the Investigator, it had become clear that participants themselves saw their experiences as a difficult journey. The concept of the patient trajectory is not new and is an accepted approach to qualitative analysis[144]. All interviews contained information on five main phases of the patient journey; the pre-diagnosis phase, the moment of diagnosis, the immediate fall out from being diagnosed, the longer-term experience of living with and receiving healthcare input for their PSC and finally, their future prognosis. Direct quotes from the interview transcripts are used to demonstrate the themes described, along with interview number (as per Table 12) to identify each participant.

Additionally, all interviewees described living with and coping with PSC as a chronic illness, of which there is much already in the published literature. Thus, a further analysis was completed comparing and contrasting the themes identified above to accepted models of chronic illness[146]. This aimed to identify areas where PSC patient experience mirrors other diseases, and thus where lessons can be learned from other more widely studied chronic illnesses. Differences were also identified, to better inform those looking to change current models of patient care specifically for the PSC cohort.

8.4.2.1 The Patient Journey

The initial analysis describes the patient journey; all interview participants described their experience of being diagnosed with PSC, the lead up to this event, and the consequences for them thereafter. This can be split into five main sections as described below and depicted in Figure 6: -

Stage 1 = Climbing the mountain (the pre-diagnosis stage)

Stage 2 = Reaching the Summit (the diagnosis event itself)

Stage 3 = Falling off the cliff (the immediate aftermath of the diagnosis event)

Stage 4 = Soldiering on (living with PSC long term)

Stage 5 = The End of The Road (Future Outcome)

These five stages will now be discussed along with exemplar quotes from the interviews:

Figure 6. Diagrammatic representation of the patient journey identified in the patient interviews

8.4.2.2 Stage 1: Climbing the Mountain (The Pre-diagnosis Stage)

This phase describes the lead up to the PSC diagnosis, what precipitated the original investigations, how long this process took and participant opinions of this. Interviewee experiences of PSC symptoms is also included within this section with the acknowledgement that symptoms were ongoing and evolving for many participants, not only pre-diagnosis.

Participants' experiences will be described in timeline form, as they themselves experienced it. Participants described a variety of paths on the road to achieving their diagnosis of PSC and the indication for the investigations that led to the diagnosis varied (Table 14).

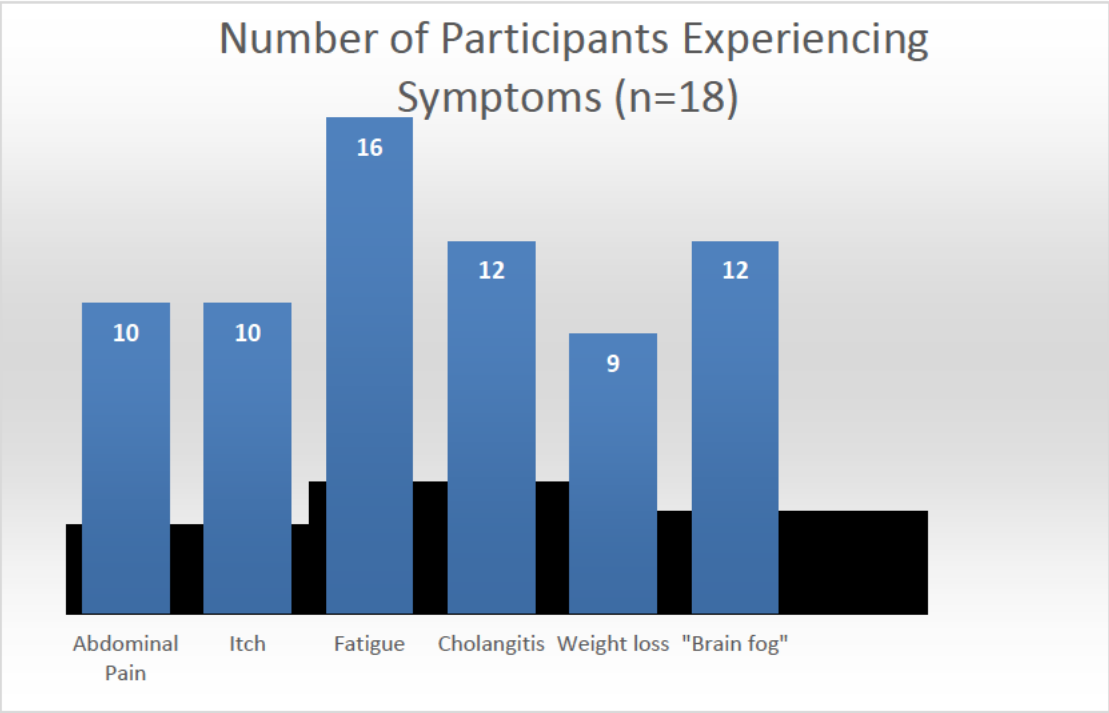
Table 14. Indications for investigations for PSC Interview participants

Indication	***Number of participants (%)***
Symptoms	14 (78%)
Pre-existing IBD	6 (33%)
Asymptomatic/Incidental	4 (22%)
Pre-existing IBD	3 (17%)

8.4.2.2.1 Symptoms

In total, all bar two participants described symptoms attributable by them to PSC, at some point over their disease course. It was common for initially mild symptoms to slowly progress throughout the participant's journey to date. The frequency of symptoms described in the interviews can be seen in Figure 7; these absolute frequencies does not necessarily reflect the importance placed on each symptom by the participants or how their quality of life may have been affected.

Figure 7. A chart demonstrating the frequency of symptoms described within the interviews



These symptoms will now be described in frequency order:

8.4.2.2.1.1 Fatigue

Fatigue was the most commonly described symptom attributed to PSC by the interview participants, present in all 16 symptomatic patients. Many participants initially dismissed this as being due to their lifestyle. However, as time went on, participants began to attribute this symptom to the PSC instead as either the fatigue worsened, other symptoms were added or once the diagnosis of PSC was made:

"I felt more tired than I ever had…I was used to just ignoring it" (019)

"It felt different to normal tiredness…a fogginess…I didn't think much to it. I thought oh, maybe I'm not getting a good night's sleep" (020)

Participants placed importance on how different their fatigue was from a normal tiredness feeling and how simply sleeping more didn't help. They described an all-encompassing weakness of their entire body and mind that left them unable to carry out their normal activities:

"It's not just like feeling tired…it's like a blanket coming over you and I just can't keep my eyes open, can't do anything" (026)

"Tired all the time…someone had pulled the plug and energy was just going down the plughole" (023)

The effect of this fatigue on everyday life for participants was variable. Four participants were able to continue working full time however the majority found themselves reducing their working hours or being unable to continue working in any capacity. Others described how even the simplest of daily tasks became unmanageable:

"I'd have to lie on the floor…I just had no energy, I'd go into work and I'd have to go and sit in the toilet for some of my shift" (017)

""I'm not trusted on my own with my granddaughter anymore because I can fall asleep at the slightest…really easily" (010)

"Felt like I was walking through treacle" (025)

8.4.2.2.1.2 "Brain fog"

This was a term frequently used by participants to describe being generally unwell or that their cognition itself was impaired. This was observed in twelve patients, all of whom also described physical fatigue; it was common for participants to associate exacerbations in one with worsening of the other.

Ten participants described generally feeling *"rotten" (027)* or *"like death" (026),* many of whom felt in hindsight that this started many years before other symptoms emerged or before their diagnosis. Other descriptions of this sensation of feeling unwell included:

"I felt weird. I felt under the weather…I just couldn't get better" (023).

"I feel like I'm sort of a bit out of body…it's like a brain fog" 016)

Eight participants described more specifically cognitive problems they had encountered, such as poor memory, concentration or changes in their personality:

"I do get this horrible brain fog and it's very negative…you're drunk but you haven't had any alcohol…I'm not a half full person when I'm in that state. I'm really half empty" (023)

"It's sort of just slowly feels like knowledge is ebbing out of, out of my brain" (024)

8.4.2.2.1.3 Cholangitis

Twelve participants described experiencing recurrent bacterial cholangitis, many of whom also described the unpredictable nature of these *"sudden attacks" (026*). Rigors and sweating were common initial symptoms, often associated with worsening of other symptoms such as itching, abdominal pain and fatigue. Jaundice was described by four participants, all of whom would become jaundiced during cholangitis episodes; therefore, this symptom is not discussed separately. Participant descriptions of cholangitis are below:

"I had the full, is it the rigors, you know where you have the shiver and shakes. I was seriously ill" (025)

"The symptoms I usually get when I know that something's going to happen…jelly legs, wooliness in the head…extreme tiredness…lack of appetite…twinges in the side or back, pain in the top of my right shoulder…nausea" (013)

Most cholangitis episodes described resulting in a hospital admission; six participants described multiple hospital stays and of being seriously unwell:

"I've had erm... five or six bouts of cholangitis. It's roughly about every eight weeks I'm ending up in hospital" (010)

"They pumped me full of antibiotics and pain relief and God knows what else to try and get the infection under control…it was just sort of like a vicious circle, it was constantly in and out with infections" (011)

Four participants described how in retrospect they were likely having cholangitis episodes long before their diagnosis. Most described how they came to accept these as normal:

"I used to call them funny do's when I had all these symptoms like, basically feeling terrible…aching everywhere, rigors…they were just something that I lived with" (026)

"I was admitted to hospital… they couldn't find what the cause was…all they put on the letter that it was Sepsis of unknown origin…I know now, looking back, with those symptoms, it must have been Cholangitis" (026)

8.4.2.2.1.4 Abdominal pain

Chronic abdominal pain was frequently described; these ten participants did also have at least one diagnosed cholangitis event in their past. The pain described by the participants could be severe:

"I could barely walk, this pain was so bad" (026)

"I just get like pain in my, my liver…like a knitting needle" (018)

All patients who described abdominal pain stated that it was intermittent, often presenting without warning or precipitant. This unpredictability was distressing; one participant stated:

"It's just that uncertainty of when is the pain going to come. Because it's not a matter of if, because I know it will. It's just when" (014)

8.4.2.2.1.5 Itch

The presence of itching was described by ten participants, three of whom did not have a history of cholangitis to date. While not the most frequently mentioned symptom amongst interviewees, it was particularly distressing:

"Itching absolutely drove me insane…nothing really got on top of it…its unbearable" (026)

"Used to itch so much it would bleed" (027)

Two male participants described the visual impact from either scratching themselves in public or the cosmetic scarring that this had left behind:

"I've ripped my skin to bits , I've got scars all over my body…I go to work and I've got scabs all over my face (016)

"itching is also bad…you scratch and…people look at you in a suspicious way" (012)

8.4.2.2.1.6 Weight loss

Weight loss was described by half of interviewees; this was universally seen by them as a worrying sign and often prompted the initial consultation leading to the diagnosis or otherwise signified a significant deterioration in their health. For five participants, this weight loss was extreme:

"I was losing weight. And that really prompted me to go and see my GP" (020)

"I'd stopped going on the scales after losing 30 pounds" (027)

"I'd lost loads of weight, I think I weighed 38 kilos" (011)

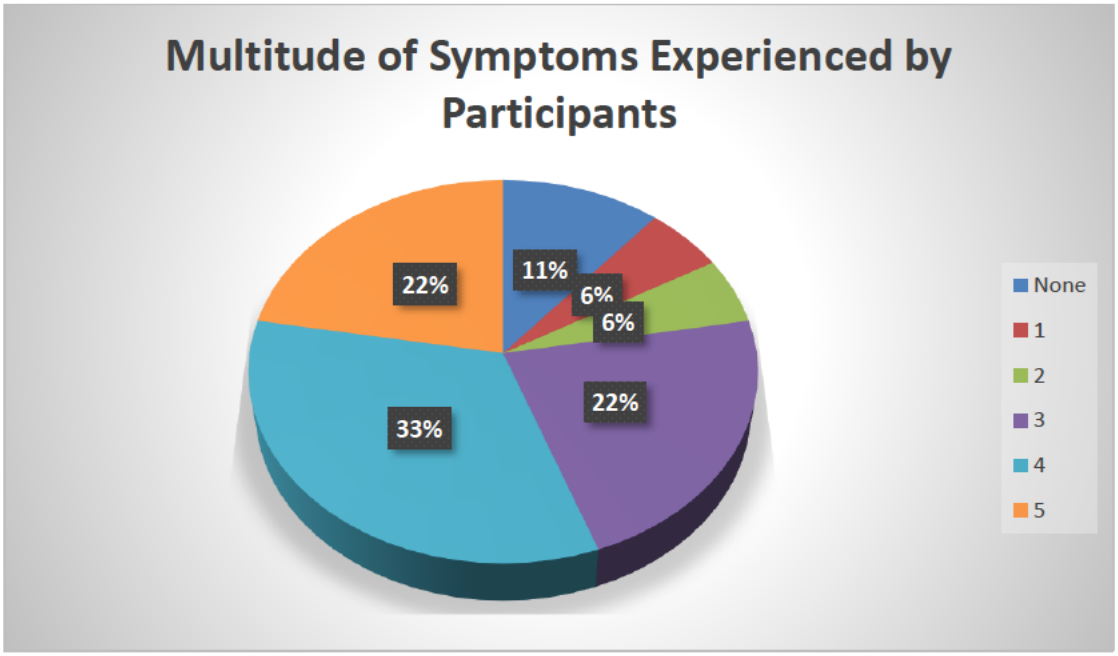
Such weight loss also seemed to alarm doctors, precipitating more urgent investigations. Often a battery of tests was completed before cancer was confidently ruled out by the doctor, potentially ignoring scan results which may have led to PSC earlier. Some participants described the reassurance they were given once cancer was ruled out but that they were subsequently discharged, without a diagnosis being made.

"I'd gone jaundiced…and I think they – well, they have said since that they did think there was some sort of cancer in there…He said, 'They've done every test under the sun….no cancer anywhere' (023).

8.4.2.2.1.7 Multiple symptoms

All but two participants were asymptomatic throughout their journey with PSC to date, however, over three quarters (14 participants, 77%) described experiencing three or more symptoms (Figure 8).

Figure 8. A chart demonstrating the multitude of symptoms described within the interviews



13 participants also had a diagnosis of IBD, with its own symptomology, treatment and complications. Participants described how they found it difficult to separate their symptoms and how they initially blamed these on their IBD rather than potentially signifying a new problem, PSC.

"I guess because I had ulcerative colitis you get used to feeling unwell and I kind of didn't make a big deal of it" (19)

"I was diagnosed with Chron's Disease which has been…a nightmare" (026)

In addition to the above, three participants described the feeling of being unwell from a young age. Two recalled being investigated as a child and discharged without a diagnosis, then being subsequently being diagnosed with PSC as an adult; these participants felt strongly that their childhood symptoms were related:

"When I was a kid I always used to complain of stomach aches and I always used to be off school with stomach aches but nothing was ever found" (011).

"I've never been a healthy person…even as a child I had a lot of trouble with my health, I was very sickly…I started having problems with my stomach…I know that that was the beginning" (012).

8.4.2.2.2 Initiating the Diagnostic Process

In total, six participants described a relatively straightforward process to diagnosis; all had a background diagnosis of IBD and were under a hospital-based gastroenterologist when the first signs of PSC arose (whether via blood test abnormalities or the development of symptoms). These patients generally described a shorter, more straight-forward process, with fewer investigations required before the diagnosis was made. Three of these patients developed symptoms of PSC developing after they were already diagnosed with IBD. The remaining three patients were asymptomatic at this time and it was new derangement in routinely checked liver tests that precipitated investigations for the diagnosis:

"Because I've got Chron's I was under Gastroenterology and followed up quite regularly…because my LFTs were abnormal, they did an MRI scan, and this showed that I'd got PSC"(026).

However, for the majority of the cohort, this diagnostic process was not straightforward. All 12 patients described how the search for a diagnosis became a lengthy and complex process involving multiple doctors, hospitals and investigations. The time from the start of symptoms

or investigation to the diagnosis ranged from three to nine years in these patients, which was felt unacceptable my most:

"It took nine years for me to be diagnosed, which is totally unacceptable" (027)

"I've lost count of how many investigations I had over the course of five years…this cycle went on for five years and I never got anywhere at all" (021)

When the diagnostic process was instigated by participants, this was usually when their symptoms reached a certain individual threshold, or was triggered by symptoms affecting specific daily tasks, such as performance at work or school. Weight loss was universally seen as a worrying sign; male participants appeared especially disturbed by the loss of weight and inability to put on muscle:

"I wasn't as strong as I used to be…a few years earlier, I could easily put on muscle whereas later I couldn't put on any muscle" (012).

"in school…my behaviour changed a lot and I was like more erratic…I'd get into college and I'd fall asleep in lessons" (011).

Most participants also described an overall slow deterioration in their health over time and not realising how ill they had become until it was pointed out to them by an external source. This was commonly a family member, who in turn helped precipitate the first consultation with a healthcare professional.

"I was beginning to look more and more unwell, had lost a lot of weight, was struggling to eat, so she (neighbour) badgered and badgered this consultant basically until he agreed to see me".

"I felt quite bad and my dear wife persuaded me, I think, to go and see the doctor".

8.4.2.2.3 The Start of Investigations

When the symptomatic participants sought medical attention, this was initially via their GP in twelve cases, and via their gastroenterologist (who they already saw for their IBD) in the rest. Initial GP consultations usually resulted in general advice and reassurance. Blood tests were taken, although this was often only after a number of consultations:

"It took them, I think it was from about August to November to do a blood test and then it showed that my liver functions were deranged" (011)

The fluctuating nature of the symptoms meant that often by the time patients saw their GPs or had their blood test checked, all had returned to normal. In this scenario it was common for further reassurance to be given as to the absence of organic disease; where this was the case, the time to reach a diagnosis seemed especially prolonged:

"*By the time I saw a gastroenterologist the liver function tests were normal and nothing further was done" (021)*

With no medical cause found for their symptoms, some participants described how they were "*dismissed" (023*) by their physician, others described how they were reassured that there was nothing wrong with them and sent on their way:

"My doctor said, 'Well, I don't know what else I can do with you really' …and I, I just sort of gave up a little bit at that point" (023).

"It was like 'well there's nothing sinister, go away" (014)

Participants described instances where the doctors themselves seemed overwhelmed with attempting to manage such a complex web of symptoms with no unifying diagnosis for them to make sense of:

"I tried to list the symptoms I was experiencing…I could see her (GP)…thinking, 'This guy - I've got to get rid of this guy'...and fair enough, I probably was a bit overwhelming with my symptoms" (023).

"I said 'I think I've got something wrong with my liver, look at my eyes, look how terrible I look' and I do get that now, if my liver's a bit funny…she (GP) started talking to me about cosmetic surgery" (023).

8.4.2.2.4 Incorrect Diagnoses

Half of all participants described how initially they were investigated for alternative diagnoses, which later proved to be incorrect. A common worry for doctors and patient's alike was that cancer might be the cause; this was especially the case for participants with weight loss; the preoccupation with excluding cancer seemed to allow alternative diagnosis based in investigation results, almost to be ignored:

"So the first words on the visit to the gastroenterologist…when I went to see him, even though he had the [MRI] results and I had actually read the results. There was a dilated bile duct. His first word, words were, 'You've probably got colon cancer so I'll have to do a colonoscopy to check that out'" (027).

Other incorrect initial conclusions mentioned included Irritable Bowel Syndrome (IBS, 023, 014), gallstones (025), alcohol excess (019, 027), sinusitis (011), psychiatric illness (023),

occupational exposure (021), a parasitic infection (020, 023), stress (011) and growing pains (011, a paediatric presentation):

"So I went back yet again and…the doctor then started talking about, 'Well, I think you might have IBS. I think you've got, you know, a bit depressed" (023).

"I had a quick visit to the GP so he did a few tests and said, 'Oh, you should drink less" (027).

During this period of symptoms pre-PSC diagnosis, participants described how they learned to manage their symptoms. Often these symptoms were fluctuating (probably representing subclinical recurrent cholangitis) and participants learned to manage these themselves:

"I occasionally had these really severe episodes…which I now know as cholangitis… …I had these mechanisms of being able to try and…sort of nurse myself through" (023)

"I used to call them funny do's…basically feeling terrible…but they'd always settle down after a day or two on their own…they were just something that I lived with" (026)

8.4.2.2.5 The Cascade of Investigations

All symptomatic patients described initial investigation via blood tests. These returning as abnormal sparked further testing, after referral to secondary care; this was either to gastroenterology or hepatology services. This appeared to vary depending on geography (i.e. whether their natural local referral hospital had specialist liver services) but also whether it was clear at that point that there was a liver problem (for example via particularly abnormal blood tests). Some interviewees described a fairly straightforward pathway of MRCP, ERCP and/or liver biopsy followed by the diagnosis; others described a lengthy process of repeated investigations and multiple referrals to other specialists or hospitals:

"What surprised me was the amount the doctors can do to work through methodically…to get to a diagnosis. I mean I had so many tests" (020)

"He (Gastroenterologist) sent me for an ultrasound… I had a CT scan, MRI and an endoscopy…I went for an ERCP" (013)

Participants described how unpleasant they found the invasive tests they had encountered throughout their PSC journey. ERCP procedures in particular were performed on five interviewees (010, 013, 019, 025, 026) were described by most as being particularly unpleasant. One participant wondered why their practitioner had favoured this invasive technique before other non-invasive investigations, such as an MRI scan. Liver biopsy was also found to be uncomfortable by many:

"Don't ask me to have a liver biopsy. I couldn't do that again, it was so horrendous " (015)

"The first test I had was an ERCP which was, I found, spectacularly awful…I was absolutely petrified about having it done …the results of that were… inconclusive so then I had an MRCP and that was much better…made me wonder why they didn't just give me that first" (019)

8.4.2.2.6 Participant reaction to the diagnostic process

Frustration was clearly demonstrated within the interviews. Ten patients described how they were seen by multiple doctors in differing settings and how little progress they felt was made. This was described as *"starting from scratch" (027)* each time and the feeling of being *"bounced" (022*) between different teams. Three participants described that they became aware that their clinicians were not sure of the diagnosis themselves and that perhaps their presentation was not straightforward:

"The doctors were saying that I was a bit of a, a strange case, a little bit of a, erm, they couldn't quite work out what the issue was" (020)

"You don't present as a sort of, nice, slots into a category case" (024)

Some participants described how their previous positive attitude to healthcare was changed due to this lengthy diagnostic process, or perhaps by being initially mis-diagnosed. This was particularly profound in three participants; these described a complete loss of faith in the medical team to believe that there was something wrong with them, and to manage them correctly:

"I knew that something was wrong…no one was really interested in my story, in helping me" (012)

"I got frozen…as far as the NHS was concerned, thinking "I'm not going to get support or help here at all" (023)

In six participants, this was exacerbated when the individual clinicians involved were interpreted as being unable to acknowledge they did not know the answers and thus gave erroneous advice that subsequently turned out to be incorrect. To interviewees, this behaviour caused additional distress and further degraded their trust in the NHS.

"I totally lost faith…to gastroenterologists because they thought they knew and they didn't. And, and they weren't honest enough to say that they didn't know" (027)

"I had said to [the Gastroenterologist] before, I was diagnosed, that I wondered if I was getting cholangitis and he said to me, "No, no, you can't possibly have got cholangitis…it wouldn't resolve without IV antibiotics". But it always did resolve on its own" (026).

As a result of these conflicts with clinicians or the ongoing lack of a diagnosis, three participants described searching for answers elsewhere including using private healthcare, dietary interventions or investigating alternative therapies:

"I just sort of started looking for alternative stuff. So I sort of thought, 'Well, maybe I'll change my diet', so I changed my diet and…I started…looking at homeopathy" (023)

"I've also started… trying alternative treatments. So, for instance, traditional Chinese medicine…Last year I've even seen a functional doctor (012)

As doctor after doctor told them there was nothing physically wrong, two participants in began to wonder if they were mentally ill, rather than physically:

"I thought, 'Oh my god, I'm mad' …and I had a sense of utter horror but also real relief" (021)

These participants described the profound effects this had; without a doctor to verify that they were indeed ill, they felt their families did not understand and instead thought badly of them for not behaving as a normal person should. Instances were described of the breakdown of family relationships due to this, which were subsequently repaired once PSC was confirmed.

"Because I hadn't got a diagnosis…to them (family), I became a fussy …and slightly oversensitive person…so when I got the diagnosis, I think everyone was relieved because I think everyone could…understand…what had been going on" (023)

8.4.2.3 Stage 2: Reaching the Summit (the diagnosis event)

The diagnosis of PSC being formal made was an important event for all participants. This section describes how the diagnosis was communicated, the initial reactions, and the importance of the information that was imparted at that time.

8.4.2.3.1 Receiving the label of PSC

The majority of participants felt that finally receiving the label of PSC helped them cope with what they were experiencing, having previously been stuck in the unknown:

"I think once you get a diagnosis you can actually handle life. You know what's going on…when you're in that unknown and you, you fear the worst" (027)

"I seem to have picked up since I've had PSC…whether that is mentally because you know then you've got your answer to the fact of why you're not well" (015)

"I know people who are perfectly well who worry because…they may have something they don't know they've got. And I always think, well at least I know what I've got… at least I'm in the system" (025)

Three participants described their initial relief to receive a diagnosis, soon quashed by the details of what PSC is:

"It seemed like such a relief after such a long time to know that I wasn't mad and there actually was something wrong… I thought 'well this is the answer to all the problems, surely in this day and age there isn't going to be an illness that you can't treat' naively" (021)

Participants with milder clinical disease appeared more psychologically affected by their diagnosis than those without. One participant, whose diagnosis was an incidental finding and whom had remained asymptomatic since, described the psychological disadvantages of knowing they had PSC and how this had affected them far more than the disease itself likely ever would.

"I've been bothered by the psychological side of living with this disease…I've known for ten years I've had PSC and to be perfectly honest, I wish I didn't know…What good is it going to do you to know…a condition that there's no treatment for, what's the point to knowing you've got it because it's not going to make any difference" (017)

8.4.2.3.2 How the Diagnosis was given

Participants described very different experiences; a third of interviewees were relatively positive about this event was handled. Having positive doctor-patient relationship appeared vital at this stage and had a big impact on the participants' experiences:

"I think Dr S was key for me…I couldn't fault him at all in terms of how he spoke to me about it…he almost took into account…the worry and stress and the overall fear I'd say of being given that diagnosis" (020)

The remaining two thirds of the cohort were deeply critical of the experience; this often centred on a perceived lack of empathy from the clinician, who had not acted as they would have expected given the bad news of having PSC (as the participants saw it) or the length of time they had been waiting for a diagnosis.

"It would probably be a textbook case of an absolutely terrible way to liaise with a patient, it was just really, really awful…it was "here's this bomb"…it was just brutal" (019).

"They said, 'It's good news. It's PSC'. So maybe if they were thinking I'd got cancer, then the PSC was good news but then you like read up about PSC and you think, 'Well, this isn't a good news story at all'" (017).

Preparation appeared key for participants; when the clinician had made time for a detailed discussion and demonstrated understanding, the experience was less distressing:

"The actual delivery of this earth-shattering news was handled appallingly badly…said "great news, you don't have PSC" and then he went, "oh hang on a minute… no, no, no sorry you do"…I just found that very, very, very upsetting that you wouldn't get that right before you saw somebody…It really felt like that person didn't care at all at what they were saying…he had no empathy at all" (019)

8.4.2.3.3 Participant Initial Reactions to the Diagnosis

Three participants had heard of PSC before they were diagnosed, all via their own research; two of these has pre-existing IBD. Personal reactions to the diagnosis often depended on in what manner it was explained to them. This was sometimes dramatic; others were more reserved about the diagnosis:

"He [the hepatologist] went, 'Oh, I'm very sorry to tell you you've got primary sclerosing cholangitis…I'm so sorry. You've got such a young family. You need to go back to the UK to your family'" (018)

"She [hepatologist] was very nice…explained I'd got PSC and what it was…she wasn't overly…"oh, you know, really sorry about this, this is really bad news and I know not what you want to hear"… she didn't lay it on heavy" (025)

Half of participants described the diagnosis as being an anti-climax; after the battery of tests they had undergone there was an expectation that a diagnosis would lead to treatment:

"You've had a lot of care and attention in terms of arriving at the diagnosis…and then it drops off a cliff because it was like "okay, we know the diagnosis…and we've taken you through all of these tests but we can't do anything about it'" (020)

'He (gastroenterologist) said, 'there's no cure and treatment … we'll just monitor you…it's obviously early stages. It means we can plan for your early transplantation'. I don't know what else he said after that because I'd walked in there as a healthy person and all I heard was 'transplant'…I was in shock (017)

8.4.2.3.4 The Importance of Information

Participants felt strongly that they needed access to good quality information; if this was present at the time of the diagnosis, the participant described a more positive experience:

"The chap was really nice and he explained. He'd obviously found something on the internet and drew a picture of the liver…and explained" (014)

I didn't get much information which I think that definitely needs to change" (016).

Participants described how the language used by the clinician was important for their experience and understanding:

"It's the first time I actually understood what was wrong with me…didn't speak to me like he (hepatologist) was like this know-it-all doctor that knew everything…he explained it in a way that made perfect sense…up until that point, I didn't even know what a liver looked like" (010).

Twelve participants stated they were given no signposting to further information at their diagnosis and were instead advised to search the internet. Few were told specifically where to find accurate sources of information and what patient support groups there were available.

"He [gastroenterologist] said, 'I haven't got anything. There's no leaflet or anything that we've got…so the only way you're going to find out is going to Google it'" (010).

The four participants who did describe being given detailed information and signposting to support groups upfront were all being seen in a tertiary hepatology unit:

"They told me that I have PSC. And at that time, I didn't really understand it…but they gave me a booklet and once I've read the booklet…some kind of an alarm went off in my head that this may be really dangerous" (012).

"The doctors gave us loads of information and they put us in contact with…a charity…that specialises in childhood liver diseases" (011).

A common reaction of participants after being diagnosed was to search for more information; this is discussed more in Stage 3 (below).

8.4.2.4 Stage 3: Falling off the cliff (the aftermath of the diagnosis)

Receiving the PSC diagnosis was a major life event for all participants. This was an additional diagnosis for nine interviewees who already had IBD; the psychological impact of the diagnosis appeared less for participants with comorbidities than for those without. This section describes participant reactions to their diagnosis, their search for information and peer support, breaking the news to others, and their newfound existential worries about the future.

8.4.2.4.1 The Search for More Information

Regardless of how much information they had already received, all but one participant began to search for more information, either by internet search or using library resources. For some, the search for information became all-encompassing:

"Every night, I would come home and I would go on the internet. I googled everything there was, so it didn't matter how old it was. I read every bit of erm, documentation that was on there relating to PSC…I just came home every day and sat reading the internet, probably for a year" (017)

"I was reading more and more I was getting more and more depressed" (12)

The information participants found was universally disheartening, including detail on high rates of liver transplantation and an overall poor prognosis.

"When I read up on these things, I come across people who have got awful, version of it that it sort of scares you at times, you think, am I going to go like that" (025)

"The first thing you do is go on the internet…I read was that there was, a prognosis of ten years. So, I thought that I'd be dead within ten years" (026)

Some participants felt such undirected searching should be actively discouraged by clinicians, due to the inaccurate and frightening information they had found. Many rationalised that the milder cases of PSC were unlikely to be so high-profile, especially on patient forums, thus giving a skewed account of reality:

"I think you're faced with information that is very, very alarming and a lot of it is… certainly from today's perspective, quite out of date" (019)

"I don't trust Google because you could have 100 people with PSC that are doing fine and coping well…but you're going to get two people who are having a bad time of it and struggling…They're the only two you're going to read about" (010).

Three participants described how they became able to filter the information they found, once they understood more about their personal situation with PSC and that this reassured them; all had early PSC:

"What I found I ended up doing was researching everything I could, getting worried by all the horror stories and then over time doing more and more research, more and more research, understanding where for myself I could discount some of the horror stories".

"It's not knowing that can be stressful so, so I'd leave (clinic appointment) with an understanding of knowing how all the research…connected to my specific case and that led me to walk out of there feeling a hell of a lot better".

Finding or being directed towards the PSC support group website seemed a positive factor for most participants, especially early in their search for information. A few participants turned to their GP for advice, unaware that most GPs might have little knowledge about PSC:

"I remember going onto the website the morning after the diagnosis. I felt awful…and I was just on my phone and reading the part of the website which was basically the 'so you've just been diagnosed with PSC'…that was really helpful. That, that was…a really good jumping off point for me" (020)

"So I thought right, I need to go and see my GP. I just said 'I need information' and she just turned her screen round and she said 'here's all the useful websites' and the first one was the PSC support, which was brilliant" (014)

However, one participant took the opposite approach and actively chose to avoid knowing more, describing their role as being simply to do what the clinicians asked them to do. In this case their spouse took over the role of information gatherer:

"I totally refused to, to read anything. My wife did. She got upset…through reading stuff on the internet, so then I literally banned her from reading it…I was just like, 'I don't want to know anymore. I'll just go on a need to know basis'" (010).

8.4.2.4.2 Existential crisis

While three participants appeared accepting of their diagnosis, 15 participants described feeling very low. Many became convinced they were going to die very soon:

"I found it very hard to cope…I couldn't think about anything else; only the fact that I'd been given, I'd been given a death sentence" (017)

"I had this cloud thinking, 'I am going to die. I'm going to die'" (018)

Most participants described a fundamental change in their future projections, and a feeling of loss for an alternate future without PSC. Some felt this immediately, whereas for others it was delayed:

"You need to mourn the life you've lost…I will never be where I thought I might be a couple of years…I won't be able to do a lot of the things that I thought I would be able to do" (024).

"I have found it painful letting go, I think, of the person that I was…there's a grieving process of – like the feeling of you've died in your own lifetime" (023)

Depression was commonly described in the months following the diagnosis. Seven participants subsequently received a formal diagnosis of anxiety or depression and a further three participants described similar symptoms. Most described how being physically ill with PSC and grieving for the loss of their future had caused their depression, rather than being an independent mental illness.

"I now suffer from depression which purely I imagine is a result of the loss of my life to be honest. I had a very full, active, physical life, a great social life, lots of friends, saw family all the time, and now I really do nothing" (021).

"I've suffered from anxiety in the past where I've had like periods of anxiousness and I think mine are more linked to…worrying about my conditions" (016).

A few participants described a similar effect of their diagnosis on relatives, who often sought support themselves:

"My mum found it very difficult to begin with because she was at the…delivery of the diagnosis and I think it, that sort of really affected her…and she actually ended up going to counselling herself" (011).

Anger was also a commonly observed feeling, whether at the unfairness of the situation (given they had led a healthy lifestyle) or the lack of treatment options. Many felt it was ironic they had a liver condition despite never drinking to excess:

"I just feel so angry about it all…we can send people to the moon, this is ridiculous…and it's just so frustrating" (015)

"I'm the perfect, healthy person. I never drank. I never smoked…I married my first boyfriend. I only ever had sex with one person. I didn't sit in the sun and sunbathe. I didn't wear make-up. I never had colour on my hair. I did everything that I thought was possible to keep myself healthy and... it didn't make any difference, did it?" (017)

The change in trajectory described by most participants was profound and included planning, housing, travel and career pathways. Half of participants described reducing their working hours, giving up work completely or retiring early due to their PSC. Some felt unable to strive for career advancement given their likelihood of progressing to serious illness:

"My husband, he just point blank said, 'We're not having any more children because a) I don't want to put you at risk, b) I don't want them to not have a mother'" (018)

"I may have to stay in England because of the fact that I will need access to healthcare and healthcare here is really exceptional" (012)

However, three participants described how they had made positive changes in their outlook:

"We've made a very, erm, positive decision about…doing as much as we can when we can… time is precious so make the best of it. Carpe diem" (027)

"It's helped me in my work, it's helped me become more…driven in a way to…achieve what I want to achieve at my professional career… I almost see positive change in trajectory it as a, my life being this window of opportunity to live life to the full 'cause you never know what might be in the future" (020)

8.4.2.4.3 Telling the world

The first thing many interviewees did after being diagnosed was to tell family and friends. The descriptions of how participants informed their families differed; some did so immediately and in person, others via online platforms and some made the deliberate decision not to tell individuals, usually elderly relatives, for fear of causing distress. Some felt that PSC was a worse diagnosis to have than cancer, which two participants had already overcome:

"We have a family chat group on Facebook…if we've got anything to pass on, as a family, we just put it in there and you can tell everybody everything at the same time" (026)

"I think I found it challenging, so I think they found it challenging, sometimes I think people react in quite a strange way. I haven't actually told my mum because she's elderly and I thought… I told her I had cancer but I thought this diagnosis is so scary" (019)

None of the participants described telling their family as a pleasant experience; many relatives became distressed by the news and it reinforced the reality of the prognosis to participants themselves:

"Telling my mother was the hardest…she was slightly upset you know, you don't want to think of your children dying" (015)

"My elder sister is quite an anxious person…when I told her she said 'oh well you'll just be able to have a liver transplant'…I thought that was quite a strange reaction" (019)

Some were keen to tell family and friends as an explanation for why they had been unwell for so long; many felt their families had grown less supportive over time and no longer believed that they were ill in the absence of a concrete diagnosis:

"They knew that…I have always been sickly…they were very…depressed about that and they've started reading on the disease themselves…I think since then they have started to be more supportive" (012)

Most participants spread their news soon after they were diagnosed and then fewer new people over time; a few participants described how despite this, this initial aftermath was the period they were less equipped themselves to do this properly. Some described how their positive experience when being told about their condition enabled them to better inform their friends and family:

"I almost feel like I'm in a better place now psychologically to be able to inform people than I was…you tend to inform family and friends just after you've had the diagnosis of course and you, and you yourself are just like all over the place" (20)

"When I first got diagnosed I felt…compelled to make a big announcement to everyone because it was a big deal for me. Actually it's not a big deal for everyone else so…it goes over people's heads…they don't know what to say" (018)

However, the majority of participants felt that despite their best explanations, most people they told did not really understand. The rarity of PSC plus general poor knowledge about liver disease in general, were cited by participants as main factors in limiting the ability of others to understand:

"I'm not sure people always take things in totally…if you tell them something they've never heard before, they can't quite take it in, so they don't…register what it is" (025)

"It kind of freaks them out that you've got an incurable disease and because it's not like cancer they can't, it's like they can't give you sympathy" (018)

The invisibility of much of their symptoms was mentioned frequently; participants felt that the severity of their illness was not appreciated by friends and family:

"I think at first when I was diagnosed…they felt that either I or doctors were making up stories…that I'm using disease as an excuse…I think they've noticed that I'm becoming jaundiced, that they started to believe me" (012)

"And I think it's because I look well that people don't think there's a problem. I – you know I think if I started to look unwell or go yellow or I think then it might put the frighteners up people" (015)

This also led to future problems with work and claiming benefits as the system didn't appreciate how their symptoms impaired their abilities to carry out daily tasks:

"It's a hidden disability and that's definitely been the issue with the benefits agency, because they look at you and see that you can put your hands on your head, yes you can walk twenty metres, you can dress yourself so there's nothing wrong with you actually, but I can't go to work" (021)

8.4.2.4.4 Stigma

Concern over how they might be treated differently once people knew their diagnosis was a common thread amongst the interview participants. Over half of participants described worries of others thinking they drank alcohol to excess or be in some other way responsible for their illness:

"My experience has been that unless I tell people otherwise they will assume that this is an alcohol related disease that I have, which I find very frustrating" (021)

"There's a huge stigma attached to having liver disease…If you told somebody you'd had a heart attack, or a stroke, or you'd got Parkinson's disease, then the reaction always is, 'Aww' but when you have a liver disease, people make judgments and think it's a lifestyle choice" (017).

Few participants had previously heard of PSC and most knew little about the causes of liver disease, except for alcohol. They recollected being repeatedly quizzed about their alcohol intake by their doctors, and doubted when they stated this was minimal. Participants described feeling they were being treated differently:

"The second I told some of the doctors, or some of the nurses, there that I'd got a liver condition…they treat you different and it was almost like, 'He is an alcoholic. He is a drinker.

He's wasting our time. We've got sick people in here and another person comes in that's self-inflicted through drink'" (010)

All participants described that their current alcohol intake was currently minimal or none. Two thirds of the interviewees described how not drinking alcohol had adversely affected their social networks:

"If you're out or, or you having dinner with friends or something you say, 'No, I'll just have water, thanks,' you know, people look at you like you've got two heads sometimes" (022)

"It's almost socially unacceptable not to drink unless you're pregnant or unless you're driving…people are constantly talking about alcohol and how drunk they're going to get and, and I want to say to them, 'You should look after your livers'" (018)

However, three participants acknowledged that this stigma might sometimes be more perceived than real and that collaborating with larger groups of patients with liver disease, including those which might be lifestyle-related, was important to help push for better liver services for everyone.

""We're all going to die in the same way, on the same liver ward, so you know, get over it, but people don't. People don't like the fact that they are associated with alcoholics, and drug addicts, and fat people…they think people…are judging them" (017)

Many were concerned about how they might also be treated differently at work; most were pleasantly surprised. However, some were worried coming clean about their PSC would affect their employment so did not divulge this.

"I was surprised, especially at work…I wasn't expecting to get support at work because it's a cut-throat place…fortunately I was wrong because people were really supportive" (012)

"I don't really tell people at work…I'm a contractor so and you know because I'm not young I sort of thought well if I tell people at work they'll probably…choose not to employ me" (019)

"Work have been a bit iffy…not my Line Manager but above them. They've, they've made it a little bit difficult at times" (026)

8.4.2.5 Stage 4: Soldiering on (living with PSC long term)

Once the initial reactions to the diagnosis had calmed, participants described how their life had been since. Many described how their symptoms affected them, particularly those of fatigue and of feeling generally unwell much or all of the time; the effects of these symptoms were discussed in the pre-diagnosis section of this analysis but were ongoing and slow deterioration was commonly described.

This section describes participant's experiences of living with PSC long term, of their medical management, and how daily life is affected by the natural fluctuations in their symptoms.

8.4.2.5.1 Medical Management

The mainstay of the medical management for PSC is supportive including symptomatic treatment, antibiotics for cholangitis, and close monitoring for complications. While UDCA does not have an evidence-base for its efficacy in PSC, half of interviewees described taking this medication. One participant described how they had seen significant improvement in their symptoms since starting UDCA, however, no participant described an improvement in their blood tests:

"A lot of my symptoms improved, I felt far less tired, far less itchy, and I think…my brain felt far less affected" (019)

Three participants described their doubts about efficacy of UDCA; two of these were aware of controversy amongst medical professionals also:

*"**T**here's no cure and err erm the only treatment nobody's very sure whether it, whether it works or not" (022)*

"I take Urso and there does seem to be a bit of a debate going on at the moment about whether Urso is really just masking and you know, producing false blood result, so I don't know" (021)

It was not clear which medications most participants had trialled for symptoms, although those participants being seen in specialist centres did seem to have undergone more aggressive symptom management. This was especially for the treatment of itch, but with varying success. Many also took medication for other illnesses, leading to a large pill burden:

"I'm currently taking over 20 different pills every day which is ridiculous" (024)

"My itching was one of the major symptoms…So they also took most of that away…and having my…ulcerative colitis under control also helped" (027)

I was given some medication for itching…but it didn't really make that much of a difference" (012)

Monitoring was seen as important by two thirds of interviewees. In the absence of treatment for their PSC, many participants were keen to undergo regular tests to check for progression. Some worried that without such monitoring, they might deteriorate and become ineligible for other treatments, such as transplant:

"Having the regular scans…which gives you wonderful reassurance…whether there's any progression…just gives you peace of mind" (027)

"I don't want to wait a year to see somebody. I'd rather just keep ticking along and somebody telling me every six months that it doesn't look bad…I probably don't need to go. I could

probably go every year but…it's unpredictable, isn't it? I could go downhill fast. There's no common pathway and, and there's no timescale" (017)

8.4.2.5.2 The Need for Specialist Care

Ten participants described being currently under multiple hospitals for their PSC, usually a local non-specialist hospital and a larger liver centre. In all such cases, it was the specialist centre taking the lead, with the local hospital performing some routine monitoring. Of the remaining participants, seven were being exclusively managed by a liver transplant centre and one in their local district general hospital; the latter described having early asymptomatic PSC.

Receiving medical care from a specialist was seen as important by many; these 11 participants felt that a specialist was needed to ensure optimum medical management. Many described stark differences in their experiences comparing local and specialist centres, especially in terms of the improved information and understanding they gained from their specialist appointments:

"I think that they really care about us, I think they have such huge passion and they have such knowledge I cannot fault their care, attention and their enthusiasm to find a cure" (015)

"I've had about seven, eight appointments at (local hospital). Didn't understand my condition at all. I had one at the (liver transplant centre) and they understood…they talk to you in a language that you understand…he didn't speak to me like he was like this know-it-all doctor" (010)

However, participants disagreed on the timing of specialist referral; some felt this should be immediately on diagnosis for everyone, others felt this was not always necessary. All agreed that a specialist was needed if they experienced any significant deterioration:

"I think when someone is diagnosed with PSC they need to be referred straightaway to the liver specialist" (016)

"I think if I got sick, I would ask for my care to be…once I start going downhill, I would want my care in the (transplant centre) immediately" (016)

"I have a lot of faith in [local hospital doctor] and he has other PSCers actually, which is the other plus. That doesn't often happen" (027)

While many participants were content with their current medical care, a common concern was the possibility of missing out on treatment available elsewhere. Many described worries about deteriorating too quickly to have the opportunity of a liver transplant. Confidence and trust in the medical team appeared to be important. Some participants felt that only they themselves were fully invested in their care as any mistakes would directly affect them, not their medical team:

"I want to know that I'm being looked after properly but if they see any erm reason to worry that they will just refer me straightaway and not hold off…I would still like to be under a more specialist hospital…I'm just worried that I'll miss out" (016)

8.4.2.5.3 System Failings

The administrative side of managing PSC was often described as challenging for participants. Poor communication between hospitals and bureaucracy was a common complaint. Most described how they had to chase up various parts of their management to ensure they actually happened:

"Transferring data and information has been a little bit of a challenge at times…it shouldn't be…Electronically that should happen" (027)

"I can access all the liver function tests through…My Health, but she (the GP) can't(014)

"That's probably one of the hardest things…it's like this wall of admin to get through" (018)

Two participants described how they wanted combined appointments with all their specialists and tests at the same time, rather than having multiple appointments on different days and navigate information transfer difficulties between the different medical teams:

"I'd really like it if I could phone up and get those appointments easily, not have to phone lots of different departments just to get like coordinated…you have to be on the ball with PSC (018)

"I would like to go to the hospital on one day and see all the different people that I need to see in one place" (024)

A third of participants described specific instances where they knew there had been a mistake made:

"It was obvious that they'd had some kind of reorganisation and had missed me off…I should have seen them" (025)

"When I went to see (specialist nurse) she was like from now on you are only going to see either me or (hepatologist) because they were aware that the care was…not very good" (016)

A lack of continuity and consistency of care was a concern for nearly half of participants; these described how receiving conflicting information from different clinicians further undermined their trust in the system:

"He (the gastroenterologist) kept on asking me why things hadn't been done. Why hadn't…been referred to this? Why hadn't I been referred to that? And I was going, 'Look, I ain't the doctor. I can't refer me…I turn up for my appointments, I get my tests done and I go home" (010)

"Everybody has a different, slightly different system…if they're in the same clinic it tends to be the same but if they're in a different hospital they have a different way of doing it and a different way of explaining it and a different outlook on it… You end you end up like not really trusting anything unless you're sat in front of your hepatologist" (018)

"I think at the time I just assumed that all doctors and hepatologists know a lot about it…I've since learned that perhaps some probably don't know as much as others" (020)

One participant was less concerned about the individual doctors and felt this was less necessary if the doctor they saw had access to all relevant information and knew about PSC.

"I've only seen (hepatologist) once, maybe twice, and I've seen about four different doctors which isn't a problem because they've got everything on record" (014)

A commonly described feeling amongst participants was confusion as to who had overall charge of co-ordinating their care, their GP, their specialist or themselves:

"Another patient has said, 'Oh, well you're responsible for your own care"…I said, 'Well, that's alright you saying that and yes, alright, I'm intelligent. I can find out things but not everybody's in that position'" (017)

"Some people have got amazing GPs that, that are really good. They know that they're in the middle. They're like the main point of communication and they coordinate all the other diseases" (018)

Two thirds of participants described the importance of having access to their medical team when needed. This access to information, support and monitoring seemed to give confidence they were being well looked after:

"I think that's one great thing about my GP is that, whether it's because of PSC or what I don't know, but I can always see her" (014)

"Last time I emailed him (gastroenterologist), I got a…out of office, erm, email back. But he still emailed me from home, telling me what to do so he'd obviously read it at home" (026)

8.4.2.5.4 Ongoing Doctor-Patient Relationship

Many participants described long running tensions with their medical team. The lack of treatment was frustrating for most; they felt that their doctors should be able to offer more, even though they knew from their own research that this was not possible. One participant described how their symptoms were not in keeping with their blood tests and how this led to further disparity with their doctor:

"We had one appointment and she (the doctor) was like… you're doing great, all of the graphs are looking good…Things are, things are actually looking better than they ever have before …but you're in tears and you're not coping and you feel like life's a mess" (024)

"If you're a patient you can't really tell the difference between a doctor not having the answers because there aren't any and a doctor not having the answers because they just don't know them" (018)

The majority of participants had educated themselves well about PSC and were able to advocate strongly for themselves in the face of a difficult to navigate medical administrative system or with doctors whose knowledge of PSC was poor. Despite this, participants found it hard to overcome their basic instincts not to challenge their clinicians:

"I don't challenge doctors…I'm not as assertive as what I should be really… maybe I haven't had the care that if I was someone that moaned a lot" (016)

"Even if you're, you know the signs, you feel confident about what's going on it still doesn't go smoothly. If, if it takes one doctor that's confident in their view it's so easy for them to overpower you" (018)

Despite what they had experienced previously, many participants still had faith in their doctors and were keen to follow their instructions in the hope of improvement. Some described a paternalistic relationship with their doctor and others more of a partnership.

"If they tell me to do something, I do it. If they say I've got to stand in that room and tap my head and rub my stomach three times a day, I will do it…All I want to do is get better" (010)

"I can't do anything about it, if it's going to happen, it will happen, I just put my faith in the doctors and nurses and myself, because obviously I have to react to things" (016)

"He [hepatologist] was really helpful in explaining different things…he welcomed me with a smile on his face erm and … I didn't feel like a patient but rather a partner" (012)

This relationship appeared inherently based on effective information exchange for many participants; where they felt they were listened to and received information in a language they could understand, their relationship with their medical team appeared stronger and more positive. The majority of participants described wanting to know as much as possible about their progress. However, not all felt they were receiving this to their satisfaction:

"As a patient I'm probably not the most forceful or I don't open up as what I should do…but I feel that, with that doctor, I just feel like I'll get shot down anyway…because like I asked him [gastroenterologist] about my liver condition and…he just said it's functioning, you know, erm whereas I'd like to know exactly…what condition my liver's in, what the last scans have shown progression-wise, you know I'd like a lot more detail" (016)

8.4.2.5.5 Fluctuating Symptoms

The fundamental uncertainty the majority of participants were experiencing is discussed in later sections. Fluctuating symptoms was a common challenge for participants to manage; this might be via self-management but at other times required treatment such as antibiotics. Many described how they knew the first signs of a worsening episode themselves. However, others worried that every minor feeling could herald the start of an exacerbation:

"That's the worst thing about it because if I get a twinge here, erm, I think, oh, is that the [gall] stone going through and if so is it going to cause an infection. If I feel woolly, erm, I think to

myself is – is that going to be the – the start of an infection so, you know, you don't know – you don't know what's going to happen" (013)

"I've had a few, few times where I've had cholangitis and the first time that was really worrying because that, I thought that that meant my PSC was progressing so I was really worried about it. Erm, but luckily the doctor straight away said it's not. It, you just, your PSC goes up and down" (018)

A common description was the feeling of having become so chronically unwell, that they were unable to see just how unwell they had become:

"Because you feel bad a lot of the time, when you do get sick you don't realise how sick you are" (016)

"We went on holiday last year and I look back at the holiday pictures and I don't realise how ill I actually looked…my face was all like gaunt…it was scary seeing those pictures and thinking how quickly I could decline without even knowing it" (016)

8.4.2.5.6 Hospital Admissions

Nearly half of the interviewees described repeated PSC-related hospital admissions, mostly for recurrent cholangitis. These participants described their difficulties accessing emergency medical care; emergency departments were cited as particularly difficult to navigate:

"I had never found access to the consultants, on an emergency basis, easy at all…is the most appallingly difficult thing to do…I swore I'd never go back…when you've got a cholangitis flare

up, you're feeling really, really unwell. The last thing that's going to do you any good is sitting in a very uncomfortable A&E area shivering away for nine hours" (023)

Almost all participants described instances where they knew more about PSC than their doctors, especially within emergency departments or an unfamiliar GP. Participants described knowing it was their PSC that was causing them to be ill but that the clinicians didn't agree, instead treating them for other things. Two participants described doctors confusing PSC and PBC and having to correct them:

"They treated me for a heart attack and I was there five and a half hours and then the doctor put me on the heart monitor again and said, 'You're not having a heart attack. You can go home' and I said, 'I told you five hours ago I wasn't having a heart attack'" (010)

"I said, 'Oh, I'm having a flare-up of cholangitis. Can I just get new antibiotics?" And he [GP] went, 'There's no such thing as a flare-up'…it's so hard to, erm, advocate for yourself when you've got a doctor that is talking to you like they know better than you and I'm thinking I wrote the leaflet on bacterial cholangitis. I know what it is, I've had it before and he honestly didn't believe me" (018)

One participant in particular was very critical of the emergency care they had received; they described in detail how they attended multiple times only to be discharged and eventually their GP referring them to a different hospital, where the experience was much better; neither of these hospitals were specialist liver centres. They also described how they felt discriminated against for having a liver disease:

"I walked into see my GP and he says, 'What are you doing here? You should be in hospital' because I was, I was like yellow. My eyes had gone yellow and, and he says, 'You should be in hospital'. I says, 'I've been twice and twice, they've sent me home… the sweat's pouring out of me but I'm still freezing cold, gone jaundiced…they was telling me I was basically wasting their time and there was nothing wrong with me" (010)

This participant described how they felt they had to push to get the correct treatment but that they were so ill they were unable to do this effectively. Most participants felt they had to advocate strongly for themselves and many learned through experience how to get better care:

"I almost had to fight for my treatment and…the more ill I became, the less I wanted to fight" (010)

"For the first, say, 18 months, you would always see doctor bottom of the list…you would be seen by anybody that was there until you learn how to navigate the system and how to make sure you always got to see Dr. Top Name on the list" (017)

The younger participants described additional challenges with the inflexibility of the hospital inpatient system; one described tension between them and the nursing staff and how they felt there should be better provision for younger patients:

"Nothing was in my control when I was in hospital so that used to cause more problems…the doctors and the nurses would just say that I can be a difficult patient but it was just because nothing was in my control so it was really hard…most young people are put in a side room and…you kind of feel isolated… I think they need to…change their attitude a little bit towards younger patients" (011)

Another participant described more positive experiences, with good communication between departments and high confidence in their management:

"My GP has done a really good job because she prepared a written summary of my conditions…and the doctors there, I think they were gastroenterologists…had a good understanding of PSC".

8.4.2.5.7 Clinical Trials & Research

Over two thirds of interviewees were keen to participate in research and many were aware of what trials were recruiting. However, most appreciated that new treatments were decades away and wanted this accelerated:

"I wish drugs could come to market quicker, put it that way. The best I've ever felt is when I was on the trial" (027)

"It gave me some hope knowing that there is so much being done about PSC, that there is so much collaboration and different type of research done into the disease" (012)

8.4.2.5.8 Peer Support

The majority of interviewees described the effect of PSC on their social relationships. Some found support but others felt isolated, having not met another PSC sufferer before. Six participants described their experiences of their friends tiring of them being ill and drifting away:

"My family, they stuck by me…I probably wouldn't have got through it without them…I think we're definitely closer" (011)

"I know I'm harping on about it…to the point where I put posts on Facebook, organ donation…the only people that like those posts are the people that have got PSC" (018)

All participants found that their social life had significantly deteriorated due to their PSC. While three participants described deliberately being more active, all symptomatic participants described instances where they no longer had the energy or confidence to go out with friends. One of the younger participants described particular difficulties at school and with difficulties maintaining their friendship circle:

"I lost a lot of friends through it…they were all at school, college and getting on with life and getting their qualifications and I was stuck in hospital" (011)

Of participants in long term relationships, all described a strong relationship with their significant other. All but four patients were in long term relationships and none had experienced a prior divorce:

"Hopefully, it's not affecting (wife) too much…I try to do as much as I can…she won't let me push myself too much" (010)

"My husband has never done ill health, so being married to me has been quite a challenge in a lot of ways…we've got an amazing relationship" (015)

"My fiancé, I've told her, you know, I've said to her, listen it's very serious and I might need a transplant at any time…she keeps her worries to herself" (016)

All described their partner as being outwardly optimistic about their PSC and hiding if they were also struggling. In two cases, it was the partners that took charge of the PSC

management, gathering information and generally organising appointments; both of these were male patients with female partners:

"My wife's quite…supportive…she won't let me, you know, wallow for too long…If you're feeling okay then, you know, life, life continues" (022)

"She (partner) was the one that had to get in touch with the consultant…she's torn her hair out in some ways 'cause she doesn't know what the best thing to do is at times" (027)

Over half of participants made conscious efforts to seek out others also with PSC; mostly via PSC Support, whose online Facebook Group and meetings were popular with participants. Liver North was also mentioned, a charitable collaboration including patients and clinicians. Participants felt these were safe spaces to ask questions of others with similar experiences and to compare their medical care with others:

"PSC support…they're really good like if you've got any sort of like questions or worries you can sort of like put a message in there and someone will get back to you with like their own personal experiences or advice" (011)

"I love the fact that in Newcastle we have,…Liver North …it's the first time I really felt that patients are involved in their disease…there's a real support network there. Um, and I really, and I think it's very much empowered me" (024)

However, meeting other people with PSC was not seen as positive by all participants. Some found it a reminder of their illness; others were warned against meeting others due to worries about how frightening it might be to meet those with more severe disease:

"I saw her [GP] this one day and I said, 'Oh, there's a support group meeting on Saturday. I'm going to go to that' and she said, 'Don't go'. She says, 'Do you want to see the future?'" (017)

"There was a girl in the wheelchair at the last meeting who'd come out of the ward. She's very, very poorly and she subsequently died. And so…I don't really want to see it…I don't want my husband to see it" (015)

Despite all being members of PSC Support, a third of interviewees described ongoing feelings of isolation, commonly cited as being due to PSC being so rare a disease that they had not met anyone else with the condition:

"I don't know anybody else with PSC so you, I suppose to a certain extent you – you feel sort of isolated in that respect" (013)

"I think it's quite isolating when you have any kind of rare disease because if you have breast cancer…you'd know somebody or you'd know of somebody who knew somebody. So you'd be able to find somebody that you could talk to or you'd be able to get some sort of close connection to that disease…When you have rare diseases, you're not going to bump into – there's so few of us" (017)

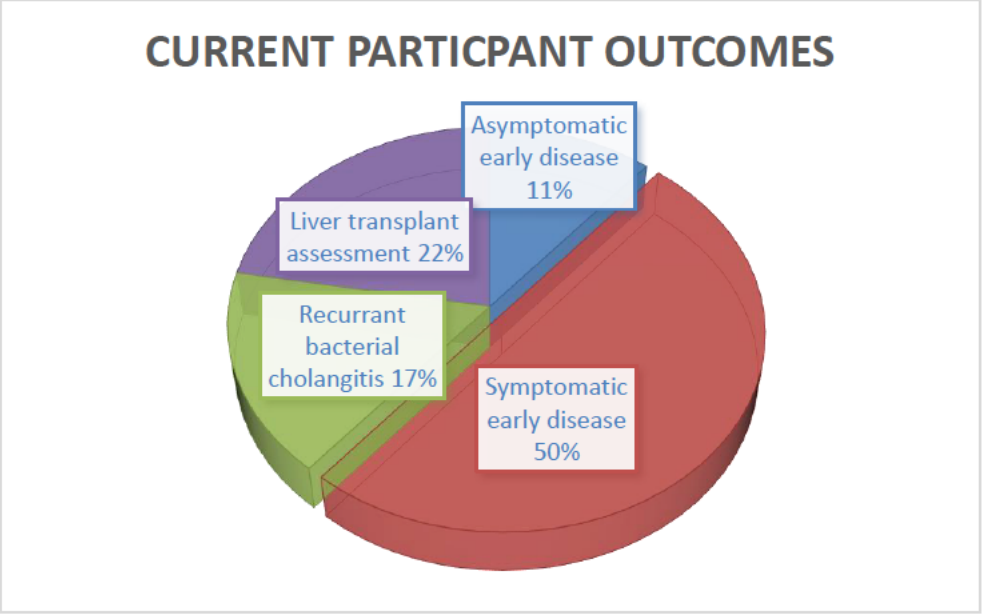
8.4.2.6 Stage 5: The End of The Road (Future Outcome)

From the moment of diagnosis, all participants described knowing that they would eventually deteriorate; liver transplant, cancer and death were described within many interviews. This section includes discussion of these endpoints as well as the uncertainty faced by most as to their prognosis. Also discussed here are participants priorities for future changes in their management, including a discussion of telemedicine.

8.4.2.6.1 Liver Transplant, Cancer & Death

Nearly two thirds of participants described having relatively stable PSC, without complications such as liver failure, recurrent cholangitis or the need for liver transplant. Four participants had previously undergone transplant assessment with an additional three experiencing regular cholangitis requiring hospital admissions. These outcomes can be seen further in Figure 9.

Figure 9: Current Outcomes for PSC interview participants



All 18 participants discussed the possibility of liver transplantation, with three currently active on the waiting list. Most felt that transplantation was a lifeline and they hoped to be offered this if, or when, the time came. The idea of not being eligible for this was felt to be unimaginable, given their poor quality (and quantity) of life without one.

"They have sort of indicated that I'm going on the list…I think I'm going to be more concerned if they turn round and say, 'No'… because I think if they say, 'Yes' I am, I can see an end but if they say…'No, you're not on the list', my quality of life at the minute is not good" (010)

"I'd prefer not to have a transplant, I'd love not to have a transplant, it's a massive operation…I'd love to just live my life erm but right now erm it's like my life's at a halt, it has just stopped" (016)

Guilt was commonly described; potentially receiving a transplant led to feelings of debt to the donor or their family, and a responsibility to carefully look after that donated liver. This was

especially the case for those who had undergone the transplant assessment process. Many understandably found the idea of transplant distressing.

"We all…feel like we grieve…it's like we've got to wait for someone to die in order for us to live…I feel sometimes that I'll, I'll be grieving for somebody I don't even know" (016)

"You've got to honour that gift…this is like every Christmas present you're ever going to get, every birthday present you're ever going to get…It's almost a duty of care really to look after that liver for, for that person, isn't it…I will look after it, as if it's one of my own kids" (010)

Those participants awaiting transplant described waiting for the call that could come anytime. In the meantime, their life was on hold:

"I want my life back, erm, and…it is quite upsetting that I'm relying on someone else basically to pass away…for me to have my life back…feel like I'm in a draw, like there's so many people with PSC that are similar to me, more advanced than me and they've not had transplants" (016)

"I absolutely hate thinking I'm going to have to have that operation to be able to erm start living my life again, so right now my life is on hold for that operation until afterwards and I can start living my life again" (023)

Overall, many of participants described knowing that transplant was in their future and how they coped with this. Some described the risks associated with the surgery and three participants described how the PSC could come back in the transplanted liver. Two participants were unsure if they would accept a transplant:

"I think what scares me the most is the fear of death but you know there's not many people that die from PSC now. I mean most transplants are successful, er, you know not many that have problems afterwards or recurring but I suppose you just kind of deal with it" (011)

"I've had a really good life, I've had an amazing marriage. I've had a brilliant business, fantastic parents and I can see that if you were in your twenties like (another PSCer), that you would want to do the liver transplant…but for me…I do not want to spend the rest of my days at the moment, being a burden and you know, just this constant round of hospital visits, I don't want that" (015)

Nearly a third of participants discussed their worries about developing cancer. Some felt that PSC was a scarier diagnosis than cancer:

I haven't actually told my mum…I told her I had cancer but I thought this diagnosis is so scary I didn't really want her to worry (019)

There are days when I wish I had cancer because at least you can try, there is actually something you can do. It might not succeed but actually you can do something, you can have some sort of treatment and it might make a difference (021)

Death was discussed by 15 participants. For most, this worry was acutest when they were first diagnosed, not helped by high profile media cases. However, over time, many became able to rationalise their personal risk of dying:

"I don't think I'm going to die tomorrow and it's not the worst thing in the world" (024)

"There was a tennis player…Elena Baltacha had it…She was a, like she was a, a pro tennis player one month and then six months later she had, she had died" (022)

"There's a good chance that I have this to the end of my life and I die of something else" (020)

8.4.2.6.2 Uncertainty

Despite worries about transplant and mortality, the inherent unpredictability and uncertainty of PSC appeared to affect them the most; as discussed by all participants. Not knowing how or when they might progress or when symptoms would hit, appeared harder than it actually happening.

"For me I think it's the fact that you don't know what the future holds…you don't know whether you're gonna be ill…if you had an end date in life then I think for someone like me that would probably be a lot easier. It's the not knowing" (015)

"So apart from the actually physical, medical aspect of the PSC, which has been horrendous at times, and the unpredictability of it is one of the worst things…it's like flicking a switch" (026)

The variability in their day-to day symptoms, without obvious correlation, was difficult for most participants to rationalise; many described not feeling able to plan for the future or even tomorrow. This had a big impact on work, social events and travel plans:

"I would be living the life of a saint and I'd get an attack…other times I was maybe pushing myself a bit hard…and not a whisper. I was fine…there was no correlation" (023).

"I never plan now. I wouldn't even plan today for the weekend because there's every chance whatever I plan to do, I probably wouldn't be able to do it" (021)

"We went on holiday a couple of years ago…I was really awful for three out of - four out of the seven days we were there…if I book a holiday and I'm going to feel ropy what's the point of going on holiday?" (014)

One participant described the rare days when they felt well, of feeling almost superhuman:

"It the moment I'm feeling brilliant. I feel normal…and this can happen for two or three days and it's almost like…a euphoria that - not that it's gone away or anything like that because I know that's not the case, but when it's good days it's like almost indestructible" (015)

8.4.2.6.3 Acceptance

Around half of participants described developing a level of acceptance, especially those with more severe disease. Descriptions included not wanting to *"give in" (014*); taking control seemed important, as did adjusting to their new life trajectory.

"You've kind of got to say like you rule your life not your PSC because if you let your PSC rule your life then you'll probably never get out of bed" (011)

"I learned…reassessing the new…getting to know the person that you are now, with liver disease and what that means" (024)

"I'm a very much a 'choosing life' person. I think I just... I want to have the best experience that I can within the constraints of what I've got" (023)

Ten participants described feeling lucky; perhaps due to having access to good medical care or transplant, or currently having milder disease. A small number felt lucky to have PSC overall, as it had spurred them to enjoy life more while they could:

"I'm very blessed, I think that…when you see the 20 and 30 year olds in the state that some of those are in…I've got off very lightly…I feel quite blessed" (015)

"I know I've said I think I'm quite lucky 'cause I'm doing all right but I don't think anyone is lucky with PSC" (018)

"I feel very grateful…because if I was born 25 years ago…I'd probably be dying"(023)

8.4.2.6.4 Helping themselves

Most participants expressed a strong desire to help themselves any way possible. Many chose to stop all alcohol intake (lest it hasten progressive disease) and described how they had made other lifestyle changes:

"I knew I had to change my lifestyle…you kind of just have to adapt your life and change it a little bit. Try and live as much of a normal life as possible" (011)

"I know that I won't be able to do…certain job…I had to make, make a lot of adjustments, I had to…organise my life around health. I have to pay more attention to health than…other healthy people" (012)

Dietary changes were felt to be key, especially by those with co-morbid IBD. Alternative therapies were also commonly explored, anything that might help their symptoms or prevent progression:

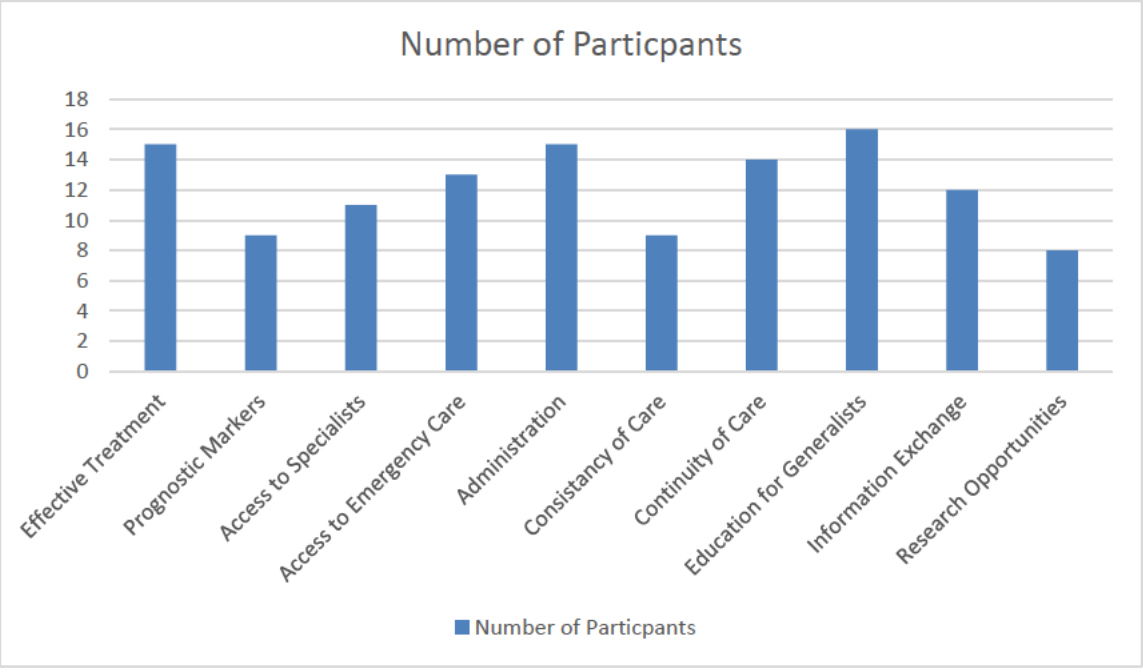
"I changed my diet...started looking at homeopathy…I had a fantastic year after I discovered the diet stuff" (023)

"I've also started er … trying alternative treatments. So, for instance, traditional Chinese medicine and er, and its herbs…I've even seen a functional doctor erm and I was really hoping that I could avoid a transplant, erm but unfortunately it didn't happen, I will need to have a transplant" (012)

8.4.2.7 How experiences can be improved

All interviewees felt strongly that their management could be improved (Figure 10). Over two thirds of interviewees wanted more research so an effective treatment could be found quicker. Other priorities included improved access to expert medical care, an easier to navigate health system and improved co-ordination with other specialities. In particular, patients wanted access to more detailed information about the progression of their own liver disease and what trajectory they were personally on. Patient priorities are discussed further in Chapter 6.

Figure 10: Interview participant priorities for improving future healthcare



8.4.2.7.1 Telemedicine

If not spontaneously discussed by participants, direct questioning was to ensure discussion of opinions regarding telemedicine. The cohort was split; a third were happy to accept a virtual consultation, a third would not, and the remainder would accept this under certain conditions, as described below.

All participants could rationalise the benefits of introducing telemedicine. Removing geographical barriers to accessing specialist care was frequently cited as a strong advantage.; interviewees felt it would improve quality of care and ensure timely referrals for transplantation. Cost efficiency was also acknowledged, along with a reduced patient burden of travel, especially for those who were unwell:

"I'd be quite happy doing it…I've chatted in clinic with some people who travel down from Cheshire and you know so they're on the road for a whole day…certainly for people travelling any distance I think it's absolutely brilliant" (014)

"I think that's a real big step forward because you've got sick people who then have 100 mile journey to get to see the, the, the specialist. So they sacrifice better care for convenience, don't they?" (017)

"If you're able to bring in the skill of a hepatologist whose 200 miles away so you can't go see them and match that hepatologist with the right patient over video then absolutely" (020)

However, nearly half of participants described how telemedicine might not be right for them personally. Two felt it was generational, with the younger generation being more comfortable with remote online technology:

"I think I'm too old fashioned for that….I would personally prefer, I think, to still see a doctor…but if the only way I could see a Specialist was through the internet erm, then I would do it" (010)

"I think there's a big difference between erm, the, the technology generation and perhaps an, an older generation" (017)

Participants often described telemedicine as being useful in certain circumstances, although not all agreed on what these might be; most commonly it was felt best in early or stable disease:

"If there isn't any erm … deterioration or improvement in a, er let's say in a disease, and the appointment is only…to have the patient come for blood tests, er that could be replaced with an, er with an online consultation" (012)

"When you are at that stage when you've got advanced liver diseases you are going to have to be face to face I think" (018)

A major concern for participants was that a virtual consultation might be inferior to one face-to-face; many felt that a video consultation could change the dynamics of the consultation and make it harder for the clinician to assess them properly. Most were hesitant at the thought of giving up all face-to-face contact and would only accept a virtual consultation with a doctor they had previously met in person and developed a rapport with:

"When I sit down with you for the first time, I'm making judgments about whether I like you as my doctor but you're also deciding that I'm a neurotic, you know, middle-aged woman that – or, you know, some old windbag who just thinks they've got everything wrong with them…I think you do, you do get something else out of having a face-to-face appointment... and most

of these, most of these relationships you're going to have with a hospital are going to go on for a long time, aren't they?"(017)

Participants felt that a face-to-face consultation might allow the doctor to better pick up non-verbal clues that might be missed remotely. Concern was raised about potentially missing important clinical signs, such as early jaundice.

"I think it's a lot of the way you say it and the way your body is when you're answering the questions…whether that would transfer over the TV screen… I'm not sure" (010)

"I think often when you're face to face with somebody you can tell whether they're being fully open with you or whether they're sort of skirting round an issue and trying to avoid *saying something" (014)*

"It might make it harder for the actual doctor because they may not be able to see you as clearly as when you're sitting in front of them. Erm, they may not pick up on your, on the vibes…If you feel nervous or frightened it may not come across as easily" (026)

Participants also mentioned the logistics of not going to the specialist hospital for their appointment and how they might not therefore receive their usual monitoring. A minority of participants described making the long journey a pleasant day out and not simply a hospital appointment:

"It might mean you need less of those tests because you're getting a better appointment, that might be a good thing but…I'd slightly worry that it might mean that people might get less tests that they need" (018)

"I actually enjoy being able to sort of think, right, I'm gonna go to (transplant centre) today, I'm get on the train. I'm gonna go up to this absolutely marvellous hospital and I have my appointment" (015)

However, some felt a virtual clinic appointment would not change the consultation; this was usually younger participants (<40 years). A small number felt the consultation even might be improved as they might be less nervous being in their own surroundings:

"I don't think it would feel much different because you can still see them, they can still see you and talk to each other" (011)

"Sometimes you, you might be less nervous on the phone…if you, at home if you're more relaxed you might remember to say everything that you need to say" (018)

Having the required technology for a successful virtual consultation was also a concern. This included whether the virtual clinic link would be reliable and what technology was needed:

"There might be disadvantages in that people don't know how to do Skype and they need a lot of guidance…every time Skype does an update you waste so much time waiting for people to figure it all out and get online" (018)

8.4.2.8 The patient journey summary

In this initial interview analysis, it is clear that PSC presents a large physical and psychological burden on those affected. Patient participants saw their experiences as a long and arduous journey and many were deeply affected by the uncertainty of where their journey would end.

Participants described numerous areas of their healthcare that they felt needed improvement. Many had experienced perceived long delays to their diagnosis and described how they should have been given much more information upfront by their doctor, most of whom appeared to know little about PSC. Some described becoming disenfranchised by the healthcare system, critical of the attitudes of its staff, and generally untrusting of anyone except a PSC specialist. Potential changes to their management such as telemedicine were seen positively to improve access to specialist care while at the same time being less onerous on the patient themselves. Despite this, many participants wanted to retain their in-person consultations, which were felt to be of more value to them than a virtual clinic might be.

While PSC itself is a rare disease, it remains a chronic illness. Around 15 million people in the UK have a chronic illness[145] and there is much in the literature surrounding the experiences of these patients. There are many accepted models of chronic illness behaviour however, it is not known how the PSC patient experience reflects or differs from this; exploring this may allow lessons learned from the management of other chronic diseases to be applied to PSC and any differences identified might allow more targeted changes, all for patient benefit.

Therefore, Part 2 of this analysis compares and contrasts the PSC patient experience with accepted models of chronic illness behaviour.

8.4.2.9 How is PSC different from other chronic diseases?

There are many accepted models of chronic illness behaviour in the literature. One publication is Sociology as Applied to Medicine edited by Graham Scambler, originally published in 1982[146]; this textbook is commonly used in the UK medical student syllabus and thus many UK-trained doctors are familiar with its contents. Within this text there is a chapter on living with chronic illness by David Locker; this chapter has been used to interpret, compare and contrast the illness behaviours of PSC patients with accepted models of chronic illness behaviour.

Within the text, David Locker discusses five major themes on the experience of chronic illness; uncertainty, family relations, disrupted biography, managing medical regimes, and the importance of information. All five themes were observed within the interviews along with the importance of the doctor-patient relationship. These themes will now be discussed; no new interview quotes are included here as they are already presented in the above timeline analysis.

8.4.2.9.1 Uncertainty

The striking theme throughout the interviews was of the uncertainty being the worst aspect of PSC. PSC has high rates of transplantation, cancer and death yet it is not always clear which patients are at highest risk. Timescales are difficult; patients can deteriorate quickly and without warning. Given the lack of effective treatment to ameliorate this progression, it is understandable that the unpredictable nature of PSC would cause great distress.

Interviewees described an almost perfect storm of uncertainty, as described by Locker[146]. This includes the often-long road to a diagnosis (pre-diagnostic uncertainty), followed by having to

cope with the uncertain long-term prognosis (trajectory uncertainty) as well as the daily fluctuations in symptoms (symptomatic uncertainty). The effects of wide variability in symptoms is recognised in the literature; the coping mechanisms employed by the patient have to constantly vary and every day therefore becomes an additional mental trial[147].

While this is not unusual in other chronic diseases, the lack of validated disease modifying treatment or monitoring strategies in PSC is unusual, and compounds this uncertainty further. Therefore, it is not surprising that PSC patients experience a large psychological burden. It is likely this impacts hugely on their health-seeking behaviour, their need for information and to find reassurance from a doctor they trust. This doctor was often a specialist and access to this was seen as highly important to many participants.

8.4.2.9.2 Family Relations and the Sick Role

Interviewees was described PSC as having a profound effect on their social and family relationships. PSC's rarity coupled with prognostic uncertainties left participants feeling isolated and undoubtedly affected partner's also. The most profound effects were observed pre-diagnosis; participants described family as becoming progressively less supportive only for this to be reversed once a diagnosis was finally confirmed.

The importance of having a diagnostic label is important. In 1951, Parsons described the phenomenon of the sick role where patient and doctor have their mutual obligations[148]; the doctor must provide treatment and otherwise legitimize the sick role while the patient must comply with the doctor's orders. In return the patient gains temporary exception from their normal responsibilities in society and cannot be held responsible for not fulfilling these.

This traditional model cannot apply in PSC; there is no effective treatment and patients often know more than their doctor so cannot blindly follow their instructions. However, the fundamental need for legitimisation of the presence of illness remained important to patients.

8.4.2.9.3 Disrupted biography

Once a diagnosis was achieved, the subsequent reactions of participants closely resembled an acute grief reaction. Participants described a period of grieving for their lost health, which for many was described as being exceptionally active. Some took this further to mourn the life they thought they would have lived but no longer was thought possible.

Similarities were observed to the accepted Kubler Ross & Kessler model, including denial, anger, bargaining, depression and acceptance[149]. Participants described anger at having PSC despite often leading a particularly healthy lifestyle, at their medical team for not managing them better, and anger at themselves for accepting previous reassurances that they were healthy despite their symptoms. Depression was also observed. Participants described feelings of existential crisis, knowing they were a ticking time bomb with an unknown expiry date. Many described needing ongoing psychological support; over half of participants subsequently received treatment for depression and or anxiety.

Participants described previously having been on a certain trajectory in their lives that was now not possible. This is well described in the literature, being described as the “loss of self”[150], a “biographical disruption”[151], or an “existential crisis”[152] observed after the diagnosis of illness, with reconstruction of this narrative being key to long term coping.

Interviewees responded variably to this loss of identity and some developed a new master identity, that of being an ill person with PSC. While the severity of the disease potentially impacted upon this, the most striking psychological impacts were observed in some of the least physically affected individuals.

Many participants had lived with IBD for years prior to the PSC diagnosis; these adjusted quicker to having PSC than those without pre-existing illness. This is potentially explained by them already having adopted the sick role and having readjusted their primary identity or expectations of what normal health is. This is supported in the literature; self-definition of disability can vary between individuals[153] and there is a health paradox where previously healthy individuals may self-identify as now less healthy than those with significant pre-existing illness[154].

A gender difference is also described, where women tend towards higher morbidity than men, despite lower mortality[155]. Of interviewees, women were observed to have objectively less severe liver disease yet a lower self-perceived quality of life. It is acknowledged that women can have stronger feelings of vulnerability to illness, greater felt stress and an overall different perception of their own health[156] when compared to men. The domestic burden carried mainly by women, even in modern times, may also impact this[157].

Adding further complexity are the co-morbidities seen with PSC and some participants demonstrated their primary illness identity to be these, not their PSC. The opposite was also observed; some participant's identity was very PSC dominant yet their doctor was less concerned due to there being objectively mild disease. Given the clinical dis-connect between subjective PSC symptoms (such as fatigue) and quantifiable biochemical abnormalities; there

is the potential for doctor and patient to have conflicting views over the severity of the disease. This “maladjustment” can lead to ongoing tensions between doctor and patient[153].

Almost all participants described difficulty in re-adjusting to their new trajectory. Many eventually accepted they would experience a slow but inevitable deterioration, but then were surprised by sudden fluctuations in their symptoms. It was thus difficult for participants to develop “narrative reconstruction”[152] i.e. a new narrative and identity within the world and to make sense of their new place within it. This was particularly profound in PSC participants and relates again to the overall uncertainty they face.

8.4.2.9.4 Managing medical regimes

Given the lack of disease-modifying treatment for PSC, most medications prescribed were to relieve symptoms, with variable success. While some participants reported a high daily pill burden (likely exacerbated by other co-morbidities), others described taking almost nothing which is unusual in typical chronic disease management. The lack of medical treatment was found frustrating by participants, adding to their lack of control over their fate and psychological burden of disease.

Important in PSC monitoring via scans and blood tests to assess for progression, thus allowing timely referral for transplantation if needed. This regular interaction with (often multiple) hospital led to administrative difficulties and errors. Participants described learning how to manipulate the health system to their advantage and ensure they received good care. However, negotiating the inflexible and confusing medical administration system was hard, especially when they were feeling unwell. Given these difficulties, participants felt that

specialist involvement was critical; again unusual in most chronic disease where services often widely available.

Participants described the burden of their medical management being less consuming than coping with the symptoms, especially fatigue which has no specific treatments. This contrasts to most chronic diseases where there are effective treatment regimens, although these in turn may be more demanding than the disease itself[158].

8.4.2.9.5 The Importance of information

Information was seen by most interviewees as vital. They described detailed research searching for a better understanding of their situation, whether it be the cause of PSC, their prognosis or where they might receive optimal medical care. This is observed commonly in chronic illness; information is purported to reduce the uncertainties faced by patients, to help them cope and leads to the formation of the "expert patient"[146].

However, given the lack of consensus on the best treatment strategies, this search for understanding commonly led to further frustration. Participants described episodes of direct conflict with doctors who thought they knew more, but did not. Distrust of non-specialist doctors was a common theme observed as many became reliant on their specialist for almost all information; they felt other sources were untrustworthy. Finding others with PSC helped reassure participants that the information they had found was accurate and that their care was the same for everyone else.

Accepting PSC was observed to be improved if participants were able to relate general PSC knowledge to their own individual circumstance. Many described wanting to know where they

were on the severity scale and quantification of any changes occurring over time. Most participants seemed certain they were on a trajectory towards liver transplant and wanted to know the timescales involved. PSC is unpredictable, leading to worsening anxiety for participants and further frustrations with their medical team.

8.4.2.9.6 Doctor-patient relationship

The relationship between them and their clinician was important to participants, whether this be a doctor or other allied health professional. The use of the word "doctor" throughout this analysis reflects the traditional descriptions within the literature but relates to all healthcare professionals managing such patients.

Three forms of doctor-patient relationship have been proposed. The original model from Szasz & Hollender[159] proposes the "active/passive" form (reflecting the traditional paternalistic medical model of disease), "co-operation-guidance" (in which the patient is more involved but the doctor continues to guide proceedings), and "mutual participation" (with equal input from both parties). In 1970, Friedson revised these to create two further categories, "guidance-co-operation" and "passive/active"[160]. In both of these it is the patient taking the lead, not the doctor. All five forms of therapeutic relationship were observed within the interviews, However, the least common of which was the original active/passive form. This traditional medical model of disease[148] is less relevant in modern day society where responsibility is now being placed upon patients to manage their disease in a more equal partnership with their doctor.

Additionally, a slow but steady loss of faith and trust in the medical system and in their doctors was described by participants. Most interviewees who initially accepted the traditional sick role learned from these their poor experiences and become their own advocates, thus changing the nature of their therapeutic relationships to a more patient-led or equal balance. Given the vacuum of treatment on offer, patients may be more motivated to find their own answers than would normally expected in chronic illness.

A further example of the tensions observed within the therapeutic relationship was the interest in exploring non-orthodox medicine, with many participants' discussing herbal and other more holistic treatments. This rebels against the medical model of disease and demonstrates how participants want to improve their holistic needs, which are not being addressed by their doctors. This is commonly seen in chronic illness; when patients are disappointed in orthodox medicine[161]. Interviewees demonstrated a strong need to meet other similarly affected individuals, such as via PSC Support. The holistic benefits of being part of such a group is described as a form of non-orthodox medicine, filling in further for the deficiencies in what traditional medicine is able to provide[155].

Patients with chronic diseases requiring lifelong medical management often develop close professional relationships with their doctors, described as "one long consultation over a lifetime"[162]. However, the difficulties in PSC create tensions within this relationship that must be overcome. Many doctors know little, if anything, of PSC which can immediately causes a rift between doctor and patient, the latter of which may assume the role of educator, as was demonstrated in many interviews. It is unsurprising therefore that interviewees placed great important on receiving consistency of care from the same trusted clinician. A "dose of doctor"[155] is described as having therapeutic benefit in itself, likely especially important when no therapeutic treatment is available.

8.4.2.9.7 Summary of analysis Part 2: Comparison with other chronic diseases

The PSC patient experience described within this thesis does mirror that described in other chronic illnesses. The importance of a diagnosis, the disrupted biography, the difficulty in managing medical regimens and the importance of the therapeutic relationship were all common themes observed and are well recognised in the literature. However, the severity of uncertainty observed in PSC is particularly high, resulting in great psychological impacts, which should be acknowledged by those managing their medical care.

8.5 Discussion

This study aimed to gather information on the patient experience of PSC including the related healthcare. Particular information was collected on opinions to alternative methods of clinical consultation such as telemedicine, linking directly into incoming changes in a large PSC cohort seen at QEHB. It also aimed to establish similarities in these experiences to other chronic diseases and to highlight particular challenges faced by PSC patients. This study has highlighted practical improvements in clinical management which are important to patients and are achievable now, while research is ongoing; this is discussed further in Chapter 6.

8.5.1 Study Findings

The main thematic analysis of this study identified the importance of the timeline. Five check-points have been identified, common in all participants, and individual sub-themes within these explored. As expected, heterogeneity of experience was observed, however, all participants described how their journey should have been more straightforward.

The lifetime patient burden of PSC has been confirmed. The majority experienced frequent physical symptoms that fluctuated without warning and were often difficult to control. Despite what is commonly described about PSC in the textbooks, fatigue was the dominant and most debilitating symptom experienced by interviewees. This is likely under appreciated by clinicians

Even in the absence of debilitating symptoms, the psychological burden of having a PSC diagnosis remained severe for most. The potential severity of PSC was clear to all participants, with some already undergoing assessment for liver transplantation. Almost all participants

described a fundamental change in their future trajectory with additional changes in their everyday lives to accommodate their PSC.

In addition to symptoms, participants described struggles in receiving optimal medical management, especially pre-diagnosis. They described having to navigate complex administrative inflexibilities across multiple healthcare providers and generally advocate for themselves; resulting dependence on specialist management was observed.

8.5.2 PSC as a chronic disease

Chronic illness affects millions of people in the UK; this study therefore conducted additional analysis to identify similarities and differences in the PSC experience, to that of other chronic diseases, using models from the established literature[146]. As expected, PSC fills many of the standard and accepted chronic disease challenges.

However, PSC has a number of features which reject these standard models of chronic illness. The absence of treatment is rare in modern medicine and traditional medical models of disease can no longer fully apply. The combination of this, in a rare disease, and the inherent prognostic uncertainties cause additional anxiety for patients and doctors alike. Common end-points of transplant, cancer or death are difficult for patients to process, with no real options for preventing these developing. This all creates particular strain on the doctor-patient relationship and repair of this seems vital to the patients' successful negotiation of the hurdles ahead. These factors set PSC aside from other chronic diseases that may have more predictable progression, disease-modifying treatment, and less fluctuation in often debilitating symptoms.

8.5.3 Limitations

The study was advertised by PSC Support via postal and online media. While valid attempts were made to purposively select participants with varying backgrounds, there was no interest received from patients from an ethnic minority. While a common phenomenon in research[163], this has introduced a selection bias into the study findings. Those who did volunteer for the study were already a member of PSC Support and are likely to have had their own agenda for wanting to be included; these may thus be less representative of the general PSC population.

The interviews asked participants to recall events retrospectively, without independent verification. These events had often occurred many years prior and at a time of great personal distress, thus introducing a recollection bias. However, these memories remain valid as an important consequence of patient experiences.

The study has included a mixture of face-to-face and telephone interviews. This was a rational decision to allow a wider range of participants to partake, however, the differing mediums could have affected the results[164]. Also acknowledged is the potential subliminal effect the researcher themselves can have on the interview results and the analysis. The interviewer and author of this thesis is a medical professional working in this field, thus may have their own subconscious agenda. While adverse effects of these potential biases were minimised, with appropriate training and supervision by experienced qualitative researchers, it is not possible for any human to be completely impartial.

Finally, the medical teams' perspectives have not been included nor have those of the management team or those in charge of financial renumeration for virtual clinics. These gaps in the literature remain unexplored and would be of use to complement or contrast against the patient experience described within this chapter.

8.5.4 Strengths

Despite limitations, a large dataset has been methodically collected of PSC patient experience, which has not previously existed. Participants were from across England, Scotland and Wales and the study included participants of a wide age range and across the severity spectrum of disease. This study has highlighted real-life challenges faced by these patients which will lead to realistic suggestions for change that could improve experiences for not only PSC patients, but also those with other chronic diseases; these are discussed further in Chapter 6.

8.5.5 Implications for further research

This interview study has confirmed the burden of disease faced by PSC patients, along with limitations in how they are currently managed. Patients need effective treatments and research must continue to focus on this. In parallel, better ways of monitoring PSC and in ameliorating it's symptoms are required. The development of improved risk stratification strategies will likely hasten new interventional clinical trials with more relevant end-points and allow for more accurate assessment of new disease-modifying drugs; this may involve imaging modalities such as quantitative MRI scanning (Chapter 5).

Changes are also needed in the way PSC is managed to ensure equal access to consistent care, without unduly burdening the patient. Telemedicine may have a role and was popular with interviewees. However many would prefer some face-to-face contact and the complexities of the clinical relationship in this cohort was evident. The potential utility and acceptance of telemedicine in PSC will be discussed further in the next Chapter.

CHAPTER 4:

Understanding the international experience of the use of telemedicine in PSC via a scoping review and investigating attitudes towards this technology in the PSC cohort at QEHB via questionnaire

9 CHAPTER 4: UNDERSTANDING THE INTERNATIONAL EXPERIENCE OF THE USE OF TELEMEDICINE IN PSC VIA A SCOPING REVIEW AND INVESTIGATING ATTITUDES TOWARDS THIS TECHNOLOGY IN THE PSC COHORT AT QEHB VIA QUESTIONNAIRE

9.1 Introduction

Earlier chapters within this thesis have confirmed the substantial burden of PSC on patients and clinicians alike. Along with new treatments, improved access to specialist care was a clear priority for patients. One proposed method of improving access to care is the use of telemedicine and this may have a role in PSC and other chronic diseases, especially those that are complex , rare, or which require specialist input.

However, the 2016 Cochrane review into telemedicine stated that cost and acceptability to patients of the use of telemedicine, were still unknown[99]. Additionally, only 36 of the 93 studies included within the Cochrane review focussed on real-time video-conferencing and no study looked specifically at patients with liver disease; just six studies were carrying out specialist consultations[99]. This is all further indication of the paucity of data in the use of this technology in liver disease, and especially in auto-immune liver diseases, such as PSC.

At the time this research was being conducted (2015-2018), QEHB was introducing video link virtual clinics into outpatient services (Chapter 1), to be piloted in the weekly PSC clinic. Given the paucity of data regarding telemedicine in rare diseases, including PSC, and the incoming QEHB virtual clinic, this was a timely and pragmatic opportunity to assess the opinions to this form of consultation in this important patient group and to support the new virtual clinic.

This chapter describes two forms of investigation into PSC patient perspectives of telemedicine. Firstly, a scoping review was performed to update on literature published since the Cochrane review. This led to a questionnaire study in a large single-centre PSC cohort

(housed at QEHB) which included questions aimed at quantifying the personal burden of attending specialist appointments and their opinions on telemedicine.

The emergence of Covid-19 necessitated the widespread and rapid adoption of virtual clinic technology internationally, without the opportunity for discussion with patient groups. This research pre-dated the pandemic and thus reflects true patient opinion untainted by recent experiences. The effects of this are discussed in more detail in Chapter 6.

9.2 Scoping Review of telemedicine in PSC

9.2.1 Rationale

Before embarking on further new investigation into telemedicine in PSC and other liver diseases, a scoping review was first performed to review the literature and to inform the direction for further study. The initial idea, planning, performance and analysis of the scoping review were completed by the Author (KA), with reflection and supervision from the supervisory team.

The rationale for performing a scoping review is to "map rapidly the key concepts underpinning a research area and the main sources and types of evidence available"[165]. This approach was appropriate as there were likely few new specific studies done on this subject in the published literature since the Cochrane review board completed their data search in June 2013, just three years prior.

9.2.2 Aims

The aim of the scoping review was to assess the literature for evidence that virtual clinics were an effective alternative to face-to-face practice for the management and monitoring of people with chronic liver disease, PSC in particular. Evidence for video consultations was of special interest, reflected the similar service incoming at QEHB.

9.2.3 Method

The scoping review was based on the five-step approach described by Arksey and O'Malley in 2005; the first published framework for conducting such reviews[166]. These five stages are:

1) Identifying the research question
2) Identifying relevant studies
3) Study selection
4) Charting the Data
5) Collating, summarising and reporting results

The literature review was completed in 2 stages; firstly, the Cochrane review search strategy was applied to the post June-2013 literature, however limiting this to include just video-conferencing techniques, to reflect the incoming QEHB virtual clinic (Stage 1). Due to low volume of results, these criteria were then relaxed and additional criteria inserted to allow a greater focus on liver disease (Stage 2).

Multiple databases were interrogated in both searches, for new articles published until November 2016. These databases were PubMed, OVID Medline, Open Grey, Cochrane Library, Embase, PsychInfo, Scopus, Web of Science and CINAHL. Reference lists were searched and duplicates were removed. All articles were considered for inclusion, if they were in the English language, included a control group on standard care and where the remote video consultation occurred with the patient present live at one end. The abstracts of potentially relevant articles were reviewed and articles were excluded as per the above criteria. For potentially relevant articles, the full article was reviewed in detail, where this was available.

Relevant articles were interrogated to appropriately collate and summarise the data from each article. A chart was created to include the authors, publication date, population studied, the number of subjects, the methodology used and the main focus of the study. Themes were then identified for discussion.

9.2.3.1 Stage 1: Re-applying the Cochrane review criteria

The Cochrane search strategy was replicated to update the review. The Cochrane review excluded studies with less than 10 participants in each arm; however, all studies were included in the initial search within this review. Full search and exclusion criteria can be seen in Box 1.

BOX 1. Scoping review stage 1 search strategy & exclusion criteria

A) SEARCH STRATEGY

Search ((telehealth OR telemedicine OR telenursing OR teleradiology)) AND (video OR "remote consultation"). Sort by: Relevance Filters: Publication date from 2013/07/01 to 2016/10/31. In English. In humans. Clinical trials.

B) EXCLUSION CRITERIA (based on the Cochrane review criteria)

1. Studies that compared different technical specifications of telecommunications technologies.

2. Studies in which the use of telecommunications technology was not linked to direct patient care.

3. Studies in which the patient was not physically present at either point of care, e.g. studies evaluating the electronic transmission of X-ray images or pathology results for routine reporting for example, 'store and forward' systems with no interaction between the patient and healthcare professional.

4. Patient monitoring systems in which the patient received only an automated voice response.

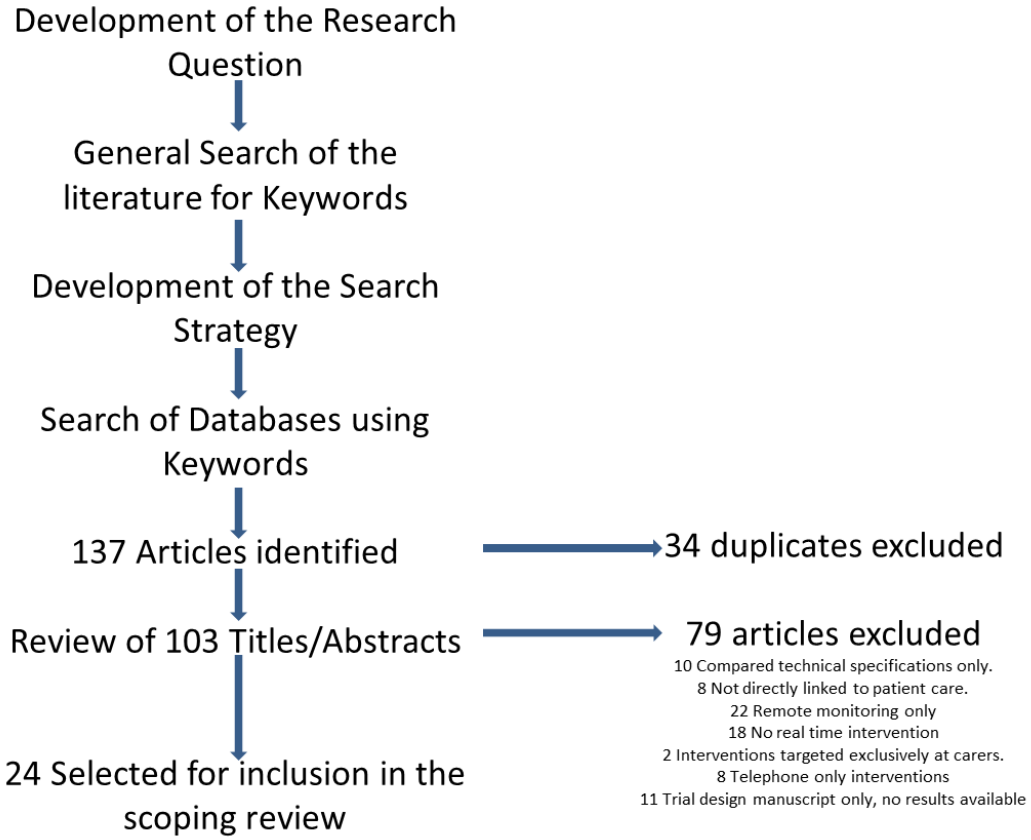
5. Interventions targeted exclusively at carers.

6. Telephone only interventions as for some conditions usual follow-up care routinely includes telephone follow-up.

7) Trial design manuscript only, no results available

103 articles were found during the literature search, however 79 of these were subsequently excluded after abstract review as falling outside the study criteria. The remaining 24 studies included were subsequently analysed. Given the small amount of literature available, the relevant abstracts were included. The search strategy is depicted in Figure 11.

Figure 11. Scoping review stage 1 search strategy flow chart



The 24 studies included were all Europe, Canada or USA based. One was only available in abstract form. A variety of medical conditions were included; twelve studied chronic medical diseases, five studied post-operative surgical management, one dermatology, one smoking cessation and five studied psychiatric disorders. A total of 3101 participants were recruited. A full summary of the characteristics of these studies can be seen as Appendix G, along with the reference list.

9.2.3.1.1 Stage 1 Scoping Review Results

While a variety of medical conditions had been investigated with telehealth interventions, none included patients with chronic liver disease, further confirming the paucity of data in this important and expanding subject area.

Some studies suggested improved outcomes in the telemedicine groups (for example in diabetic control, heart failure diagnosis, and in post-traumatic stress disorder). Five studies reported no differences in outcomes between the groups, however did report cost and or time savings in the telehealth group. Patient satisfaction in their telehealth experience was reported to be at least equivalent in all but one study; the latter involved patients undergoing plastic surgery. However, the addition of a telemedicine programme to chronic obstructive pulmonary disease care did not reduce acute admissions. Mortality was increased in another telehealth group suffering diabetic foot ulcers. One study reported 22% of participants experiencing technology problems.

These results indicate that telehealth outcomes may be at least equivalent to standard care for some medical conditions, but not all. No evidence was found in chronic liver disease.

Where equivalence exists in outcomes and patient satisfaction, economic savings and or patient preference may justify the use of telemedicine. However, while evidence exists that in some situations telehealth may result in inferior outcomes, or where there are significant technological barriers, caution must be taken when introducing new telehealth services.

9.2.3.2 Stage 2: Relaxing the Cochrane criteria

Neither the 2016 Cochrane review, nor the above updated search, were able to identify any liver-specific studies for the use of telemedicine in conjunction with remote video consultations. Thus, the inclusion criteria were subsequently relaxed with additional criteria to specify liver disease. Studies with under ten participants were now included and the date limitations and need for it to be a clinical trial were moved. The full search and exclusion criteria can be seen in Box 2.

BOX 2. Scoping review stage 2 search strategy & exclusion criteria

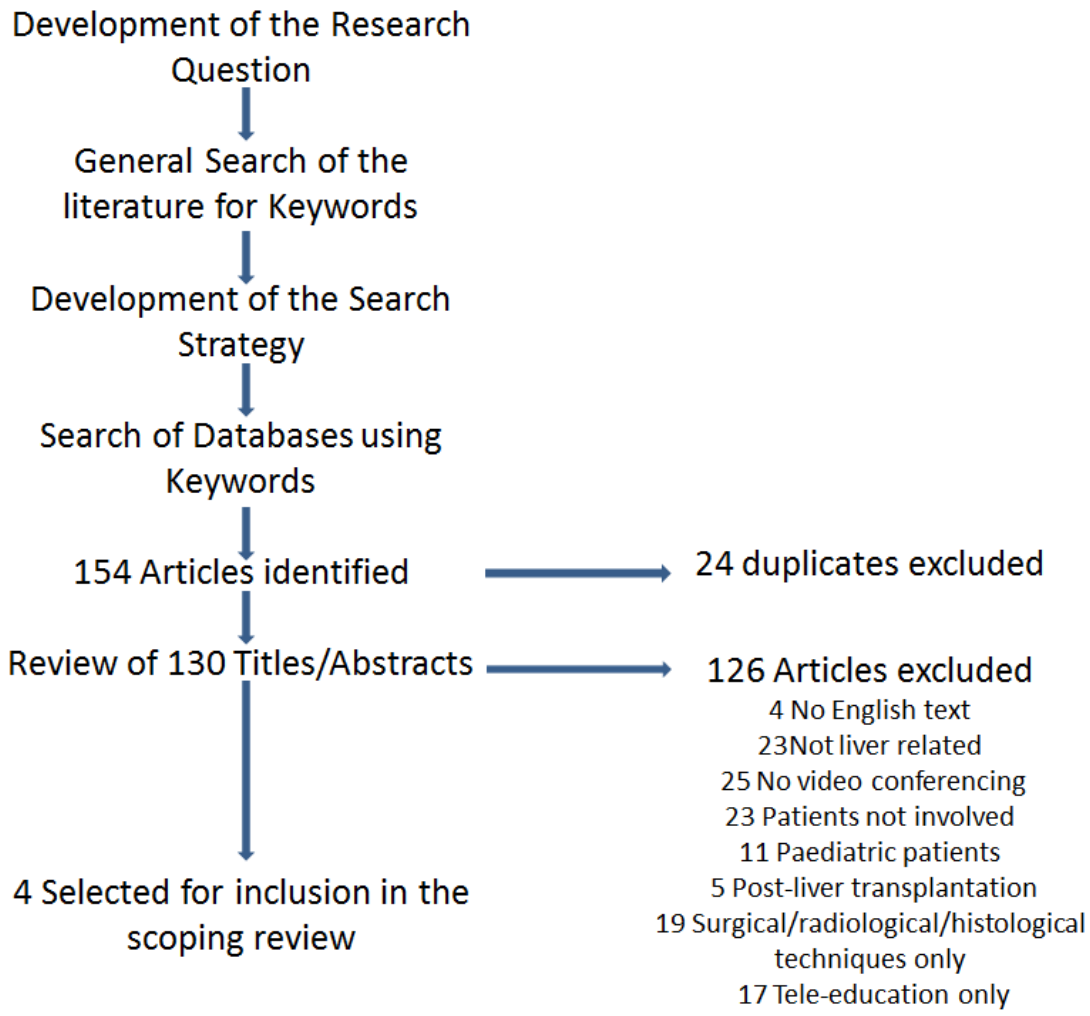
Search all fields: ((liver) OR (hepatol*)) AND (tele* OR "virtual clinic"). Sort by: Relevance

Filters: In English. In humans.

Exclusions included paediatric patients, video surgical techniques rather than consultations, tele-education rather than consultation and those who had already undergone liver transplantation, as these patients represent very specific groups which likely differ from the norm and these will not initially be included within the local virtual clinic service.

130 potentially relevant articles were found, after excluding 24 duplicates and including the reference search. All abstracts were reviewed and 103 were excluded as per the above criteria. The remaining 27 articles were reviewed in detail, with a further 22 excluded. 5 articles were remaining however 1 article had no abstract or data available. The search strategy is depicted in Figure 12.

Figure 12. Scoping review stage 2 search strategy flow chart



The four included studies were all UK, USA or Australia based, however three manuscripts were only available in abstract form; these were included given the low volume of results. A total of 209 patients were included, 150 of which had a diagnosis of hepatitis C virus (HCV). Most studies were quantitative evaluations of patient satisfaction via questionnaire. A summary of the characteristics of these studies can be seen Appendix G, along with the reference list.

The remaining full manuscript was reviewed in more detail. In their 2008 article, Rossaro et al[167] described the need for a telemedicine service to reach patients with HCV in rural California and their experience of providing such a service to 103 patients. Overall, they concluded that their service had identified significant numbers of patients needing treatment in rural communities that may not have otherwise had access to this care. They also concluded that the telemedicine service was effective in identifying and treating these patients; overall, 23% of patients were recommended for treatment. While 2% required listing for liver transplantation, both died before this could be completed, with resulting concerns as to whether identifying these patients earlier may have produced a different outcome. Overall, this study indicated that telemedicine applied in the correct areas can lead to improved access to specialist care in HCV.

9.2.3.2.1 Scoping review Stage 2 Results

All included studies were evaluations of patient satisfaction via questionnaire. Telemedicine was of interest to patients, especially to those in rural areas or whom otherwise struggled to travel. The technology used was found to be reliable and patients felt that communication quality was unaffected. Patient satisfaction was high and most felt that they received the same standard of care as a face-to-face appointment. Overall, most patients felt that telemedicine consultations were easier and more convenient than traditional consultations. One study performed a cost analysis, suggesting telemedicine clinics to be cost effective compared to standard care.

However, there remained little published evidence for the benefits telemedicine by remote consultation in chronic liver disease. Three of the four studies identified included only HCV

patients and focused on patient satisfaction, rather than efficacy. Additionally, HCV now has high cure rates with modern oral therapy taken for as little as eight weeks[168]. This contrasts to most chronic liver disease cohorts, especially PSC, which has no curative treatment and in whom patients affected have higher symptom burdens requiring extended specialist input over decades, rather than weeks.

In summary, neither the Cochrane review nor the above scoping reviews identified an evidence-base for the efficacy or patient satisfaction of the use of telemedicine in liver disease, especially in rare liver diseases such as PSC. Thus, further investigation into this is warranted, especially given the incoming virtual clinic at QEH. The following section describes a questionnaire study designed to further investigate the attitudes to telemedicine within the PSC cohort.

9.3 Investigating QEHB PSC patient attitudes towards telemedicine via questionnaire

9.3.1 Rationale

The above scoping review demonstrated a paucity of evidence in the literature for the use of telemedicine in PSC (and liver disease in general), thus justifying further research before the routine introduction of this technology into clinical care. Given time and financial constraints, a questionnaire directed at patients attending the weekly QEHB PSC clinic was the most appropriate and practical method of broadly identifying patient opinions of telemedicine.

The original idea, planning, creation of the questionnaire template, submission to QEHB for approval, distribution and collection of questionnaires, and analysis of the questionnaire data were completed by the author (KA) with supervision from the thesis supervisory team.

9.3.2 Aims

The major aim for the questionnaire study was to assess pre-transplant patient opinion of virtual clinics, given the incoming QEHB virtual clinic. This complements data demonstrated in the previously described cohort study (Chapter 2) and interviews with patient-participants (Chapter 3).

A further aim was to demonstrate the patient-related burden of PSC-related healthcare. The personal burden of attending QEHB clinic appointments, including employment (given the potential for medical appointments to impact upon this), travel times and cost, are likely to be altered by the introduction of telemedicine. However, this data is unknown and was unable to be demonstrated within the standard electronic medical records (Chapter 2).

Additionally, it was acknowledged that some patients with other AILDs were also seen in the same clinic. Including such patients was therefore was an opportunity to compare and contrast these patient cohorts to those with PSC; there seemed no logical reason to exclude them.

Specific objectives for the questionnaire were to investigate the:

1) Potential impact of telemedicine on a patient experience of outpatient clinic management including data on the frequency and longevity of follow up, employment, travel time, travel distance and the personal costs associated with this.
2) Attitudes and satisfaction of patients to the current in person clinic arrangement (including free text responses) to allow for repeat assessment of any changes once the virtual clinic was implemented and to guide further changes for patient benefit
3) Attitudes of patients to the future introduction of a virtual clinic including acceptability and concerns (including free text responses)
4) Access to the technology required to access the virtual clinic

Despite inevitable overlap with the QEHB cohort study (Chapter 2), full demographics were collected for the questionnaire participants, given the potential for selection bias with the questionnaire completion. This allows for contextualisation of the survey responses relating to the wider QEHB cohort; this is discussed further in the final Discussion chapter (Chapter 6).

9.3.3 Methods

The research adhered to the principles identified in the 1975 Declaration of Helsinki[126] and in Good Clinical Practice[127]. Patient confidentiality was maintained at all times and information governance was also strictly adhered to, as described below. While the questionnaires were anonymous, patient-identifiable information was still present therefore these were stored securely within a locked cabinet behind swipe-card access at the University of Birmingham. Electronic logs were kept encrypted with codes known only to the lead sub-investigator (KA), who was already part of the clinic team.

9.3.3.1 Development of the questionnaire proforma

The questionnaire was designed using the approved QEHB standard proforma for patient feedback. This was then adapted to ask additional questions relevant to the study aims. The Rand VSQ-9 satisfaction tool was also included as it is an internationally validated method of assessing patient satisfaction[169]; this tool asks respondents to rank their experiences of nine key domains including the quality of the communication with their clinician and any administrative difficulties they encountered. Each category is ranked poor to excellent and subsequently given numerical values; these questions can be seen in Table 20, within the below results section.

Free text options were included to encourage more detailed feedback on topics of importance to patients and to engage the target population more; this potentially encourages higher response rates and allows for subsequent qualitative analysis[170].

The draft proforma was submitted to both the QEHB Liver Patient and Public Involvement (PPI) group (6 respondents) and the Chair of PSC Support; these results and subsequent amendments can be seen in Appendix H. The questionnaire was approved by the QEHB audit team (registration 12973) and the QEHB Patient experience manager. The full final proforma can be seen as Appendix I.

9.3.3.2 Questionnaire distribution

The questionnaire was distributed to all patients attending the weekly PSC clinic for 12 weeks between 9th January and 30th March 2017. Return rates were monitored weekly. All participants attending the dedicated PSC clinic were given the proforma as they booked in for their appointment. Clip-boards, pens and a sealed post pox were prominently placed, along with clear labelling and instructions, including for the questionnaire to only be completed once per person and not repeated on subsequent visits. The investigator (KA) was available in the clinic area to answer any questions.

After six weeks of data collection, an interim analysis of return rates was completed. As this was over 80%, data collection continued with ongoing monitoring. At week 12 the return rate dropped to 47% and the investigator (KA) was aware of individuals returning for repeat appointments within the data collection period; the study was therefore halted at this point.

9.3.3.3 Statistical methods

The patient demographics, disease variables, referral information and acceptance of the virtual clinic were reported according to data type. Continuous variables were reported as medians and range. Categorical variables were reported as frequency and percentage.

Comparisons were made between the groups accepting or rejecting the virtual clinic and those with PSC or other diagnoses using Mann-Whitney tests for continuous variables, with Fisher's exact test used for nominal variables and with $p<0.05$ deemed to be indicative of statistical significance. Respondents who did not specify their diagnosis were treated as non-PSC. Blank answers were removed when calculating PSC vs non-PSC results.

Patient satisfaction was analysed using the accepted Rand VSQ-9 analysis guidance, whereby each answer is allocated a number from 0-100 in equal distributions (poor = 0, fair = 25, good = 50, very good = 75, excellent = 100)[169].

The free-text boxes were analysed using content analysis, a standard method in qualitative research and one which allows for both qualitative and quantitative assessment of the responses[171]. The free text responses were analysed into common categories, which in turn were collated together into similar clusters until specific themes emerged. There were three free text questions. Two questions asked specifically about positive and negative aspects of the PSC clinic experience; these were collated together into common themes with positive and negative aspects in each theme subsequently explored. The final free-text box was open questioning on perspectives about a future virtual appointment; this was analysed in the same way, with responses divided into common themes and further subdivided into positive and negative comments.

Responses containing data in multiple themes were pooled accordingly. For example, a free text comment made in Questionnaire 13 was, “The medical staff I have seen during my visits appear very technically competent and I am able to have good discussions with them re my condition” was categorised within the “quality of care theme” as well as the “information exchange theme”.

9.3.4 Results

During the study period, 168 pre-transplant patients attended the PSC clinic with 103 questionnaires returned, a final return rate of 61.5%. The questionnaires were numbered consecutively from 1 to 103 for analysis purposes; two were <5% complete so were excluded, leaving 101 questionnaires for analysis.

9.3.4.1 Diagnoses

The majority of respondents had PSC (n=72, 72.1%) with a further 14 having PBC or AIH (13.9%). All patients had a diagnosis that would be considered "rare" according to the accepted definition of a prevalence of less than 5 in 10,000 of the population[172]. The "other" diagnoses included IgG4 disease, Caroli's disease and hepatic pseudotumours (Table 15).

Table 15. Diagnosis of Questionnaire Respondents

Diagnosis	***Number of respondents n (%)***
PSC	72 (71)
AIH	9 (9)
PSC & AIH	3 (3)
PBC	2 (2)
Biliary Atresia	1 (1)
Left blank	2 (2)
Pending diagnosis	3 (3)
Other	9 (9)

Data are reported as N (%) and are based on n=101, unless otherwise specified

9.3.4.2 Demographics and Disease History

The majority of respondents were of working age (18-64 years, 83 respondents, 82%). Half were diagnosed at QEHB or the local children's hospital (50 cases) and the remainder by hospitals further afield (50 cases, 1 left blank). 21 respondents (20%) described experiencing a previous PSC-related hospital admission with 13 (13%) having undergone liver transplant assessment; the results of the latter were unknown.

A range of disease severity and longevity was observed; 43 had been diagnosed within the last 5 years (43%), however for 29 (29%) this was over a decade. 32 patients described their diagnosis taking over 12 months from the start of investigations (32%). The PSC cohort were more likely to be male (60% vs 35%, p=0.039) than non-PSC respondents; no other demographic differences were observed (Table 16).

Table 16: Demographics of questionnaire respondents

Factor	*Whole Cohort (n=101)*	*Diagnosis*		*p-value*
		PSC n=75 (%)	*Non-PSC n=26 (%)*	
Age (Years)				1.000
16-17	1 (1.0)	1 (1.3)	0 (0)	
18-24	21 (20.8)	21 (28)	3 (12)	
25-49	43 (42.6)	43 (57)	12 (46)	
50-64	19 (18.8)	19 (25)	6 (23)	
65-74	12 (11.9)	12 (16)	2 (8)	
75+	5 (5.0)	5 (7)	3 (12)	
Ethnicity				1.000
White	86 (85.2)	65 (87)	21 (81)	
British Asian	9 (8.9)	5 (7)	4 (15)	
Afro-Caribbean	5 (5.0)	4 (5)	1 (4)	
Mixed	1 (1.0)	1 (1)	0 (0)	
Gender (male)	54 (53.5)	45 (60)	9 (35)	**0.039**
Occupation				1.000
Full Time	36 (35.6)	28 (37)	8 (31)	
Part Time	6 (5.9)	4 (5)	2 (8)	
Self-employed/Carer	9 (9.0)	8 (10)	1 (4)	
Retired	22 (21.8)	14 (19)	8 (31)	
Unemployed	17 (16.8)	11 (15)	6 (23)	
Student	11 (10.9)	10 (13)	1 (4)	
Time since diagnosis (n=99)				1.000
<5 year	43 (42.6)	34 (45)	12 (35)	
6-10 years	27 (26.7)	21 (28)	6 (23)	
10+ years	29 (28.7)	20 (37)	9 (34)	
Time to diagnosis (n=99)				1.000
12+ months	32 (32.3)	28 (38)	5 (20)	0.141
24+ months	21 (21.2)	17 (23)	4 (16)	0.578
Place of Diagnosis (n=100)				1.000
QEHB/BCH	50 (49.5)	34 (46)	16 (62)	
Other hospital	50 (49.5)	41 (54)	9 (35)	
Admission for PSC (n=100)				0.273
Yes	21 (20.8)	15 (20)	8 (32)	
No	79 (78.2)	60 (80)	17 (68)	
*>2 admissions**	5 (29.4)	4 (36)	1 (17)	0.358
Transplant Assessment (n=100)				0.508
Yes	13 (12.9)	11 (15)	2 (8)	
No	87 (86.1)	65 (85)	23 (91)	

*Data are reported as N (%) and are based on n=101, unless otherwise specified. BCH – Birmingham Children's Hospital. *of 17 completed responses (21 with admissions minus 4 left blank for number of admissions). Comparisons were made using Mann-Whitney tests for continuous variables, with Fisher's exact test used for nominal variables. Bold indicates p<0.05*

9.3.4.3 Symptoms

Commonly described symptoms of PSC were enquired about; the results can be seen in Tables 17 & 18. Blank responses were recorded as no symptom. Symptoms were present in 87 patients (87%); these were commonly experienced at least weekly (n=61) or daily (n=47). Most of the cohort described three or more symptoms (67%); multiple symptoms were more common in the PSC cohort than in the remainder (72% vs 48%, p=0.049). Itch was more common in the PSC cohort (76% vs 40%, p=0.001); no other differences in symptoms were found. Additional symptoms described by patients included bloating, nausea, headache, jaundice, joint pain, ankle swelling and heartburn.

Table 17. Symptom type reported by questionnaire respondents

Symptom	***PSC (n=75)***	***Non-PSC (n=26)***	***p-values***
Fatigue	61 (81)	17 (68)	0.170
Itch	57 (76)	10 (40)	**0.001**
Poor concentration	46 (61)	14 (56)	0.645
Abdominal pain	44 (59)	12 (48)	0.354
Cholangitis	35 (47)	13 (52)	0.652

Data are reported as N (%) and are based on n=101, unless otherwise specified. Bold type indicates significance at the p>0.05 level). Comparisons were made using Fisher's exact test. Bold indicates p<0.05

Table 18. Symptom frequency reported by questionnaire respondents

Symptom	***Frequency of Symptoms (n=101%)***				
	Daily	***Weekly***	***Monthly***	***Less than monthly***	***Never***
Fatigue	35 (34.7)	18 (17.8)	8 (7.9)	16 (15.8)	24 (23.8)
Itch	25 (24.8)	12 (11.9)	7 (7.9)	20 (19.8)	20 (19.8)
Poor concentration	22 (21.8)	29 (10.9)	6 (5.9)	21 (20.8)	41 (40.6)
Abdominal pain	11 (10.9)	31 (10.9)	9 (8.9)	21 (10.8)	49 (48.5)
Cholangitis	5 (4.9)	10 (9.9)	7 (6.9)	24 (23.8)	55 (54.5)

Data are reported as N (%) and are based on n=101, unless otherwise specified. Comparisons were made using Fisher's exact test. Bold indicates p<0.05

9.3.4.4 Geography and referral patterns

QEHB was the local hospital for 24 respondents (24%), this was not diagnosis dependant (p=0.174). Of the remaining 78 patients, 8 lived in Wales (8%) with the remaining living elsewhere in England. Reasons for QEHB referral varied; most commonly this was for post-diagnosis specialist management (n=56). The most common frequency of QEHB follow up was 6-monthly (n=78), Table 19).

Table 19: Referral reason and frequency of appointments for questionnaire respondents

Factor	***Total cohort (n=101) Number (%)***
Reason for referral	
Diagnosis	34 (33.7)
Ongoing management	56 (55.4)
Trials	10 (9.9)
Transition care	10 (9.9)
Unsure	8 (7.9)
Left blank	6 (5.9)
OLT assessment	8 (7.9)
Second opinion	16 (15.8)
Patient preference	6 (5.9)
Frequency of QEHB appointments	
6 weekly	6 (5.9)
3 monthly	31 (30.7)
6 monthly	41 (40.6)
Yearly	18 (17.8)
First appointment	2 (2.0)
Left blank	3 (3.0)
3 monthly or more often	37 (38.5)
6 monthly or more often	78 (81.3)

Data are reported as N (%) and are based on n=101, unless otherwise specified.

9.3.4.5 Patient burden of healthcare interventions

Travel times also varied however, 51 respondents stated their journey was >1 hour (51%), and 27 stated this was over >2 hours or required a self-funded overnight stay (27%, Table 20). Most attended by car (n=70) while 64 brought a relative, partner or friend with them (64%). Attending the appointment required leave from employment in 37 respondents, 43% of which was unpaid. An additional 13 respondents had flexible working hours but would need make up the time elsewhere.

The mean estimated cost for patients to attend QEHB was £20.40 (range £0-£109) with no significant difference between diagnostic groups (p=0.815). Factoring in the appointment frequencies, the mean yearly cost was found to be £69.61 (range £15.60-£948.30). It was not clear if some respondents may have included just their own travel costs or for those they travelled with also. These figures do not include lost earnings when unpaid leave from work was required.

Table 20: Personal burden of attendance at QEHB appointments in questionnaire study

Factor	*Whole Cohort (n=101)*	*Diagnosis*		*p-value*
		PSC n=75 (%)	*Non-PSC n=26 (%)*	
Travel duration				
Under 30 minutes	13 (12.9)	7 (10)	6 (24)	
30-60 minutes	35 (34.7)	30 (41)	5 (20)	
1-2 hours	25 (24.8)	20 (27)	5 (20)	
2+ hours	24 (23.8)	16 (22)	8 (32)	
Overnight Accommodation	2 (2.0)	1 (1)	1 (4)	
Left blank	2 (2.0)	1 (1)	1 (1)	
>60 minutes	51 (52.5)	37 (50)	14 (56)	0.649
>120 minutes or overnight stay	26 (27.3)	17 (23)	9 (36)	0.292
Travel Method				1.000
Car	70 (69.3)	50 (67)	20 (79)	
On foot	1 (1.0)	0 (0)	1 (4)	
Public transport	28 (27.7)	24 (32)	4 (16)	
Left blank	2 (2.0)	1 (1)	1 (1)	
Who was at the appointment?				0.810
Left blank	2 (2.0)	1 (1)	1 (4)	
Patient alone	35 (35.4)	27 (36)	8 (32)	
Patient accompanied	64 (64.6)	47 (64)	17 (9)	
Was time off work needed to attend?				
Paid Leave	21 (20.8)	15 (20)	6 (23)	0.782
Unpaid Leave	16 (15.8)	14 (19)	2 (8)	0.229
No (flexible hours)	13 (12.9)	11 (15)	2 (8)	0.506
Not applicable	51 (50.5)	35 (47)	16 (62)	0.256

Data are reported as N (%) and are based on n=101, unless otherwise specified. Comparisons were made using Mann-Whitney tests for continuous variables, with Fisher's exact test used for nominal variables. Bold indicates p<0.05

9.3.4.6 Patient satisfaction

When questioned about satisfaction using the standardised Rand VSQ-9 scoring formula, most respondents answered all components (n=79, 71%). Mean overall score was 72 (range 30.6-100) with no difference seen in diagnostic groups (PSC: mean 74.1 vs non-PSC: mean 63.4, p=0.300). This compares to mean scores in the published literature of 89.8 for patient satisfaction of physiotherapists in orthopaedics[173] and 73.7 in nurse practitioners in multiple sclerosis[174].

Some domains were consistently ranked more highly than others (Table 21); these included the quality of explanations given to the patient, the skills of the clinicians and their personal manner (all scored over 90). Lowest scoring metrics were the convenience of the location and the appointment time delays (both below 60). PSC patients were more likely to rank the explanation and technical skill domains higher than non-PSC patient participants (p=0.027 and 0.033 respectively).

Table 21: Rand VSQ-9 satisfaction scores from clinic questionnaire responses

Component	*Number of respondents*	*Rand Score mean (SD)*			*p-value*
		Whole Cohort	*PSC*	*Non-PSC*	
How long you waited to get an appointment booked	98	70	72	65	0.321
Convenience of the location of the appointment	97	58	58	58	0.959
Getting through to the office by phone	85	61	60	62	0.768
Length of time waiting for the appointment to start	97	59	59	61	0.794
Time spent with the person you saw	89	73	76	66	0.094
Explanation of what was done for you	92	77	81	68	**0.027**
Technical skills of the person you saw	93	82	85	73	**0.033**
The personal manner of the person you saw	93	87	88	82	0.170
The visit overall	93	79	81	75	0.262

Data are based on n=101, unless otherwise specified. Comparisons were made using Mann-Whitney tests for continuous variables, with Fisher's exact test used for nominal variables. Bold indicates p<0.05

9.3.4.7 Free text responses

In total, 88 respondents completed at least one free test response. Appendix J shows the demographics of these; they were similar to the whole questionnaire cohort in terms of gender (p=0.536), diagnosis (p=0.451), ethnicity (p=0.839), locality to QEHB (p=0.796) and presence of symptoms (p=0.645).

9.3.4.7.1 Clinic satisfaction free test responses

Patients were asked the best and worst parts of their clinic experience; 82 responded in this section. Of these, 24 comments were positive, 2 negative and the remaining 56 were mixed. Many patients made more than one specific point within their free text response giving a total of 191 comments.

During analysis, a number of common categories emerged (Table 22) which will be discussed in turn with exemplar quotes. The most negative comments were seen in the convenience category (54 comments, 28.3%) with very few observed in other categories. The most positive comments were of the personal touch experience (25 comments, 13.5%), closely followed by the importance of monitoring as reassurance and the clinic amenities (24 comments apiece, 12.4% each). 5 patients made additional comments about their illness; these were all negative.

Table 22. Themes from the questionnaire free text responses on positive and negative aspects to the current QEHB in-person clinic

Theme	*Number of comments (n=191)*	
	Positive	*Negative*
Convenience/Amenities/Efficiency	24 (12.6%)	54 (28.3%)
Specialist/Well-informed	16 (8.4%)	0 (0%)
Quality of care	22 (11.5%)	1 (0.5%)
Monitoring/Reassurance	24 (12.6%)	0 (0%)
Information Exchange/Interaction	19 (9.9%)	1 (0.5%)
The Personal Touch	25 (13.1%)	0 (0%)
Personal Disease Experience	0 (0%)	5 (2.6%)
Total	130	61

Variables are presented as number (% total of all comments).

9.3.4.7.2 Convenience, Amenities and Efficiency

When commenting on the clinic amenities and location, 24 comments were positive (18% of all positive comments). Respondents appreciated the joint PSC clinic with other investigations and a gastroenterologist available the same morning. One patient said *"I am very pleased that such a clinic came to life where I can see both a Hepatologist and a gastroenterologist on the same day" (Q83).*

There had been a recent change of location of the clinic from the main liver outpatient's area to the Centre for Rare Diseases; many commented on now shorter waiting times and less overcrowding. One respondent stated *"In the past overcrowding and delays have been a problem. The new facilities seem to be a significant improvement, with reduced waiting times" (Q10).*

However, this praise was not universal and some respondents mentioned long waiting times resulting in a poorer experience. One patient commented that they waited for "*$1^{3/4}$ hours in a very cold and draughty waiting room. Then feeling very rushed because they were so far behind" (Q80).* It is worth noting that one of the clinics had unusually long delays due to staff sickness.

The new clinic location was also further away from other hospital amenities, resulting in longer walks for some patients; this was commented upon along with some confusion as to clinic location itself. One patient stated that *"Collecting medicine from the other main building is annoying as it's on the other side of the building" (Q45)* and another that they "*went to the wrong department as letter was not clear" (Q62).* One patient did not approve of the clinic name itself, the Centre for Rare Diseases, *"I was somewhat shocked of the new location of the*

clinic and feel the name of the clinic could be more sensitive e.g. "rare medical condition" (Q65).

Overall 54 of the total 61 negative comments (88%) were regarding the inconveniences of attending the outpatient clinic. Theses concentrated on the logistical difficulties of travelling to the hospital, including long and costly journey times, especially when they were already feeling unwell. One patient commented, "*appointments are hard…long way to travel when feeling ill" (Q82).* Other negatives included organising time off work along with the personal costs of travel and parking, *"£30 is OK every 3 months but on occasions where I need to come back sooner it becomes expensive. I also have to book full days off work if dates clash" (Q103).* Long travel distances were described by 21 respondents and monetary costs by 13.

Again, however, some patients viewed the long journey as more positive, either as an opportunity to visit the surrounding area or for shopping opportunities nearby, *"Journey is NOT difficult - can be opportunity to shop in Birmingham" (Q28).*

9.3.4.7.3 Specialist well-informed care and overall high quality of care

Taken together, these two themes saw a high frequency of positive comments (38 comments, 29% of the total). Many comments were themed around their trust that the physician was providing them with high quality specialist care. One patient commented, "*"I feel I am being looked after in the best place and by the best team" (Q19).* Attributes of the clinicians mentioned included professional, experienced and thorough, *"The medical staff…appear very technically competent and I able to have good discussions with them re my condition"(Q13).*

The single negative comment in this category was regarding an ongoing unknown diagnosis, "*it is taking far too long to find out what is wrong with my liver" (Q40).* Although many respondents had been negative about the personal inconveniences the clinic, a common qualifier was that this was justified for the high level of medical care they received. One patient said, "*Far away! But worth it for specialist care" (Q38),* and another commented*, "sometimes a long wait - worth it to see the right person" (Q11).*

9.3.4.7.4 Monitoring, Reassurance and Information Exchange

These categories contained the most comments overall, making up 33% of all positive comments and indicating the importance of this to patients. The reassurance received from being monitored, and gaining up to date information on their condition was a common perspective. One patient said, *"Checking on my condition and tests done to see any changes. Monitoring is important to me" (Q22)* and another stated that they felt *"reassured that I am improving and that I'm in the hands of experienced professionals" (Q48).*

The process of information exchange between the doctor and patient was also key; patients generally felt involved in their care, that their doctor was highly knowledgeable and could answer their questions honestly. One patient said, *"specialist liver knowledge, good understanding and information on how to go about daily life" (Q50)* and another commented that *"It does help to be able to ask questions and receive very good answers" (Q29).*

9.3.4.7.5 The Personal touch

Respondents commonly described personal qualities of the clinical team; 25 of the 130 positive comments were in this category (19%). Many commented the clinic staff were friendly and helpful, *"The staff are very friendly and make you feel relaxed" (Q37).* Some specified a particular doctor or nurse who they felt particularly contributed to their positive experience. One patient said, ""*Dr [redacted] is a brilliant clinician, who has always does his best for me" (Q5).* Seeing the same clinicians over time was also mentioned; *"consistently seeing the same doctor" (Q75 and Q49)* was important to patients.

9.3.4.7.6 Personal disease experience

A small number of respondents chose to make additional comments about their personal feelings of their illness and how attending the clinic made them feel; these were all negative. One patient said that attending the clinic meant, *"I have to face the fact that I am ill" (Q6)* and another cited uncertainty about their future prognosis, *"I am not sure what the future holds. It's just a waiting game" (Q52).*

Overall, patients were positive about their experiences and many justified their personal inconveniences with the perceived benefits they received from attending the clinic; "worth it" was a commonly seen phrase.

9.3.4.8 Attitudes to telemedicine

Patients were asked their opinion on having a future virtual clinic appointment both quantitatively and with a free text option. 97 patients completed this section of the questionnaire (72 PSC, 25 non-PSC). Overall 67 participants (69%) would accept a virtual clinic appointment; 50 (52.5%) for some appointments and 17 (18%) for all (Table 23). However, 16 patients (16%) would completely decline and 14 were unsure (14%). The non-PSC group were more likely to be unsure than the PSC group (p=0.026); no other differences were found between the diagnostic groups.

Table 23. Acceptance of future virtual clinic appointments for questionnaire study

Acceptance of Virtual clinic	*PSC (n=72)*	*Non-PSC (n=25)*	*p-value*
Yes – all appointments	14 (19%)	3 (12%)	0.547
Yes – some appointments	39 (54%)	11 (44%)	0.487
Unsure	8 (11%)	8 (32%)	**0.026**
No	11 (15%)	3 (12%)	1.000

Data are reported as N (%). Comparisons were made using Fisher's exact test. Bold indicates p<0.05.

Younger patients were more likely to accept a virtual clinic, as were those employed and without previous PSC-related hospital admissions (Table 24). Patients who needed to formally organise leave from work (whether paid or unpaid) were more likely to accept all future appointments as being virtual (p=0.012).

Acceptance of the virtual clinic was not statistically different between gender (p=0.079), travel time (at any time cut off), travel cost or if QEHB was the patient's local hospital or not (p=0.600). An appointment frequency of 6 weekly was the only frequency of follow up more likely to accept a virtual appointment (p=0.049)

Table 24. Factors affecting acceptance of a virtual clinic appointment for the questionnaire study

Demographic		***Acceptance of a virtual clinic appointment (n=97)***		
		Yes	***No/Unsure***	***P-value***
Gender	Male	39 (40%)	12 (12%)	0.079
	Female	26 (27%)	19 (20%)	
Current Patient Age	<50	49 (51%)	12 (12%)	**<0.001**
	>50	16 (16%)	19 (20%)	
Previous PSC-related hospital admission	Yes	0 (0%)	20 (21%)	**0.019**
	No	17 (18%)	59 (61%)	
Current employment	Working/student	46 (47%)	12 (12%)	**0.013**
	Unemployed/retired	21 (22%)	18 (19%)	
Formal leave from work required to attend QEHB	Yes	23 (24%)	11 (11%)	1.000
	No/NA	41 (42%)	20 (21%)	
Time between QEHB appointments	Up to 6 weeks	8 (6%)	0 (0%)	**0.049**
	>6 weeks	55 (57%)	31 (32%)	
Travel time from home to QEHB	<60min	32 (33%)	14 (14%)	0.664
	>60min	31 (32%)	17 (18%)	
QEHB is the patient's local hospital	Yes	13 (13%)	8 (8%)	0.600
	No	52 (54%)	23 (24%)	

Data are reported as N (%). Bold indicates significance at the p<0.05 level. Comparisons were made using Fisher's exact tests.

9.3.4.8.1 Familiarity with technology

To access the virtual clinic, patients would need access to a computer (or other smart device) and a reliable internet signal. When questioned on this, complete responses were seen in 93 of the questionnaires with 77 respondents using this technology frequently (83%, Table 25). Less frequent technology use was associated with reduced acceptance of the virtual clinic (p=0.002)

Table 25. Technology usage of questionnaire respondents and acceptance of a virtual clinic appointment

Technology Usage	***Number of patients (n=93)***	***Acceptance of virtual clinic***		
		Yes (all or some)	***No/Unsure***	***P-value***
Smart Phone				
Daily/Weekly	77 (83%)	59 (63%)	18 (19%)	**0.003**
Monthly/Never	16 (17%)	5 (5%)	11 (12%)	
PC/laptop/tablet				
Daily/Weekly	77 (83%)	58 (62%)	19 (20%)	**0.002**
Monthly/Never	16 (17%)	5 (5%)	11 (12%)	

Data are reported as N (%). Bold indicates significance at the p<0.05 level. Comparisons were made using Fisher's exact tests.

9.3.4.8.2 Acceptance of telemedicine free text responses

Free text responses in this section were made by 73 respondents, with 141 specific comments being identified; half of comments were favourable toward the virtual clinic and half were against (n=70 & 71 respectively). Using content analysis, seven categories were identified, five of which reflected those found previously in this study (Table 26). Two additional categories were detected; these were concerns regarding flexibility between virtual and in-person consultations and access to the required technology.

The most commonly observed positive theme was that of improved convenience with the virtual clinic, as is discussed further below. Negative comments most commonly cited the loss of the personal touch (19.9% of all comments) closely followed by the patient wish to retain some face-to-face clinics going forward (17% of all comments); the latter was included within the negative category as a reflection that patients felt the virtual clinic was not satisfactory in all situations or over time.

Table 26. Themes from the questionnaire free text responses on attitudes to telemedicine

Theme	*Number of comments (n=141)*		
	Pro-virtual clinic	*Anti-virtual clinic*	*Total*
Convenience/Efficiency	35 (24.8%)	1 (0.7%)	36 (25.5%)
Quality of care	3 (2.1%)	14 (9.9%)	17 (12.0%)
Monitoring/Reassurance	3 (2.1%)	13 (9.2%)	16 (11.3%)
Information Exchange/Interaction	5 (3.5%)	6 (4.3%)	11 (7.8%)
The Personal Touch	2 (1.4%)	28 (19.9%)	30 (21.3%)
Access to technology	0 (0%)	7 (5.0%)	7 (5.0%)
Flexibility/Choice	0 (0%)	24 (17.0%)	24 (17.0%)
Total	48	93	

Data are reported as N (% of all comments). Bold reflects themes also observed earlier in the chapter.

9.3.4.8.3 Perceived convenience and efficiency of telemedicine

This popular theme made up 73% of all positive comments and 26% of all comments. Particular convenience factors of a virtual clinic were cited as saving the patient time and travel costs as well as reducing work and childcare disruption. One patient said of the virtual clinic, *"It would be greatly more convenient. I have to take whole days out of work and plan 6 months in advance at present" (Q53)* and another stated, *"Saves time and money if done over the internet. I'm a full-time mum and it's difficult to get child care" (Q45).*

Some altruistic comments were detected including thoughts that a virtual clinic might be more time efficient for doctors, allow patients to be seen more quickly, or free up funds for research. One patient said it would be *"more convenient to patient and hopefully doctor, plus less people to clog hospitals" (Q37)* while another commented that they were, *"willing to make the best use of the Consultant's time…do not want to be a burden on the service" (Q78)*.

However, one respondent commented that a virtual clinic would be no more convenient for them as they would still need time off work; they stated that it *"would only be useful for weekends and evenings due to work" (Q94).* Others commented that the ability of the in-person clinic to combine appointments with other tests or specialist consultations made this more efficient for them and thus they could justify the travel inconveniences. One patient stated, "*Sometimes they combine consultant appointments with MRIs etc so that's handy and worth travelling down for, but if it's just a chat to give me an update then doing it virtually is a good idea" (Q38)*.

9.3.4.8.4 Quality of care, Monitoring and Reassurance

Concerns were raised by some respondents that the virtual clinic might not provide them with the same level of care, monitoring and reassurance as a normal consultation would, echoing results seen in patient interviews (Chapter 3). These themes contained 11 positive 37 negative comments, 34% of the total. Undergoing their normal monitoring tests was a priority for patients. One patient stated, "*it would be fine for routine monitoring as long as physical checks, blood tests etc still took place and care was not compromised" (Q80)*. Ensuring that any change did not compromise their care, was commonly observed.

The lack of physical presence during a virtual consultation led to worries that early warning signs of deterioration might be missed or that communication might be affected. One patient said, *"I think doctors still need to physically assess you" (Q50)* and another stated*, "sometimes you need face to face to understand non-verbal communication" (Q88).* Concerns were also raised that the dynamic of the clinic experience would change and that a virtual consultation would be of reduced quality; one patient said, *"I feel that some things may not get sorted in as much depth and perhaps the virtual clinic might become informal" (Q81).*

Some respondents felt that the same quality of consultation could occur virtually but with the proviso that they saw the same clinicians they already knew in person. This established in-person therapeutic relationship gave additional reassurance to patients. One patient stated that the virtual clinic, *"would be more convenient…but in the reassurance that I would still be able to see/speak to the same specialist doctors" (Q99).*

9.3.4.8.5 The personal touch and Information exchange

As mentioned above, the personal touch of in-person consultations, especially when exchanging information, was felt to be of important to patients. Many commented that they would prefer to be face-to-face with their clinician; these themes totalled 41 comments, 48% of all negative comments. This was especially observed in older respondents; one said "*"I am too old to take in all information unless face to face" (Q55).*

In general, patients thought that the in-person clinic was more personal and that they gained more reassurance from this. Some described worries that the communication or interaction between doctor and patient would be altered by being virtual. One patient said, *"I personally would not want to discuss my health issues, worries with a virtual clinic. There would be no personal touch" (Q62).* This lack of personal interaction led to further concerns over reduced quality of care when consulting virtually. One patient said, *"A face to face conversation leads to better interactions and increases the chance of "the odd remark" leading to a valuable discussion about an issue that the patient thought unimportant or minor" (Q10).*

However, others felt that communication would not be impaired virtually yet have the added benefits of improved personal convenience. One stated, "*Consultation is a conversation I have never been examined during a consultation so virtual would be more efficient for me" (Q26)*.

9.3.4.8.6 Flexibility and Disease dependency

Almost unanimous amongst respondents was the need to retain the option of in-person clinics, either to maintain personal relationships with the staff or as their disease progressed. This category made up 24 of the 141 comments (17%). Most respondents in favour of virtual consultations would prefer a hybrid, with only some clinics virtual and on a trial basis. One stated that the virtual clinic would be, "*good for some appointments but would still need to be seen face to face for reassurance" (Q70)*, and another stated *"I would be interested to see how well it worked, a trial period, for me before I could make a decision" (Q18)*.

Circumstances felt appropriate for the clinic by patients were when their PSC was stable, the consultation was routine, or when other investigations were not required. On patient stated, "*This would be sufficient for some appointments if I am stable/improving, as it is a long way to come for seeing the consultant for a few minutes" (Q48).* Most felt that they would prefer an in-person appointment when they were unwell or when the discussion was likely to be more complex or need physical examination. One patient said, "*when physical assessment is a possibility I would rather come in to give you the best possible evidence" (Q82).* However, one respondent felt the opposite, they commented that "*virtual appointments would be really convenient especially if I am not feeling too well and in pain. Also, I wouldn't require anyone to drive me into the hospital" (Q87).*

9.3.4.8.7 Access to technology

Seven respondents stated said they were either unable to access the required technology or were concerned that their internet connection was too poor for a good quality virtual consultation (10%). One patient said, *"We have very poor internet connections and we are not really technology savvy" (Q19).* One respondent required an interpreter for their consultation which they felt wouldn't work as well for a virtual consultation.

9.3.4.9 Summary of all free text responses

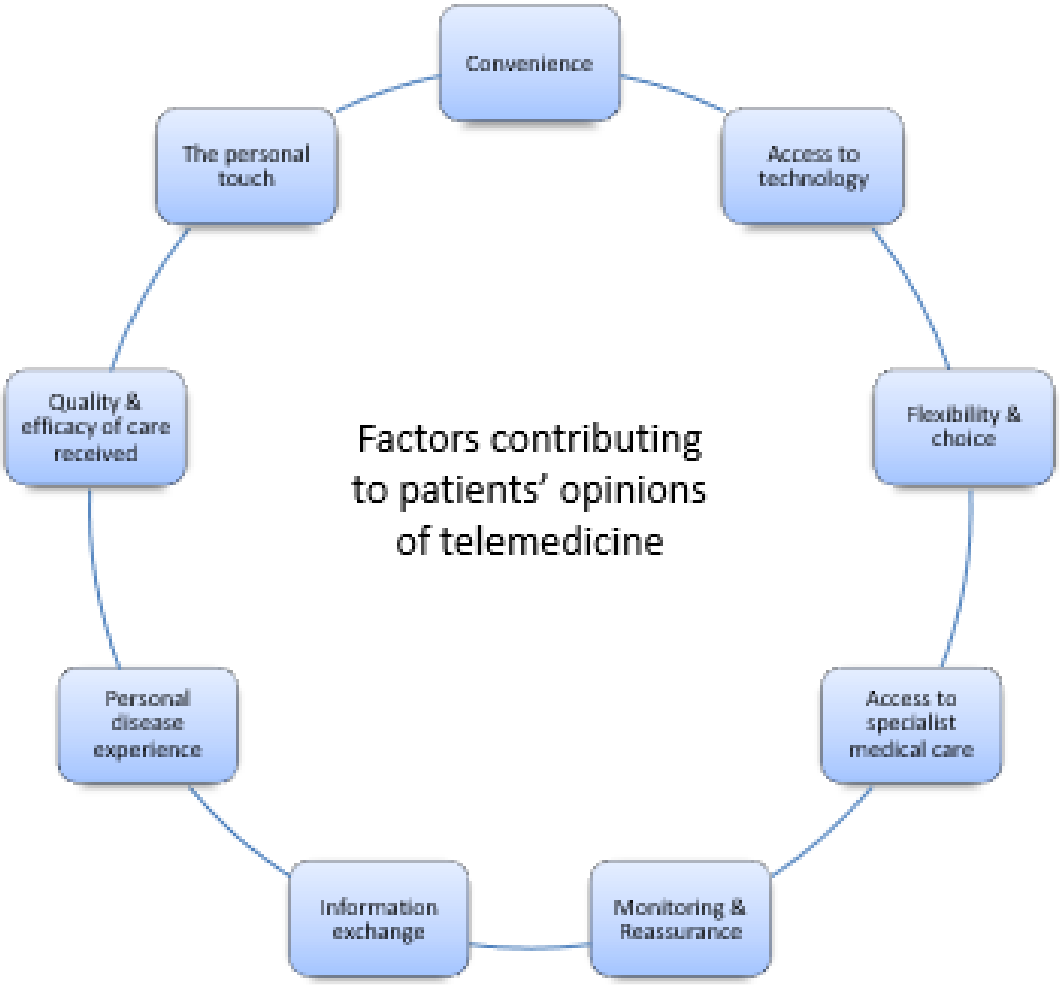
Analysing the data from all free text responses has identified nine key areas of importance to patients when introducing a virtual clinic (Table 27 & Figure 13). As expected, the convenience theme remained the most common (34% of all comments) followed by the importance of the personal touch (17%), quality of care (12%) and monitoring (12%).

Table 27. Key themes of importance from the questionnaire study free text responses

Theme	***Number of comments (n=332)***		
	Positive	***Negative***	***Total***
Convenience & Efficiency	59 (17.8%)	55 (16.6%)	114 (34.3%)
Quality of care	25 (7.5%)	15 (4.5%)	40 (12.0%)
Monitoring & Reassurance	27 (8.1%)	13 (3.9%)	40 (12.0%)
Information Exchange & Interaction	24 (7.2%)	7 (2.1%)	31 (9.3%)
The Personal Touch	27 (8.1%)	28 (8.4%)	55 (16.6%)
Specialist/Well-informed	16 (4.8%)	0 (0%)	16 (4.8%)
Personal Disease experience	0 (0%)	5 (1.5%)	5 (1.5%)
Access to technology	0 (0%)	7 (2.1%)	7 (2.1%)
Flexibility/Choice	0 (0%)	24 (7.2%)	24 (7.2%)
Totals	178	154	332

Data are reported as N (% of all comments). Bold reflects categories common to both general clinic questioning and the virtual clinic.

Figure 13. Summary diagram of the themes important to PSC patients when accessing their medical care and the potential introduction of virtual clinics



9.3.5 Discussion for the questionnaire study

While previous chapters have confirmed the large personal and medical burden of PSC, questions remained about how standard healthcare interventions impacted upon patients and how incoming changes to this, such as telemedicine, might be viewed. This chapter aimed to explore what was already known about telemedicine in PSC, initially via a scoping review with subsequent questioning of a real-lift clinic cohort, and with additional questioning to demonstrate the current personal burden of healthcare interventions.

Despite the interest in introducing of telemedicine into the routine clinical care for patients with PSC at QEHB, the scoping review found no direct evidence for the efficacy or acceptability of this intervention in this patient group, and very little for chronic liver disease as a whole. This justified further investigation, performed via the subsequent questionnaire.

9.3.5.1 Demographics

The majority of respondents did have PSC and all patients had a rare liver disease. The rationale for including all clinic attenders (rather than those just with PSC) proved justified; no major differences were found between the demographics, disease severity, personal burden of disease and attitudes to telemedicine between the PSC and non-PSC respondents. The findings may thus be generalisable to other chronic or rare disease cohorts.

PSC patients were more likely to be male and to experience pruritus, as reflects the literature[175]. PSC patients were also more likely to experience multiple symptoms than other diagnoses, a new finding. Thus, the particular patient burden of PSC is again confirmed,

lending further weight to similar conclusions demonstrated in previous chapters and further justifying this thesis overall.

Heterogeneity was observed in terms of disease stage, home location, referral reason and time since diagnosis. This demonstrates the spectrum of disease and geography seen at QEHB; that this centre manages patients with mild disease as well as advanced suggests the results may be applicable to other hospitals with similar patient cohorts and other regional liver transplant units. It also further suggests the ongoing inequality of specialist hepatology services across the UK[46]. This is suboptimal for patients and difficulties accessing specialist care were frequently cited in the aforementioned interview study. Importantly, while most patients perceive specialist care to be superior than local management, it is not known whether there are objective differences in clinical outcomes, especially in those with early and stable disease.

9.3.5.2 The personal burden of PSC-related healthcare at QEHB

The personal burden of PSC as a disease, as well as the impact of healthcare interventions and overall disease severity has again been confirmed as of great importance to patients, further corroborating the findings from the previous chapters.

The time and financial burden of PSC-related healthcare from a patient perspective has not previously been published and these factors are not routinely considered by clinicians. While close monitoring is necessary to manage PSC, there is inevitably an added burden of this intensive management strategy on patients. This needs to be considered more fully when considering changes to clinical services, especially for specialist care where travel times can

be considerable. It is in potentially alleviating some of the personal burden of attending hospitals that makes telemedicine appealing for many patients.

9.3.5.3 The current in-person clinic model

Despite the challenges faced by patients in attending the clinic, VSQ-9 satisfaction scores remained high for many aspects of the clinic experience. Higher scoring metrics were related to clinical care with lower metrics discussing personal inconveniences of attending (such as travel, parking and delays). While telemedicine has the potential to improve the personal inconveniences for the patient without compromising clinical care, it was ensuring this balance that was of concern to patients. Repeated measurement of patient satisfaction and clinical outcomes are needed once the QEHB virtual clinic is introduced to ensure patient satisfaction as well as the quality of care received, are not affected.

Patients felt strongly about the long-term requirement for close monitoring of their PSC, also observed in qualitative interviews (Chpater3). However, such monitoring involves regular blood tests and imaging as well as verbal consultations. The QEHB clinic can perform most required interventions under one roof and often on the same day. In contrast, a virtual clinic requires alternative methods of performing these tests, perhaps by services local to the patient. Given difficulties navigating multiple healthcare providers cited in patient interviews, it is important that the benefits of telemedicine are not outweighed by difficulties organising the same investigations locally and the results communicated to QEHB in a timely manner.

9.3.5.4 Attitudes toward telemedicine

Given the importance patients placed on their face-to-face interactions with their specialist, it was expected that acceptance of a virtual appointment would not be unanimous. Younger patients were more favourable to this technology; confidence with online platforms is likely a contributing factor. A minority of patients could not access the technology needed for a virtual appointment. Travel time and cost were not associated with acceptance of the virtual clinic, suggesting that individuals decide for themselves whether their QEHB appointment is "worth" the effort needed to get there.

The PSC group were more unsure about telemedicine than the non-PSC group. It is understandable how PSC patients may be more dependent on clinicians than other cohorts; without a treatment and with an uncertain prognosis, PSC patients may more dependent on personal reassurances from their specialists; they did not want to miss out and felt they were best placed under an expert team who may have access to due developments first.

Concerns were raised that a virtual consultation would be inferior to an in-person appointment. Some stated that video consultations would be more efficient for the doctor, implicating these might be shorter or otherwise less complete. While perfectly possible to have the same reassuring conversations via a virtual medium, potentially even more frequently than before, patients felt that without being physically present with their clinician, these reassurances might not have the same impact. Many patients were thus concerned that telemedicine may disadvantage them or reduce the quality of the care they received.

These concerns will need addressing before the majority of patients would accept telemedicine into their long-term medical care. The virtual clinic is unlikely to be physically possible for some patients and will not be accepted by some of the remainder. Therefore, it is

likely that both in-person and virtual clinics will be required going forward, with consideration needed as to how this hybrid system might work and how patient choice will be factored in. Anecdotally, patients with advanced or unstable disease may benefit more from in-person appointments, however the journey for these patients is especially arduous. Evidence-based criteria for who is safe to be seen virtually are needed and are under development[176].

9.3.5.5 Limitations

The current clinic PSC cohort is approximately 480 patients (Chapter 2). This questionnaire sampled under a fifth of the entire cohort and with a return rate of just over 60%. While acceptable return rates are not universally agreed, 60% is usually the minimum accepted for reliable results[177]. Research participants are self-selecting, with non-responders more likely to be male (important given the male predominance of PSC), younger, a have a lower level of education and with unhealthier lifestyles[178], all of which may create bias in the results. One respondent cited needing an interpreter and it is likely that other non-English speakers would have been unable to complete the questionnaire. That one of the clinics encountered staffing problems and ran abnormally overtime may also have affected the responses given.

The questionnaire design was more likely to pick up frequent clinic attenders, given its short data collection period; this may impact on responses. While clear instructions were given to only complete the questionnaire once, patients may have done so in error. Clarification of this is tricky given the anonymous nature of the study; no questionnaires appeared similar enough to be suspicious of accidental duplication.

Additionally, it is possible that the handling of missing data could have further introduced error. It was presumed that blank symptom frequency boxes meant that particular symptom

was not being experienced; the symptom burden for this cohort may thus have been underestimated.

Finally, while the questionnaire was anonymous, patients may have felt unable to be too critical, either for fear of repercussions or an uneasiness given the questionnaire was completed within the outpatients department. That patients do not always give their true opinion is well established in the literature and age or health status are independently associated with satisfaction scores[179]. Social desirability bias is a recognised phenomenon whereby participants over-report positive aspects in the hope that they will be seen more favourably as a result, even when feedback is anonymous[180]. While impractical on a larger scale, in-depth investigation of patient experiences with qualitative interviewing is likely a more accurate method of gaining true patient opinion (Chapter 3).

9.3.5.6 Implications for practice and further research

Despite some limitations, this study provides a relevant and pragmatic view of the current QEHB PSC clinic cohort, their experiences of healthcare and their opinions of telemedicine. This was untainted by the emergence of Covid-19 and thus represents a truer view of inherent patient opinion than could be gathered now; this will be discussed further in Chapter 6.

The Cochrane review into telemedicine and the updated scoping reviews described here found little evidence for the effectiveness of telemedicine in liver disease, and none for PSC. Despite interest in this medium from clinicians and patients alike, it must be shown to provide at least equivalent clinical outcomes before it's long-term use can be advised. Patient experience and patient-reported outcome measures are becoming increasingly important; this questionnaire study has identified key concepts of concern to patients for their

healthcare. PSC patients may need more reassurances when switching to a virtual clinic than other cohorts, given their need to maintain a close relationship with their specialist.

This study has confirmed the burden of disease and medical intervention on patients, the heterogeneity and severity of disease seen in the QEHB PSC clinic, and explored some complexities in patient attitudes to the introduction of telemedicine. This study has identified a number of important areas importance to patients for their healthcare and which need addressing; these are discussed further in Chapter 6. Maximising convenience for the patient must balance with maintaining high quality care, effective monitoring systems, and preserving crucial doctor-patient relationships.

PSC patient experiences were similar to other rare chronic liver disease diagnoses, suggesting these findings may be transferable to other patient cohorts. However, PSC patients were more likely to be unsure about telemedicine, perhaps due to the fundamental challenges that a lack of disease-modifiable therapy and an uncertain prognosis can bring to the patient experience. This is all complementary evidence of the burden of PSC on patients and healthcare providers alike.

Before introducing a permanent virtual clinic in this cohort or deciding how much of the current socially-distanced system to retain long-term, clear protocols are needed for whom is to be invited to take part and how they would undergo necessary blood and imaging tests elsewhere, with results fed back accordingly. Monitoring of patient feedback and care quality indicators are also required. Consideration should also be given to clinician attitudes, as these have not been explored.

In conclusion, while not suitable for everyone, telemedicine does have a part to play in disrupting traditional medical management and is likely one method of improving experiences

for PSC patients as well as other chronic diseases. Another avenue of improving patient and clinician experiences in PSC is to develop improved methods of risk stratification. This would lead to more accurate prognostication, allowing clinicians to prioritise higher risk patients for new treatments and to reassure lower risk patients, perhaps even discharging the latter back to local secondary care services. Quantitative MRI techniques are one potential method of achieving this, as described in the following chapter.

CHAPTER 5

A prospective evaluation of the utility of Multi-parametric MRI imaging in predicting clinically meaningful outcomes in primary sclerosing cholangitis and other autoimmune liver diseases

10 CHAPTER 5: A PROSPECTIVE EVALUATION OF THE UTILITY OF MULTI-PARAMETRIC MRI IMAGING IN PREDICTING CLINICALLY MEANINGFUL OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS AND OTHER AUTOIMMUNE LIVER DISEASES

10.1 Introduction

As demonstrated in prior chapters, PSC patients have a need for improved methods of risk stratification and disease phenotyping. The widely used ALP measurements have acknowledged limitations[9] and there is thus an unmet need for development in this area. These may be used to prepare patients better for disease progression, in planning timely liver transplantation, and for use as novel exploratory markers or end-points in vital therapeutic clinical trials. This is also relevant to other forms of AILD, for example, to better non-invasively titrate immunosuppression in AIH and to identify high risk PBC patients to prioritise for newly licensed second line therapies. Non-invasive mpMRI techniques are of particular interest given the excellent imaging of the entire liver and biliary tree that can be obtained, and utility has been demonstrated in the non-invasive assessment of liver disease[181] .

The Liver*Multiscan*™ MRI scanning protocol (Chapter 1) is one mpMRI technique, with the cT1 scores generated via this algorithm correlating with clinical outcomes in liver disease and other validated markers of liver fibrosis and inflammationin[121,123,182]. However, previous studies have focussed on the non-alcoholic steato-hepatitis, or viral hepatitis cohorts; this technology has not been investigated in AILD. The following chapter therefore describes a large prospective proof-of-concept evaluation of the utility of this in the risk stratification and phenotyping of PSC, PBC and AIH.

10.2 Aims

The aim of this study was to assess the utility of mpMRI in a cohort of real-world patients with AILD. The study objectives were to investigate the ability of mpMRI to:

1) Characterise AILD disease phenotypes.
2) Correlate with existing non-invasive markers of liver inflammation and fibrosis in AILD.
3) Correlate with disease progression or regression, potentially predicting clinically significant events in AILD.

10.3 Method

10.3.1 Study design

This study was funded by the NIHR as an academic collaboration between the University of Birmingham (acting as sponsor), UHB NHS Trust and Perspectum Diagnostics. Local ethical approval was gained via the National Research Ethics Service (West Midlands, Black Country, reference WM/14/0010) along with appropriate data sharing, confidentiality and collaboration agreements. The study was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN39463479) and was NIHR project number 15912. All principles identified in the 1975 Declaration of Helsinki[126] and GCP principles[127] were observed throughout the study. All patient-identifiable information was kept encrypted on NHS Trust servers.

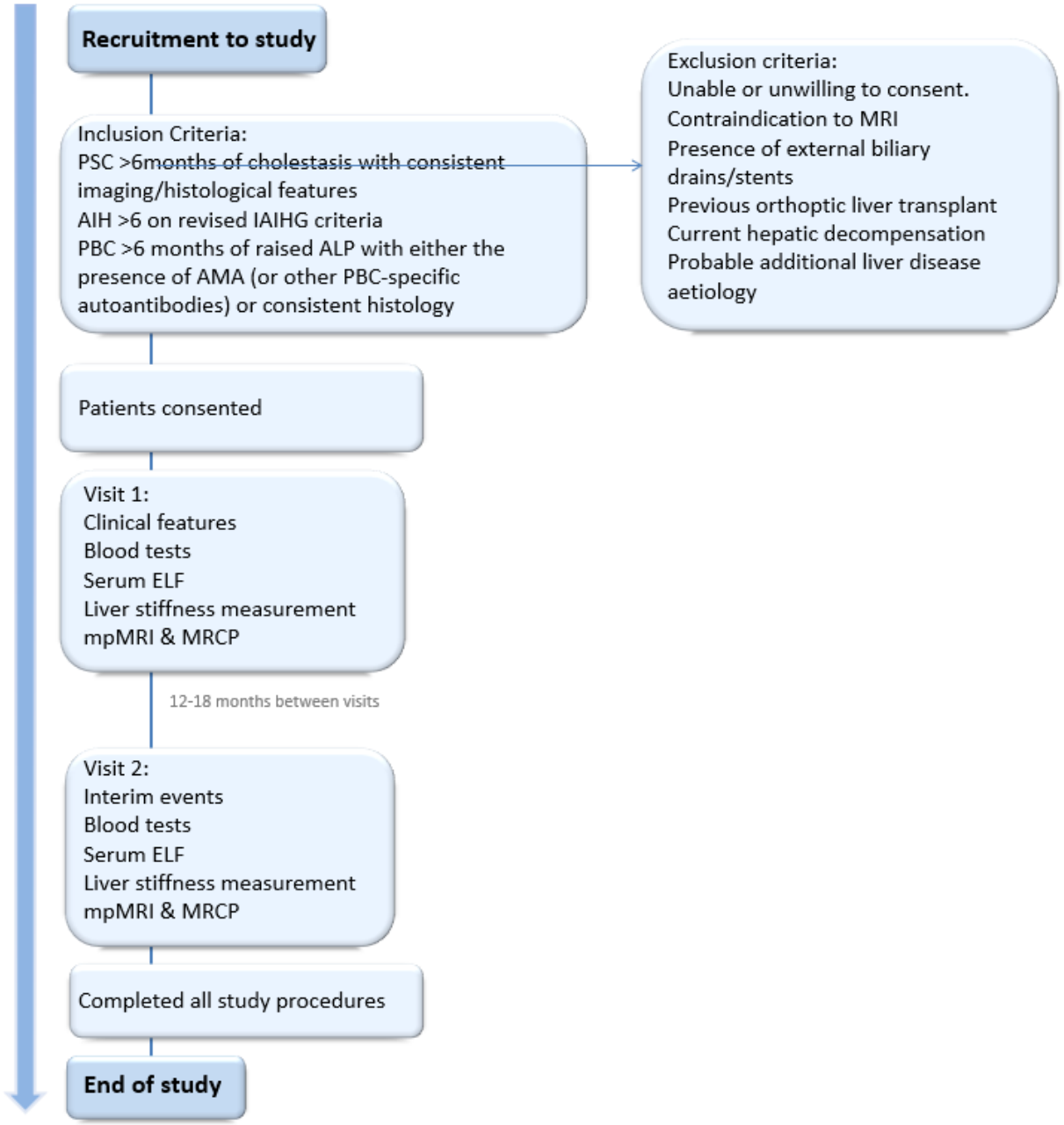
A single-centre prospective observational study of adult patients with an established diagnosis of AILD was performed. Patients were assessed on two identical visits, 12-18 months apart. On each visit, patients underwent non-invasive assessment including clinical details, medication history and clinical events, blood panel analysis (including full blood count, clotting, inflammatory markers, renal function and liver tests), ELF testing (Siemens Healthineers, Germany), liver stiffness assessment (Fibroscan, Echosens, Paris, France) and un-contrasted MRI including both a standard MRCP and Liver*Multiscan*®. Liver stiffness assessment was completed by certified operators and accepted if ten valid readings were obtained with an IQR<30%. The decision regarding appropriate probe size was indicated via the Fibroscan machine automatic probe selection tool. Where possible all procedures were completed together or within a 21-day window, after a four hour fast. Where possible,

research visits coincided with existing QEHB appointments to reduce inconvenience to patients. Figure 14 shows a summary of all study procedures.

Given the decline in patient and clinician enthusiasm for repeated histological assessment in liver disease, it was not felt appropriate to include a de novo liver biopsy within the study protocol. The study was designed to be pragmatic and based on a real-world cohort with limited resources. Thus, the study was not formally powered, however the final study size was felt reasonable for what do remain rare diseases.

Figure 14. Summary of study procedures, recruitment and follow up for the MRI study

(PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis, IAIHG- international AIH group, PBC – primary biliary cholangitis, AM – anti-mitochondrial antibody, ELF- enhanced liver fibrosis, mpMRI- multiparametric magnetic resonance imaging, MRCP – magnetic resonance cholangiopancreatograhy)



10.3.2 Recruitment

Of the 186 patients to be recruited for this study, this was to be split equally amongst PSC, AIH and PBC. While recruitment aimed for equal numbers of high and low risk patients in each group (discussed later), the final assessment of individual risk category was based on the results from Visit 1. Recruitment was from the QEHB AILD clinics, with consecutive clinic lists searched for potential participants. The Patient Information Sheet (PIS) was disseminated to these individuals at their clinic appointment, with the lead sub-investigator available to answer any questions. Follow-up was via telephone call around a week later to assess interest, before proceeding to booking in Visit 1. The full study documents including protocol can be found in Appendices K & L.

The inclusion and exclusion criteria for the study can be found in Table 28. The high-low risk stratification reflected current American Association of the Study of the Liver (AASLD) and national guidance[9].This mirrored currently recruiting clinical trials at QEHB for PBC and PSC which used evidence-based biochemical cut-offs as inclusion criteria[9,67,81]. AIH risk criteria was based on the AASLD criteria for complete and incomplete biochemical response[183], which also mirrored the UK-AIH research consortium risk grouping criteria[184]. Full risk stratification criteria are summarised in Table 29 and other important definitions including diagnoses and outcomes for the study are summarised in Table 30. Normal laboratory reference ranges at QEHB are found in Appendix B.

Table 28. MRI Study Inclusion & Exclusion criteria

Disease	*Inclusion Criteria*	*Exclusion Criteria*
PSC	At least a six-month history of cholestasis (defined as an ALP above the normal reference range at QEHB) AND With consistent imaging or histological findings (such as bile duct stricturing on ERCP/MRCP or peri-ductal fibrosis on biopsy).	Unable or unwilling to consent AND/OR Contraindication to MRI procedure AND/OR Presence of external biliary stents or drains AND/OR Previous orthoptic liver transplant AND/OR Current hepatic decompensation (such as large volume ascites or encephalopathy) AND/OR Probable additional liver disease aetiology (such as viral hepatitis, non-alcoholic steatohepatitis or secondary sclerosing cholangitis)
AIH	Historical liver biopsy with a revised IAIHG score of at least 6 AND Had been established on treatment for at least 12 months with no change in treatment planned for the next 12 months.	
PBC	At least a six-month history of cholestasis (via a raised ALP) AND at least one of the following: Positive AMA (or other PBC-specific antibodies such as anti-sp100 or gp210) AND/OR Consistent changes on liver biopsy	

Table 29. Study Risk Stratification Criteria as assessed at Visit 1 of the MRI study

Disease	*Definition of treatment response*	*High Risk Study Cohort*	*Low Risk Study Cohort*
PSC	No recommended therapy. Monitor closely to assess appropriate timing for transplantation.	ALP >1.5 times the upper limit of normal at Visit 1 (BUTEO trial criteria 30)	ALP <1.5 times the upper limit of normal AND otherwise normal liver tests AND no evidence of progressive cirrhosis/decompensated liver disease
AIH	Complete biochemical response to immunosuppression (normal ALT, IgG) AND no ongoing active inflammation on repeat histology (AASLD criteria 183)	Ongoing abnormal liver tests AND/OR progressive cirrhosis AND/OR requiring 10+mg of prednisolone (UK-AIH Group 2b criteria[184])	Normal ALT, AST and IgG AND requiring <10mg prednisolone AND no evidence of progressive cirrhosis nor any history of decompensated liver disease (UK-AIH Group 2a criteria[184])
PBC	Complete biochemical response to UDCA:- ALP <1.67xULN (Toronto criteria 87) OR bilirubin ⩽1 mg/dL (17 µmol/L), ALP ⩽3× ULN, and AST ⩽2× ULN (Paris criteria 88) OR decrease in AP >40% of pre-treatment levels (Barcelona criteria 89)	ALP ≥ 1.67x ULN (Toronto criteria87) OR Bilirubin >ULN but less than X2ULN (POISE trial criteria[185]) OR Bilirubin > ULN but ≤ 5x ULN OR ALP > 3x ULN (COBOLT trial criteria[186])	Normal liver tests AND no evidence of progressive cirrhosis nor any history of decompensated liver disease

Table 30. Other Important Study Definitions for the MRI study

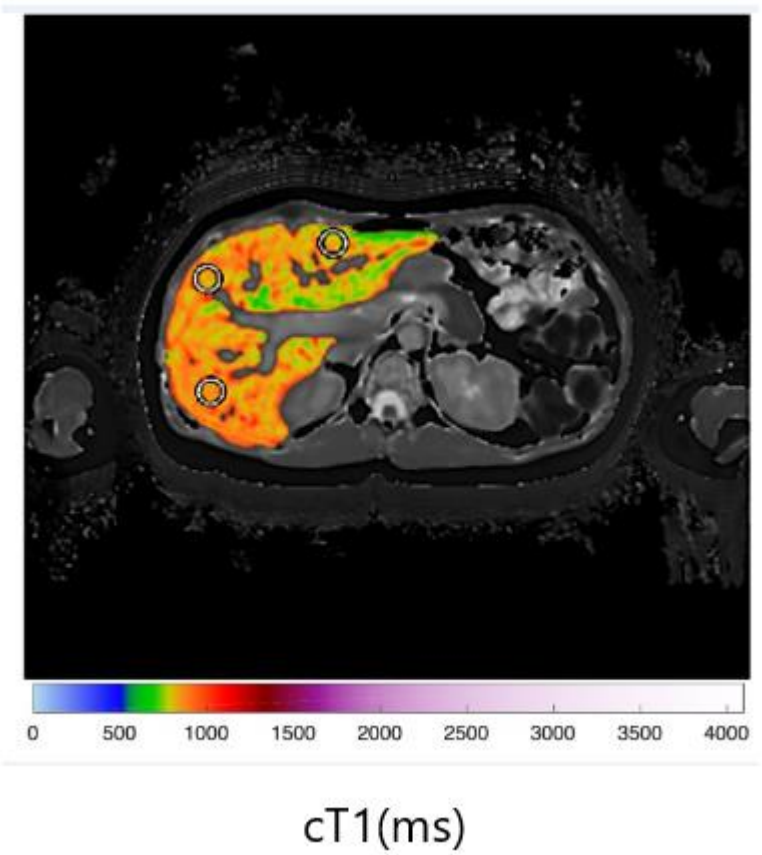
Variable	*Definition*
Large Duct PSC	Chronic cholestasis with an abnormal biliary tree seen via cholangiogram (via ERCP/MRCP) that is consistent with sclerosing cholangitis AND in the absence of a secondary aetiology.
Small Duct PSC	Chronic cholestasis with normal biliary tree imaging but with changes on liver histology consistent with PSC AND in the absence of a secondary aetiology.
Bacterial cholangitis	A worsening of cholestasis associated with typical cholangitis symptoms (increased pruritus, abdominal pain or fever) AND which was treated as such by a qualified clinician
IBD flare	An increase in bowel symptoms typical of IBD (such as diarrhoea or rectal bleeding) AND which was treated as such by a qualified clinician
AIH flare	A new ALT level above the upper limit of normal associated with a simultaneous rise in IgG AND which was treated as such by a qualified clinician
Complete AIH treatment response	All liver tests and IgG within normal range
Partial AIH Treatment response	IgG raised but in the context of otherwise normal liver tests
Incomplete AIH treatment response	Ongoing abnormal transaminase levels (ALT and/or AST) despite treatment for AIH.
Portal hypertension	The presence of at least one of the following – oesophageal varices, ascites, splenomegaly and/or low platelet count ($<50x10^9$).
Cirrhosis	An irregular liver edge on ultrasound AND/OR the presence of portal hypertension AND/OR a historic liver biopsy consistent with cirrhosis (elastography readings were not included in this definition, as these may have reflected underlying inflammation rather than cirrhosis).
Model for End-stage Liver disease score (MELD)	A predictor of survival in patients with cirrhosis; uses serum creatinine, sodium, bilirubin as well as INR and any recent history of haemodialysis[39].
AST to Platelet Ratio index (APRI)	Validated as a method of predicting the presence of fibrosis or cirrhosis in hepatitis C virus infection[103].

10.3.3 MRI protocol

The mpMRI scanning protocol was installed, calibrated and phantom tested on one 3.0 Tesla Siemens Verio MRI scanner (Siemens Healthcare GMBH, Erlangen, Germany) based at QEHB; all scans for the study were conducted using this. In the rare event of scanner malfunction, the MRI was re-scheduled within the 21-day window. Four single transverse slices were captured through the liver centred on the porta hepatis. Images were anonymised with a clinical trial number known only to the lead sub-investigator (KA) and uploaded to a secure web portal for offsite analysis using the Liver*Multiscan*® software (Perspectum Ltd., UK). The imaging analysis was completed by investigators trained in abdominal anatomy and artefact detection; cT1 maps of the liver were delineated into whole liver segmentation maps using a semi-automatic method. This produced whole liver cT1 values for which a whole liver mean cT1 and mode cT1 could be derived. CT1 IQR, a measure of the spread of cT1 values across the liver that gives information on disease heterogeneity, was also extracted from the whole liver segmentation maps.

The mpMRI metrics used for the study were cT1 mode, mean and IQR. From published literature using the same scanning algorithms, cT1 values in a low-risk population range from 573 to 852ms (median 666ms)[187]. A visual representation of the cT1 values was produced where the liver parenchyma is colour coded according to the cT1 value of each pixel. Low cT1 is represented by green increasing to yellow, orange and red for the highest cT1 results (Figure 15).

Figure 15. Example image of a semi-automatic liver cT1 map in a patient with AIH with additional three manually placed regions of interest.



10.3.4 Statistical Methods

Comparisons were made between the two risk groups for each disease subset, based on their features at Visit 1. Continuous variables were reported as medians and range. Categorical variables were reported as frequency and percentage. Confidence intervals were reported at the 95% level throughout.

Comparisons between patients with and without certain events at Visit 1 (e.g. cirrhosis, ALT flare, large duct PSC) were made using Mann-Whitney tests, with Fisher's exact test used for nominal variables. Correlations between the range of surrogate markers measured at Visit 1 (liver stiffness, APRI, ELF, MELD, INR) along with baseline and follow up cT1 measures were assessed using Spearman's correlation coefficients (rho).

Diagnostic accuracy of all markers were assessed using ROC curve analyses; these were divided into three categories: MRI, non-invasive and serum. The marker with the largest area under the curve (AUROC) in each category was identified and compared using the "roccomp" command in Stata (*Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Where a significant difference was detected between the three markers, post-hoc pairwise comparisons were performed, with the p-values Bonferroni adjusted to account for multiple comparisons.

For the AIH cohort, once patients with ALT flare at baseline were excluded, analysis for the remaining complete responders was then performed and similar analysis was performed to assess the prognostic accuracy of all markers, with respect to flares occurring during the follow

up period. Similar analyses were done for the PSC and PBC cohorts with future liver transplant assessment.

To further quantify the relationship between non-invasive metrics and future ALT flares, univariable binary logistic regression models were produced, which included the markers as continuous covariates. The goodness of fit of these models was assessed visually, with log-transformations applied, as required, in order to improve model fit. Multivariable binary logistic regression models were then produced, in order to assess whether combining the markers could improve both diagnostic and prognostic ability, with respect to flares. AUROCs were then calculated for the resulting models, and compared to those of the best individual markers.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), unless stated otherwise, with $p<0.05$ deemed to be indicative of statistical significance throughout.

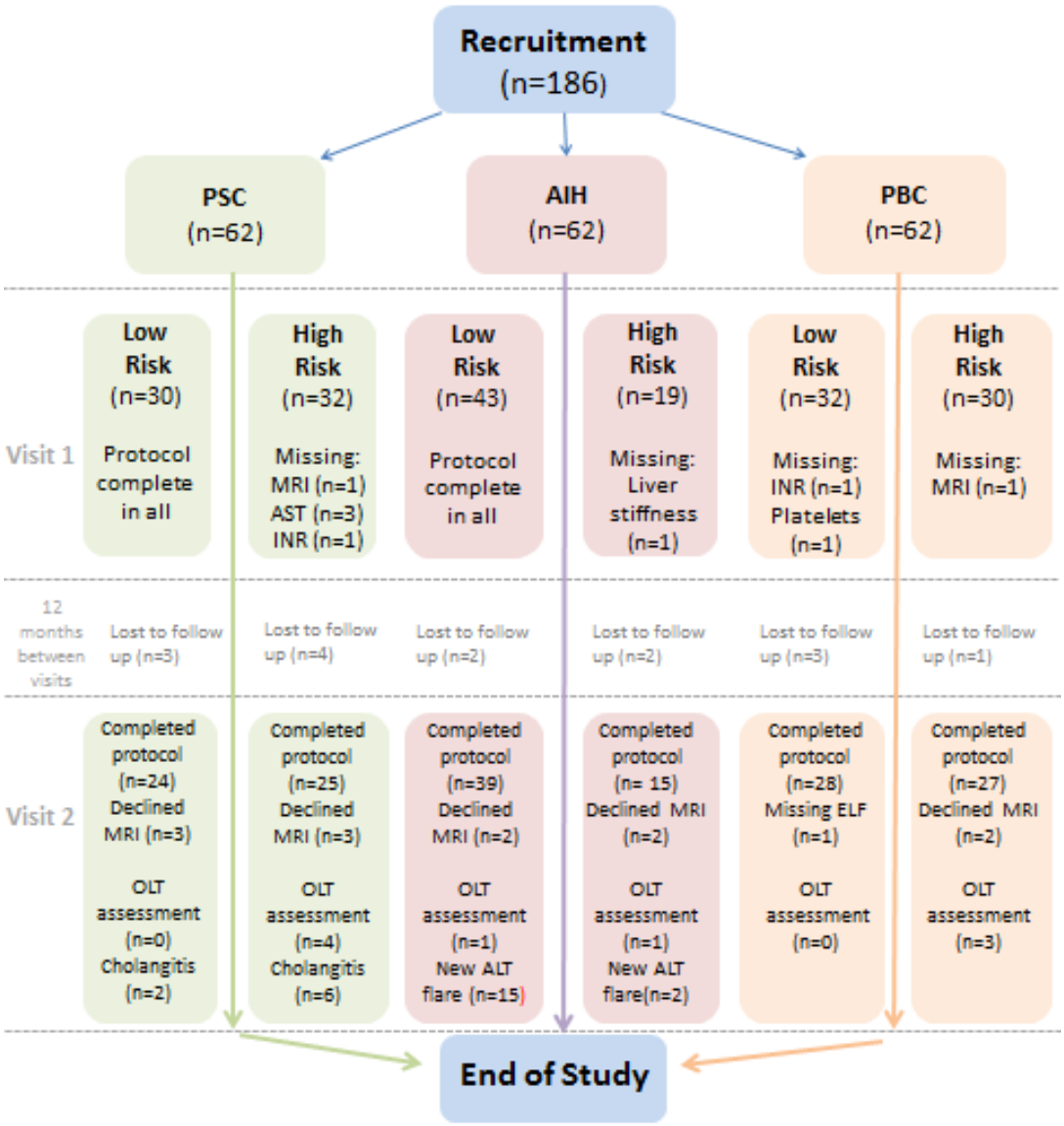
10.4 Results

In total, 186 patients were consented and recruited to the study, with 62 patients in each disease group. Risk stratification was based upon biochemical results at Visit 1. Figure 16 shows the follow up and completion rate for the study. All patients lost to follow up were due to patient choice with some declining the follow up MRI however agreed for all other study procedures to be completed.

At Visit 1, two MRI scans were of poor quality and unable to be analysed using mpMRI algorithm (PSC & PBC, both high risk cohorts); these patients were subsequently excluded from MRI analysis. Due to technical difficulties or laboratory errors, a small number of other metrics were absent (Figure 16); all ROC curve analysis was done for each variable separately to account for this and to allow inclusion of that participant for other analyses.

159 patients completed all study procedures (85%). All follow up was completed within 18 months (median 12.0 months). Patients who did not complete the follow up visit MRI were included in Visit 1 analysis however excluded from Visit 2 MRI analysis.

Figure 16: Flow chart showing the recruitment, risk stratification & outcomes for the MRI study cohort.



10.4.1 Demographics of the whole cohort

The recruitment demographics of the cohort at recruitment and corresponding MRI results are seen below (Tables 31 & 32). Differences were observed between the disease cohorts, with PSC patients being overall younger (median age 41 years vs 55 years in AIH and 54 years in PBC, p<0.001), more likely to be male (37% male in PSC vs 11% in AIH and 8% in PBC, p<0.001), and with a lower BMI (26kg/m^2 in PSC vs 28 kg/m^2 in both AIH and PBC). PSC patients were also less likely to be of White British or European ethnicity (p=0.001).

Those with cholestatic liver disease cohort (PSC & PBC) displayed higher ALP values than the AIH cohort (p<0.001, Table 30). Platelet count, ALT, and AST were lower in the AIH cohort (p=0.014 and p<0.001 respectively) however other markers of disease severity and fibrosis were similar in all groups.

MRI metrics also differed; the PSC cohort demonstrated mean cT1 898ms (range 760-1154ms) compared to 913ms in AIH (range 789-1038ms) or 891ms in PBC (range 873-1079ms). All three AILD cohorts had higher cT1 values than the 666ms (range 573-852ms) reported in healthy populations[187]. PBC participants had a lower cT1 IQR than the other cohorts (p=0.013).

Table 31. Patient Demographics at Recruitment (Visit 1) for whole MRI study cohort

Factor	*PSC cohort (n=62)*	*AIH cohort (n=62)*	*PBC cohort (n=62)*	*p-value*
Patient Characteristics				
Age (Years)	41 (18 – 70)	55 (22-80)	54 (30-81)	**<0.001**
Gender (% Male)	37 (60%)	11 (12%)	5 (8%)	**<0.001**
Body Mass Index (kg/m^2)	26 (19—34)	28 (18-41)	28 (19-40)	**0.002**
Ethnicity				**0.001**
White *Asian/British Asian* *Other*	46 (76%) 10 (16%) 5 (8%)	55 (89%) 5 (8%) 2 (3%)	60 (97%) 2 (3%) 0 (0%)	
Markers of disease activity & severity				
ALP (IU/L)	193 (62 - 1101)	73 (34-192)	153 (62-990)	**<0.001**
ALT (IU/L)	59 (12 - 487)	21 (9-219)	35 (10-225)	**<0.001**
AST (IU/L)*	34 (8-446)	24 (12-193)	37 (16-163)	**0.001**
Bilirubin (µmol/l)	11 (4 - 62)	10 (4-57)	10 (3-67)	0.225
Platelets (x10^9/L)	254 (30 - 474)	212 (40-352)	230 (48-405)	**0.014**
IgG (g/L)	12.8 (10.6-27.3)	11.4 (4.1-27.2)	12.2 (6.8-28.8)	0.451
MELD	7 (6 - 13)	7 (6-14)	6 (6-13)	0.775
APRI	0.43 (0.05 – 22.64)	0.30 (0.09-9.97))	0.42 (0.12-5.26)	0.509
FIB-4	1.00 (0.20 – 11.37)	1.40 (0.28-19.03	1.57 (1.04-15.09)	0.104
ELF	9.30 (7.08 – 12.65)	9.38 (7.67-12.67)	9.72 (7.24-14.61)	0.124
Liver stiffness (kPa)**	7.7 (3.9 - 75.0)	6.9 (2.9-27.7)	7.6 (2.7-75.0)	0.118
Cirrhosis	21 (34%)	25 (40%)	18 (29%)	0.414
Evidence of portal hypertension	16 (26%)	15 (24%)	13 (21%)	0.812

*Data are reported as median (range), with p-values from Mann-Whitney tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05. *n=59 for PSC cohort. **n=61 for AIH cohort, due to missing data.*

Table 32: Multi-parametric MRI metrics at Recruitment (Visit 1) for whole MRI study cohort

Factor	*PSC (n=61)*	*AIH (N=62)*	*PBC (N=61)*	*P value*
cT1 Whole Mean (ms)	898 (760 – 1154)	913 (789-1038)	891 (873-1079)	0.874
cT1 Whole Mode (ms)	797 (600 – 1050)	816 (705-951)	812 (629-1024)	0.283
cT1 Whole IQR (ms)	123 (77 – 481)	121 (73-268)	109 (106-215)	**0.013**

Data are reported as median (range), with p-values from Mann-Whitney tests. Bold p-values are significant at p<0.05.

10.4.2 Liver biopsy

Histological assessment was not part of the study protocol however consent was gained to gather data on any previous histological assessment performed (Table 33). AIH patients were more likely to have undergone liver biopsy than patients with cholestatic liver disease ($p<0.001$). PBC patients were less likely to have undergone biopsy than those with PSC ($p=0.020$). It was observed by the investigator that varying terminology was used within the histology reports, making standardisation of the fibrosis assessment difficult.

Table 33. Previous liver histology results for whole MRI study cohort.

Cohort	*Prior liver biopsy*	*Result available*	*No fibrosis*	*Mild fibrosis*	*Moderate Fibrosis*	*Severe fibrosis*	*Cirrhosis*	*Lag time (years)*
PSC	32 (52%)	24 (72%)	2 (7%)	12 (40%)	7 (23%)	2 (7%)	1 (3%)	5 (1-17)
AIH	62 (100%)	50 (83%)	11 (22%)	17 (34%)	10 (20%)	6 (12%)	6 (12%)	4 (1-28)
PBC	18 (29%)	11 (61%)	3 (27%)	7 (64%)	0 (0%)	1 (9%)	0 (0%)	7 (1-20)

Data are reported as N (%) or as median (range).

10.4.3 mpMRI correlates with existing markers of disease activity and severity

Baseline correlations between MRI metrics and other surrogate markers of liver inflammation at Visit 1 were analysed (Table 34). Similar findings were observed at Visit 2 (Appendix M). Mean cT1 correlated with markers of liver inflammation in all disease cohorts; this included ALT, AST and IgG in the AIH cohort (ALT: p=0.033, AST: p=0.014 and IgG: p=0.015) and IgG alone in both the PSC (IgG: p<0.001) and PBC cohorts (IgG p=0.006).

Mean cT1 also correlated with surrogate markers of disease severity in all cohorts; in AIH (INR: p=0.005, MELD: p=0.020, ELF: p=0.022, liver stiffness: p<0.001), in PSC (MELD: p<0.019, liver stiffness: p<0.038) and PBC (liver stiffness, ELF, both p<0.001). ALP correlated with mean cT1 in PBC (p=0.026) but not PSC (p=0.817). ALP in PSC was correlated to cT1 IQR (p<0.001).

The association between mpMRI disease heterogeneity (cT1 IQR) and serum liver tests also showed correlations in all cohorts; in AIH (platelets: p=0.001, AST: p=0.003, bilirubin: p<0.001), PSC (platelets: p=0.002, ALT: p=0.002, ALP: p<0.001, bilirubin: p<0.001) and in PBC (platelets: p<0.001, AST: p=0.044, bilirubin; p=0.003). CT1 IQR also correlated with other markers of disease severity including liver stiffness and APRI in all three cohorts (p<0.001) and in cholestatic liver disease with ELF (PSC p=0.002, PBC p<0.001) and MELD (p<0.001).

The three disease cohorts then underwent further disease-specific analysis, described below.

Table 34. Correlations between MRI metrics with other markers at Visit 1 (whole cohort).

	PSC (n=61)			AIH (n=62)			PBC (n=61)		
	cT1 mean	*cT1 mode*	*cT1 IQR*	*cT1 mean*	*cT1 mode*	*cT1 IQR*	*cT1 mean*	*cT1 mode*	*cT1 IQR*
Correlation with Serum Liver and Serum Liver tests									
Platelets	0.040 p=0.759	**0.257** p=**0.045**	**0.391** **p=0.002**	-0.146 p=0.256	0.038 p=0.771	**-0.401** **p=0.001**	-0.164 p=0.211	-0.132 p=0.314	**-0.459** **p<0.001**
ALT	-0.104 p=0.427	-0.236 p=0.068	**p=0.386** **0.002**	**0.272** **p=0.033**	0.226 p=0.077	0.176 p=0.171	0.069 p=0.597	0.030 p=0.817	0.169 p=0.193
AST	0.012 p=0.927	-0.212 p=0.110	**0.500** **p<0.001**	**0.311** **p=0.014**	0.165 p=0.200	**0.349** **p=0.005**	0.206 p=0.111	0.162 p=0.213	**0.259** **p=0.044**
Bilirubin	0.204 p=0.115	-0.094 p=0.473	**0.537** **p<0.001**	0.242 p=0.058	0.17 p=0.180	**0.494** **p<0.001**	0.144 p=0.270	0.107 p=0.412	**0.375** **p=0.003**
ALP	0.030 p=0.817	-0.203 p=0.117	**0.443** **p<0.001**	0.203 p=0.114	0.169 p=0.189	0.036 p=0.782	**0.265** **p=0.026**	0.222 p=0.086	0.218 p=0.091
IgG	**0.448** **p<0.001**	**0.244** **p=0.001**	**0.279** **p=0.029**	**0.308** p=**0.015**	**0.266** **p=0.037**	0.194 p=0.131	**0.351** **p=0.006**	**0.309** **p=0.015**	0.248 p=0.054
Correlation with Surrogate Disease severity markers									
Liver Stiffness	**0.267** **p=0.038**	0.014 p=0.912	**0.589** **p<0.001**	**0.578** **p<0.001**	**0.392** **p=0.002**	**0.523** **p<0.001**	**0.495** **p<0.001**	**0.468** **p<0.001**	**0.457** **p<0.001**
APRI	0.017 p=0.900	**-0.285** **p=0.030**	**0.607** **p<0.001**	**0.304** **p=0.016**	0.122 p=0.346	**0.462** **p<0.001**	0.234 p=0.071	0.185 p=0.156	**0.434** **p=0.001**
MELD	0.205 p=0.114	-0.074 p=0.573	**0.46** **p<0.001**	**0.327** **p=0.009**	0.247 p=0.053	0.204 p=0.112	0.071 p=0.586	0.024 p=0.855	**0.429** **p=0.001**
ELF	0.138 p=0.290	-0.079 p=0.543	**0.390** **p=0.002**	**0.317** **p=0.012**	**0.251** **p=0.050**	0.196 p=0.128	**0.398** **p=0.001**	**0.338** **p=0.008**	**0.435** **p<0.001**
INR	**0.303** **p=0.019**	0.159 p=0.225	0.173 p=0.187	**0.418** **p=0.001**	**0.295** **p=0.020**	0.224 p=0.081	0.205 p=0.112	0.142 p=0.274	**0.369** **p=0.003**

Data are reported as Spearman's rho correlation coefficients and p-values. Bold values are significant at p<0.05. Liver stiffness was unavailable for one patient (AIH), two MRIs were of insufficient quality for analysis and two INR values were also missing (one each from PBC &PSC) and three AST values were also missing (PSC), thus analysis is based on n=61, n=60 and n=59 respectively. Significant associations are highlighted in bold.

10.4.4 PSC

10.4.4.1 PSC cohort additional demographics

Additional PSC-specific demographics are seen in Table 35. The high-low risk group demographics were similar, with lower BMI observed in the high-risk cohort (p=0.014). Markers of disease activity and severity were worse in the high-risk cohort. Visit 1 mpMRI values showed higher cT1 IQR values in the high-risk group (p=0.001).

10.4.4.2 PSC Patient Outcomes & Follow-up

Four patients in the PSC cohort were successfully assessed for liver transplantation, all in the high-risk group (p=0.114), and one participant underwent transplant surgery during the study period. Eight patients (13%) underwent treatment for bacterial cholangitis (six high-risk, two low-risk, p=0.258). No de novo cirrhosis, portal hypertension or cholangiocarcinoma were diagnosed during the study. Figure 17 shows exemplars of the MRI findings in the PSC study cohort.

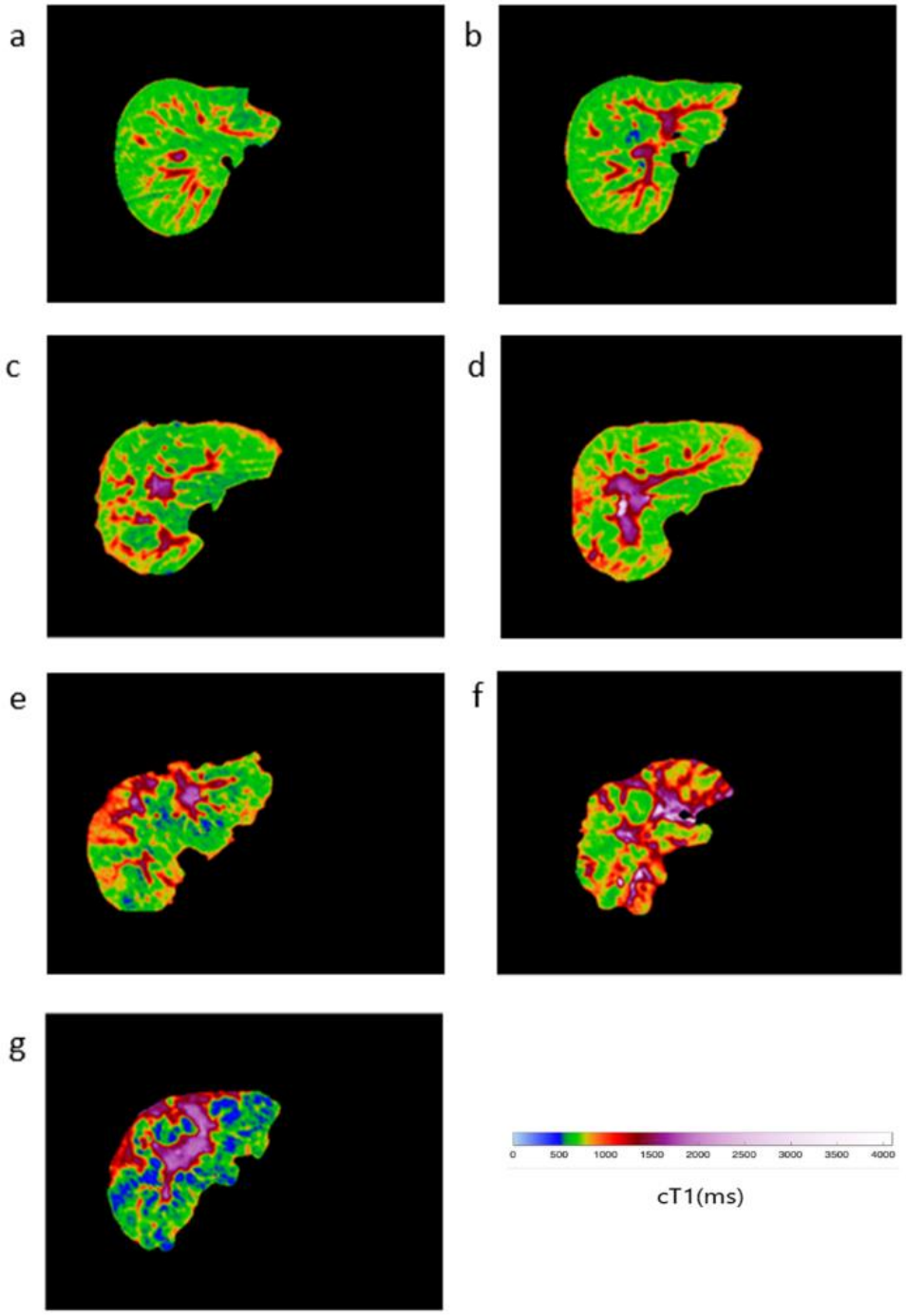
***Table 35. MRI PSC cohort demographics at recruitment (Visit 1) based on study risk criteria* (ALP)**

Factors	*Low risk (n=30)*	*High risk (n=32)*	*p-value*
Patient Characteristics			
Age (Years)	42.5 (18.0-70.3)	40.2 (18.3-65.8)	0.455
Gender (% Male)	19 (63%)	18 (56%)	0.613
Body Mass Index (kg/m^2)	26.8 (20.6-34.2)	24.5 (19.7-33.0)	**0.014**
Ethnicity			
White	23 (77%)	24 (75%)	1.000
British Asian	6 (20%)	4(13%)	0.502
Other	1 (3%)	4 (13%)	0.355
Large duct PSC	28 (93%)	26 (81%)	0.258
Inflammatory PSC (ALT>5xULN)	0 (0%)	4 (13%)	0.114
UDCA Prescribed	13 (43%)	11 (34%)	0.603
Median dose of UDCA (mg/kg)*	10.8 (5.0-16.1)	10.4 (6.0-15.4)	0.418
Inflammatory Bowel Disease			
Diagnosis of IBD	24 (80%)	26 (81%)	1.000
*Ulcerative colitis****	22 (92%)	23 (88%)	1.000
*Chrons Disease/Indeterminate****	2 (8%)	3 (12%)	
Current IBD treatment (n=50)			
None	13 (26%)	6 (12%)	0.054
5ASA	9 (18%)	18 (36%)	**0.045**
Corticosteroids	1 (2%)	3 (6%)	0.613
Azathioprine	2 (4%)	3 (6%)	1.000
Biological therapy	1 (2%)	2 (4%)	1.000
History of colorectal surgery	7 (14%)	1 (2%)	**0.024**
Flare <12 months prior to recruitment	4 (17%)	3 (11%)	0.703
IBD flare during follow up****	0 (0%)	2 (6%)	0.492
Markers of Disease activity & Severity			
ALP (IU/L)	98 (62-193)	381 (165-1101)	**<0.001**
ALT (IU/ml)	27 (12-175)	105 (26-487)	**<0.001**
Bilirubin (µmol/l)	10 (4 – 25)	17 (4 – 62)	**0.003**
Platelets (x10^9/L)	250 (110 – 429)	256 (30 – 474)	0.414
MELD	6 (6-10)	7 (6-13)	**0.020**
UKELD	45 (41-51)	47 (40-51)	**0.032**
APRI	0.27 (0.05 – 0.76)	0.87 (0.18 – 22.64)	**<0.001**
FIB-4	0.84 (0.20 – 4.19)	1.24 (0.40 – 11.37)	**0.008**
ELF	8.46 (7.08 – 10.61)	10.30 (7.94 – 12.65)	**<0.001**
Liver stiffness (kPa, n=61)	6.3 (3.9-11.9)	11.8 (5.1-75.0)	**<0.001**
Cirrhosis	6 (20%)	15 (47%)	**0.033**
Low risk (Modified Mayo PSC Score <0)**	27 (90%)	19 (66%)	**0.008**
MRI Metrics			
cT1 Mean (ms)	891 (789-1121)	914 (760-1154)	0.157
cT1 Mode (ms)	802 (707-1050)	792 (600-1087)	0.714
cT1 IQR (ms)	109 (81-178)	132 (77-482)	**0.001**

*Data are reported as median (range), with p-values from Mann-Whitney tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05. *In patients on UDCA.** In patients with complete data (n=59/30/29).*

Figure 17. Example colour-coded images of MRI liver segmentation cT1 maps in MRI patients with PSC according to clinical risk group at Visit 1 and interim events/outcomes.

a) LAMP-151. Low risk group at Visit 1 with ALP 142, cT1 IQR 90ms.
b) LAMP-151. No change clinically by Visit 2, ALP 134, cT1 IQR 105ms.
c) LAMP-072. Low risk group at Visit 1 with ALP 121, cT1 IQR 158 ms.
d) LAMP-072. Interim cholangitis with Visit 2 ALP 143, cT1 IQR 153ms.
e) LAMP-084. High risk group at Visit 1 with ALP 959, cT1 IQR 266ms.
f) LAMP-084. Interim transplant assessment with Visit 2 ALP 582, cT1 IQR 407ms.
g) LAMP-058. High risk group at Visit 1 with ALP 303, cT1 IQR 481ms. Interim liver transplant so no Visit 2 data.



10.4.4.3 Correlation and prediction of clinically important outcomes

The association of mpMRI and other non-invasive tests to current cirrhosis or high-risk criteria was assessed (Table 36). Current cirrhosis was associated with cT1 IQR (AUROC 0.713, p=0.007), liver stiffness (AUROC 0.778, p<0.001) and bilirubin (AUROC 0.832, p<0.001). Large duct PSC was associated with higher cT1 IQR (AUROC 0.756, p=0.020) and lower platelet count (AUROC 0.773, p=0.013) than small duct PSC. Cirrhosis was associated with higher ALP (AUROC 0.672, p=0.028) and more so with bilirubin (AUROC 0.832, p<0.001)

Future transplant assessment was not associated with study high-risk classification (p=0.114), modified Mayo PSC score (p=0.062), UDCA use (p=0.151), ethnicity (p=1.000) or IBD status (p=0.578). This outcome was predicted by cT1 IQR (AUROC 0.895, p=0.009), liver stiffness (AUROC 0.897, p=0.005) and inverse platelet count (AUROC 0.987, p=0.001). CT1 IQR was higher in those subsequently assessed for transplant (mean cT1 IQR: 130ms vs 291ms, p<0.001).

Comparisons were made between the best markers from the three modalities (mpMRI, elastography and serum markers) in the association with important clinical outcomes; none were statistically superior (Table 37). Liver stiffness >11kPa increased the risk for future transplant assessment from 0% to 21% (sensitivity 100%, specificity 74%); cT1 IQR >240ms increased this risk from 2% to 75% (sensitivity 75%, specificity 98%).

Future bacterial cholangitis was associated with IgG (AUROC 0.822, p=0.024) however not with other surrogate marker of disease activity, mpMRI metrics or high-risk stratification. In the high-risk cohort, IgG >15.0 increased the risk of future cholangitis from 0% to 31% (sensitivity of 100%, specificity 59%).

Table 36. The association and predictive values of non-invasive tests to current or future clinically important outcomes for the MRI PSC study cohort.

	Large Duct disease (n=61)		*Cirrhosis (n=61)*		*Transplant Assessment (n=61)*	
	AUROC (SE)	*p-Value*	*AUROC (SE)*	*p-Value*	*AUROC (SE)*	*p-Value*
MRI metrics						
cT1 mode	0.544 (0.114)	0.693	0.445 (0.080)	0.480	0.647* (0.124)	0.329
cT1 mean	0.531 (0.112)	0.781	0.577 (0.084)	0.324	0.728 (0.179)	0.130
cT1 IQR	**0.756 (0.092)**	**0.020**	**0.713 (0.070)**	**0.007**	**0.895 (0.085)**	**0.009**
Elastography						
Liver stiffness	0.664 (0.116)	0.138	**0.778 (0.059**	**<0.001**	**0.897 (0.070)**	**0.005**
Serum Markers						
Platelets	**0.775* (0.069)**	**0.013**	**0.772* (0.070)**	**0.001**	**0.987* (0.015)**	**0.001**
INR* **	0.574 (0.107)	0.526	0.541 (0.086)	0.601	0.732 (0.207)	0.123
ALT	0.570 (0.099)	0.529	**0.662 (0.069)**	**0.039**	0.711 (0.106)	0.162
AST**	0.580 (0.119)	0.497	**0.701 (0.071)**	**0.013**	0.791 (0.082)	0.054
ALP	0.640 (0.122)	0.204	**0.672 (0.079)**	**0.028**	0.748 (0.091)	0.100
Bilirubin	0.612 (0.128)	0.310	**0.832 (0.057)**	**<0.001**	**0.958 (0.026)**	**<0.002**
IgG	0.651* (0.089)	0.172	0.588 (0.079)	0.261	0.675 (0.195)	0.244
MELD	0.624 (0.107)	0.262	**0.720 (0.070)**	**0.005**	**0.974 (0.020)**	**0.002**
APRI Score**	0.670 (0.111)	0.146	**0.771 (0.069)**	**0.001**	**0.959 (0.027)**	**0.002**
FIB-4 Score**	0.695 (0.101)	0.096	0.638 (0.089)	0.089	**0.945 (0.040)**	**0.003**
Mayo Risk Score**	0.580 (0.112)	0.497	**0.666 (0.085)**	**0.040**	**0.666 (0.064)**	**0.040**
ELF	0.511 (0.117)	0.923	**0.771 (0.069)**	**0.001**	**0.921 (0.041)**	**0.005**

*Bold values are significant at p<0.05 with the best marker for each modality also being underlined. *Inverse relationship, i.e. a higher value of the marker was associated with a lower risk. **n=58 due to missing data, ***n=60 due to missing data.*

Table 37. Comparisons of ROC curves for the best predictors of current/future outcomes of the MRI PSC study cohort

	Strongest Predictor			
Outcome	***MRI***	***Elastography***	***Serum Markers***	***p-Value***
Large Duct Disease	cT1 IQR	Liver Stiffness	Platelets	0.653
Cirrhosis	cT1 IQR	Liver Stiffness	Bilirubin	0.313
OLT Assessment	cT1 IQR	Liver Stiffness	Platelets	0.369

Comparisons are between the AUROCs of the most predictive markers from each of the three categories.

10.4.4.4 Use of Ursodeoxycholic Acid

The effect of UDCA in PSC was then evaluated (Table 37). The UDCA-taking cohort had higher BMI (p=0.002) and mode cT1 (p=0.042) but lower bilirubin (p=0.021) and APRI scores (p=0.012). ALP was no different (p=0.448, Table 38).

Table 38. MRI Study Patient Demographics at Recruitment based on Visit 1 UDCA use

Factor	*Statistic*			
	Whole cohort	*On UDCA (n=24)*	*No UDCA (n=38)*	*p-value*
Patient Characteristics				
Age (Years)	41.1 (18.0 – 70.3)	49.9 (18.0-65.2)	38.6 (18.3-70.3)	0.251
Gender (% Male)	37 (60%)	17 (71%)	20 (53%)	0.190
Body Mass Index (kg/m2)	26.3 (19.7— 34.2)	27.0 (20.0-34.2)	24.5 (19.7-33.0)	**0.002**
White ethnicity	46 (76%)	18 (75%)	28 (74%)	1.00
Diagnosis of IBD	50 (81%)	18 (75%)	32 (84%)	0.511
Markers of disease activity & severity				
ALP (IU/L)	193 (62 - 1101)	170 (66-512)	246 (62-1101)	0.448
ALT (IU/L)	59 (12 - 487)	55 (16-165)	69 (12-487)	0.150
Bilirubin (µmol/l)	11 (4 - 62)	10 (4 – 25)	14 (4 – 62)	**0.021**
Platelets (x10^9/L)	254 (30 - 474)	260 (132 – 474)	242 (30 – 429)	0.074
INR	1.0 (0.9-1.4)	1.0 (1.0-1.2)	1.0 (0.9 – 1.4)	0.054
MELD	7 (6 - 13)	7 (6-9)	7 (6-13)	0.988
APRI	0.43 (0.05 – 22.64)	0.31 (0.15 – 1.15)	0.62 (0.05 – 22.64)	**0.012**
FIB-4	1.00 (0.20 – 11.37)	0.91 (0.30 – 3.77)	1.05 (0.20 – 11.37)	0.127
ELF	9.30 (7.08 – 12.65)	8.85 (7.84 – 10.82)	9.85 (7.08 – 12.65)	0.181
Liver stiffness (kPa, n=61)	7.7 (3.9 - 75.0)	7.7 (5.3-23.4)	7.6 (3.9-75.0)	0.828
MRI metrics				
cT1 Whole Mode (ms)	797 (600 – 1050)	818 (685 – 726)	794 (600 – 1050)	**0.042**
cT1 Whole Mean (ms)	898 (760 – 1154)	908 (808 – 1109)	888 (760 – 1154)	0.211
cT1 Whole IQR (ms)	123 (77 – 481)	117 (77 – 423)	125 (81 – 482)	0.508

Data are reported as median (range), with p-values from Mann-Whitney tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05.

10.4.5 AIH

10.4.5.1 AIH cohort additional demographics

At Visit 1, 50 patients (81%) were in complete biochemical remission. The remaining 12 (19%) demonstrated abnormal liver tests and/or IgG. Despite current biochemical remission, seven remained high risk as per the study protocol, all due to ongoing high corticosteroid doses with evidence of previous flares when this dose was reduced. Thus, 19 patients were overall classed as high risk for the purposes of this study. All patients were currently on immunosuppressant medication (Table 39).

10.4.5.2 Visit 1 ALT Flare associates with markers of disease activity and fibrosis

The Visit 1 demographics of those with a current ALT flare or other high-risk features (n=19) were similar to the low risk cohort (n=43, see Table 40). Of participants on single agent therapy (n=28, 45%), those on azathioprine were more likely to have normal liver tests (n=21, p=0.038).

Disease activity and severity markers were raised in the high-risk group including ALT, IgG (both p=<0.001), bilirubin (p=0.016), MELD score (p=0.005) and liver stiffness (p=0.007). ELF was not raised in higher risk patients (p=0.051), neither were mpMRI metrics (Table 40).

Table 39. Immunosuppression usage in the MRI AIH cohort

Medication type	*Number (%)*
Single agent therapy	28 (45%)
Corticosteroid	3 (5%)
Azathioprine	21 (34%)
MMF	3 (5%)
Biological therapy	1 (2%)
Dual agent therapy	34 (55%)
Azathioprine & Corticosteroid	21 (34%)
MMF & corticosteroid	8 (25%)
Corticosteroid & biological therapy	5 (8%)

Data are reported as number (%).

Table 40. MRI AIH cohort demographics by biochemical response criteria at Visit 1

Factor	Whole Cohort (n=62)	Biochemical Response at Visit 1		p-value
		Complete (n=43)	*Incomplete/otherwise high-risk features (n=19)*	
Patient characteristics				
Age (Years)	55 (22-80)	57 (22-80)	46 (27-73)	0.261
Gender (% Female)	51 (82%)	34 (79%)	17 (89%)	0.478
Body Mass Index (kg/m^2)	28 (18-41)	29 (20-39)	26 (18-40)	0.084
Ethnicity				1.000
Caucasian *British Indian* *Other*	55 (89%) 6 (10%) 1 (2%)	37 (86%) 5 (12%) 1 (2%)	18 (95%) 1 (5%) 0 (0%)	
Type 1 AIH	61 (98%)	43 (100%)	18 (95%)	0.129
Anti-SLA antibody positive (n=56)	16 (29%)	10 (27%)	6 (32%)	0.761
Markers of disease activity & severity				
Platelets (x10^9/L)	212 (40-352)	227 (44-352)	164 (40-324)	**0.004**
INR	1.0 (0.9-2.8)	1.0 (0.9-1.4)	1.1 (1.0-2.8)	**<0.001**
ALT (IU/L)	21 (9-219)	18 (9-35)	47 (10-219)	**<0.001**
AST (IU/L)	24 (12-193)	22 (12-38)	42 (19-193)	**<0.001**
IgG (g/L)	11.4 (4.1-27.2)	10.2 (4.1-15.8)	17.8 (8.6-27.2)	**<0.001**
Bilirubin (µmol/l)	10 (4- 57)	9 (5-20)	12 (4-57)	**0.016**
MELD	7 (6-14)	6 (6-11)	7 (6-14)	**0.005**
AST:ALT	1.23 (0.43-2.27)	1.23 (0.70-1.92)	1.04 (0.43-2.27)	0.177
APRI	0.30 (0.09-9.97)	0.25 (0.09-1.80)	0.52 (0.23-9.97)	**<0.001**
FIB-4	1.40 (0.28-19.03)	1.36 (0.28-6.91)	1.69 (0.56-19.03)	**0.018**
ELF	9.38 (7.67-12.67)	9.37 (7.67-11.62)	9.84 (8.71-12.67)	0.051
Liver stiffness (kPa,n=61)	6.9 (2.9-27.7)	6.2 (2.9-27.7)	8.6 (3.1-26.3)	**0.007**
Cirrhosis	25 (40%)	13 (30%)	12 (63%)	**0.024**
Portal hypertension	15 (24%)	5 (12%)	10 (53%)	**0.001**
MRI Metrics				
cT1 Mean (ms)	913 (789-1038)	909 (789-1029)	928 (858-1038)	0.078
cT1 Mode (ms)	816 (705-951)	817 (705-951)	813 (750-922)	0.478
cT1 IQR (ms)	121 (73-268)	116 (73-230)	129 (85-268)	0.090

*Data are reported as median (range), with p-values from Mann-Whitney tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05.*Excludes patients with ALT flares at Visit 1. **The proportion of patients that returned for Visit 2.*

10.4.5.3 AIH Patient Outcomes & Follow-up

Of the 50 patients with normal Visit 1 liver tests, 48 returned for Visit 2 (96%), of whom 45 (90%) completed the second mpMRI (Figure 14). 16 new ALT flares were observed during follow up (32% of initial complete responders), either between visits (n=9, 56%) or were newly identified at Visit 2 (n=7, 44%). No patients developed de novo clinical cirrhosis or portal hypertension during the study period. Imaging exemplars of Visit 1 and 2 findings with respect to outcomes can be seen in Figure 18.

10.4.5.4 Predicting future ALT flare events

The strongest predictor of future ALT flare was a lower Visit 1 AST:ALT (AUROC 0.849, p<0.001, Table 41). Of the mpMRI metrics, cT1 mode was the strongest predictor of future flare (AUROC 0.727, p=0.009) and was not inferior to AST:ALT (p=0.631, Figure 19). Multivariate analysis found these markers to be significant independent predictors of future flares, with odds ratios of 1.37 per 10ms (95% CI: 1.08 – 1.76, p=0.011) for cT1 mode and 0.40 per 0.1 units (95% CI: 0.22 – 0.72, p=0.003) for the ALT:AST ratio. Combining these markers (AUROC of 0.955, SE: 0.028, p<0.001) was not a significant improvement on the ALS:AST ratio alone (AUROC: 0.899, p=0.180).

The optimal cut-off values were then identified for the markers, based on the values that maximised the Youden's J statistic. Of those with cT1 mode <810ms, 10% encountered a future flare, compared to 57% if this metric was 810+ms (87% sensitivity, 64% specificity). None of the twelve patients with cT1 mode < 800ms at baseline had a subsequent flare event.

Of those with AST:ALT 1.2+, 11% had a future flare, compared to 75% of those with values <1.2 (80% sensitivity, 86% specificity).

Liver stiffness did not predict future flare (AUROC 0.502, p=0.983), nor did ELF (AUROC 0.501, p=0.992).

Figure 18. Example colour-coded images of liver segmentation cT1 maps in MRI patients with AIH according to clinical risk group at Visit 1 and interim events/outcomes.

a) LAMP-146. Low risk group at Visit 1 with ALT 9 IU, cT1 mode 737ms.
b) LAMP-146. No ALT flare during follow up with Visit 2 ALT 16IU, cT1 mode 734ms.
c) LAMP-024. Low risk group at Visit 1 with ALT 27IU, cT1 mode 914ms.
d) LAMP-024. Interim ALT flare, ALT at Visit 2 68IU, cT1 mode 1078ms.
e) LAMP-045. High risk group at Visit 1 with ALT 31, cT1 mode 850ms.
f) LAMP-045. Interim ALT flare, ALT at visit 2 206IU, cT1 mode 911ms.
g) LAMP-156.High risk group at Visit 1 with ALT 32 IU, cT1 mode 915ms. Interim liver transplant so did not complete Visit 2.

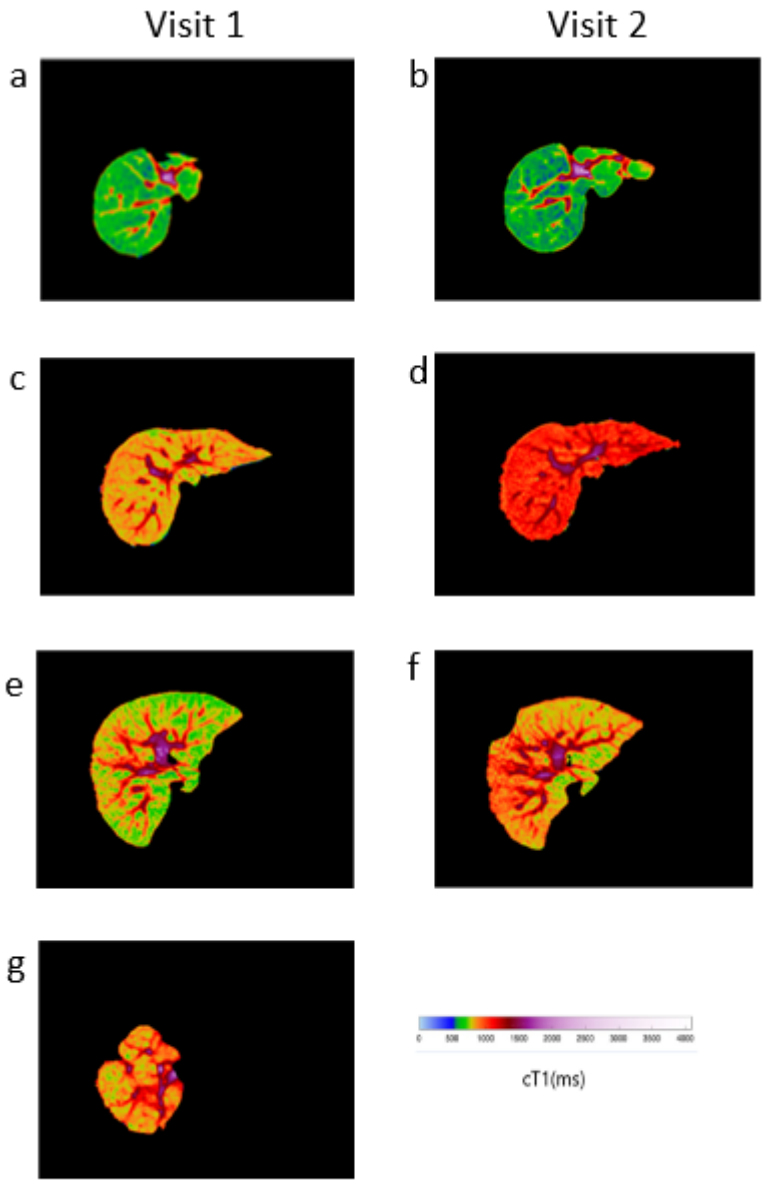
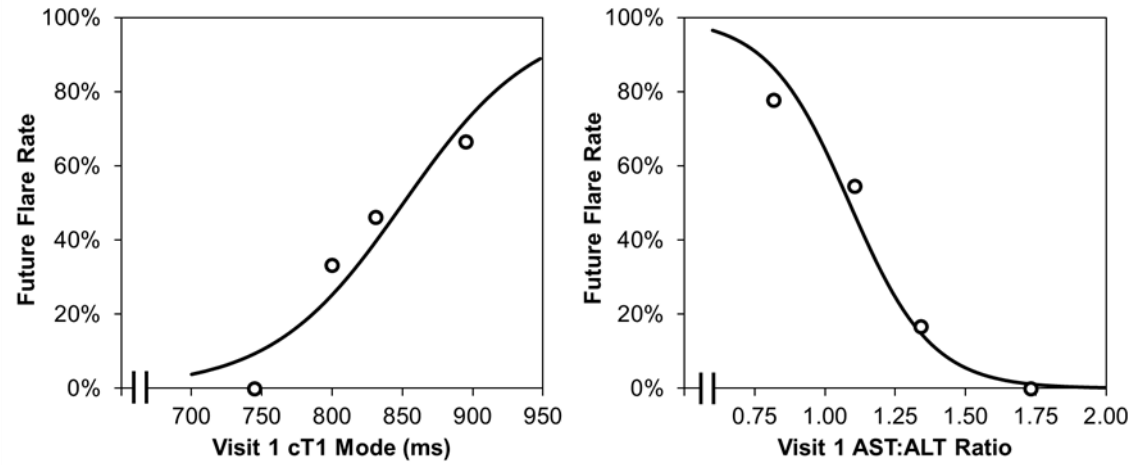


Table 41: The prognostic accuracy of Visit 1 markers with respect to future ALT flares in the MRI AIH cohort

Factor	*All cases (N=50)*		*Complete response at Visit 1 (n=43)*		*Incomplete response at Visit 1 (n=7)*	
	AUROC (SE)	*p-Value*	*AUROC (SE)*	*p-Value*	*AUROC (SE)*	*p-Value*
MRI Metrics						
cT1 mean	0.654 (0.077)	0.076	**0.683 (0.080)**	**0.050**	0.600* (0.219)	0.699
cT1 mode	**0.727 (0.070)**	**0.009**	**0.793 (0.068)**	**0.002**	0.600* (0.219)	0.699
cT1 IQR	0.649* (0.086)	0.087	**0.707* (0.088)**	**0.027**	0.800 (0.179)	0.245
Elastography						
Liver stiffness**	0.502* (0.091)	0.983	0.531 (0.101)	0.743	0.850* (0.154)	0.175
Serum markers of disease activity & severity						
Platelets	0.578 (0.089)	0.368	0.568 (0.098)	0.468	0.700 (0.202)	0.439
INR	0.578 (0.086)	0.368	0.592 (0.092)	0.327	0.500 (0.228)	1.000
ALT	**0.744 (0.086)**	**0.005**	**0.779 (0.085)**	**0.003**	0.600 (0.303)	0.699
AST	0.556 (0.094)	0.519	0.531 (0.102)	0.740	0.800 (0.195)	0.245
Bilirubin	0.552* (0.087)	0.553	0.604* (0.093)	0.268	0.800 (0.179)	0.245
IgG	0.529 (0.083)	0.735	0.562 (0.090)	0.508	0.500 (0.221)	1.000
MELD	0.567 (0.091)	0.442	0.571 (0.099)	0.445	0.500 (0.228)	1.000
AST:ALT	**0.849* (0.066)**	**<0.001**	**0.899* (0.048)**	**<0.001**	0.500 (0.354)	1.000
APRI Score	0.519* (0.096)	0.830	0.526* (0.105)	0.779	0.600* (0.219)	0.699
FIB-4 Score	0.586* (0.086)	0.321	0.567* (0.094)	0.476	0.600* (0.303)	0.699
ELF	0.501 (0.092)	0.992	0.562 (0.097)	0.508	1.000* (0.000)	0.053

*All patients with flares at visit 1 were excluded, leaving N=50 for analysis. Bold values are significant at p<0.05 with the best marker for each modality also being underlined. *Inverse relationship, i.e. a higher value of the marker was associated with a lower risk. **n=49 due to missing data. Bold p-values are significant at p<0.05*

Figure 19: Associations between markers measured on visit 1 and future ALT flare rates in AIH patients with complete response at visit 1. The trendline is from a univariable binary logistic regression model, whilst points represent the observed rates of subsequent flares within quartiles of the distribution, and are plotted at the mean of the intervals.



Analyses are based on the N=43 patients who had complete response at visit 1. Points represent the observed rates of subsequent flares within quartiles of the distribution, and are plotted at the midpoints of the intervals. Trend lines are from univariable binary logistic regression models, with the stated marker as a continuous covariate.

10.4.6 PBC

10.4.6.1 PBC cohort additional demographics

Additional PBC-specific demographics can be seen in Table 42; the high-risk group were younger (median age 52years vs 60 years, p=0.029) and less likely to be currently taking UDCA (87% vs 100%, p=0.049) compared to the low risk cohort. Serum markers of disease activity and severity were higher in the high-risk cohort, along with mpMRI derived metrics (mean CT1: 932ms VS 888ms, p=0.029, cT1 IQR: 125ms vs 105ms, p=0.009.

10.4.6.2 Correlation and prediction of clinically significant events

Analyses were then performed to use Visit 1 markers studies to identify patients who were high risk, had cirrhosis or whom went on to require liver transplant assessment within the study period (Table 43). As with PSC and AIH, cT1 IQR was associated with the presences of cirrhosis (AUROC 0.845, p<0.001), as were liver stiffness (AUROC 0.924, p<0.001), inverse platelet count (AUROC 0.960, p<0.001) and ELF (AUROC 0.932, p<0.001).

Two patients (7%) underwent transplant assessment during the study period; both were identified as high-risk at Visit 1. No other significant events were observed. UK PBC score was highly predictive of future transplant assessment (AUROC 0.992, p=0.019) however ELF and liver stiffness were not (p=0.105 and p=0.061 respectively), nor were MRI metrics (Table 43).

Exemplar MRI images for the PBC cohort can be seen in Figure 20.

Table 42. MRI PBC cohort demographics at recruitment (Visit 1) based on study risk criteria

Factor	*Low risk (n=32)*	*High risk (n=30)*	*p-value*
Patient Characteristics			
Age (Years)	57 (30-81)	51 (36-70)	**0.027**
Gender (% Male)	4 (13%)	1 (3%)	0.355
Body Mass Index (kg/m2)	28.6 (19.0-38.4)	25.8 (22.3-40.4)	0.315
Ethnicity (% Caucasian)	31 (97%)	29 (97%)	1.000
Taking UDCA	32 (100%)	27 (90%)	0.107
UDCA dosage (mg/kg)**	13.7 (8.5-20.1)	14.0 (6.3-18.8)	0.715
UKPBC score			
*UKPBC 5**	0.47 (0.00-3.20)	3.47 (0.2-29.47)	**<0.001**
*UKPBC 10**	1.56 (0.00-10.30)	11.16 (0.67-68.92)	**<0.001**
*UKPBC 15**	2.89 (0.00-18.33)	19.8 (1.24-88.64)	**<0.001**
Reduced survival on globe score	1 (3%)	15 (50%)	**<0.001**
Transplant assessment during study	0 (0%)	3 (10%)	0.107
Markers of Disease activity & Severity			
ALP (IU/L)	94 (62-170)	353 (133-990)	**<0.001**
ALT (IU/L)	24 (10-67)	57 (14-225)	**<0.001**
Bilirubin (µmol/l)	7 (3-27)	16 (3-67)	**<0.001**
Platelets ($x10^9$/L)*	244 (151 – 405)	203 (48-397)	**0.029**
MELD	6 (6-10)	8 (6-13)	**<0.001**
IgG (g/L)	10.9 (6.8-22.3)	14.7 (8.3-28.8)	**<0.001**
APRI*	0.28 (0.12 – 0.83)	0.65 (0.26-5.26)	**<0.001**
FIB-4*	1.33 (0.54 – 3.15)	2.20 (0.76-15.09)	**0.002**
ELF	8.93 (8.03-11.18)	10.55 (7.24-14.61)	**<0.001**
Liver stiffness (kPa, n=61)*	6.0 (2.7-26.3)	11.9 (3.7-75.0)	**<0.001**
Cirrhosis	0 (0%)	18 (60%)	**<0.001**
MRI Metrics (n=61)			
cT1 Mean (ms)*	878 (773-1058)	928 (729-1080)	**0.008**
cT1 Mode (ms)*	798 (701-1024)	836 (629-1000)	0.055
cT1 IQR (ms)*	104 (76-177)	115 (79-215))	**0.027**

*Data are reported as median (range), with p-values from Mann-Whitney U tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05. *Based on N=61 due to missing data in one patient **In patients on UDCA.*

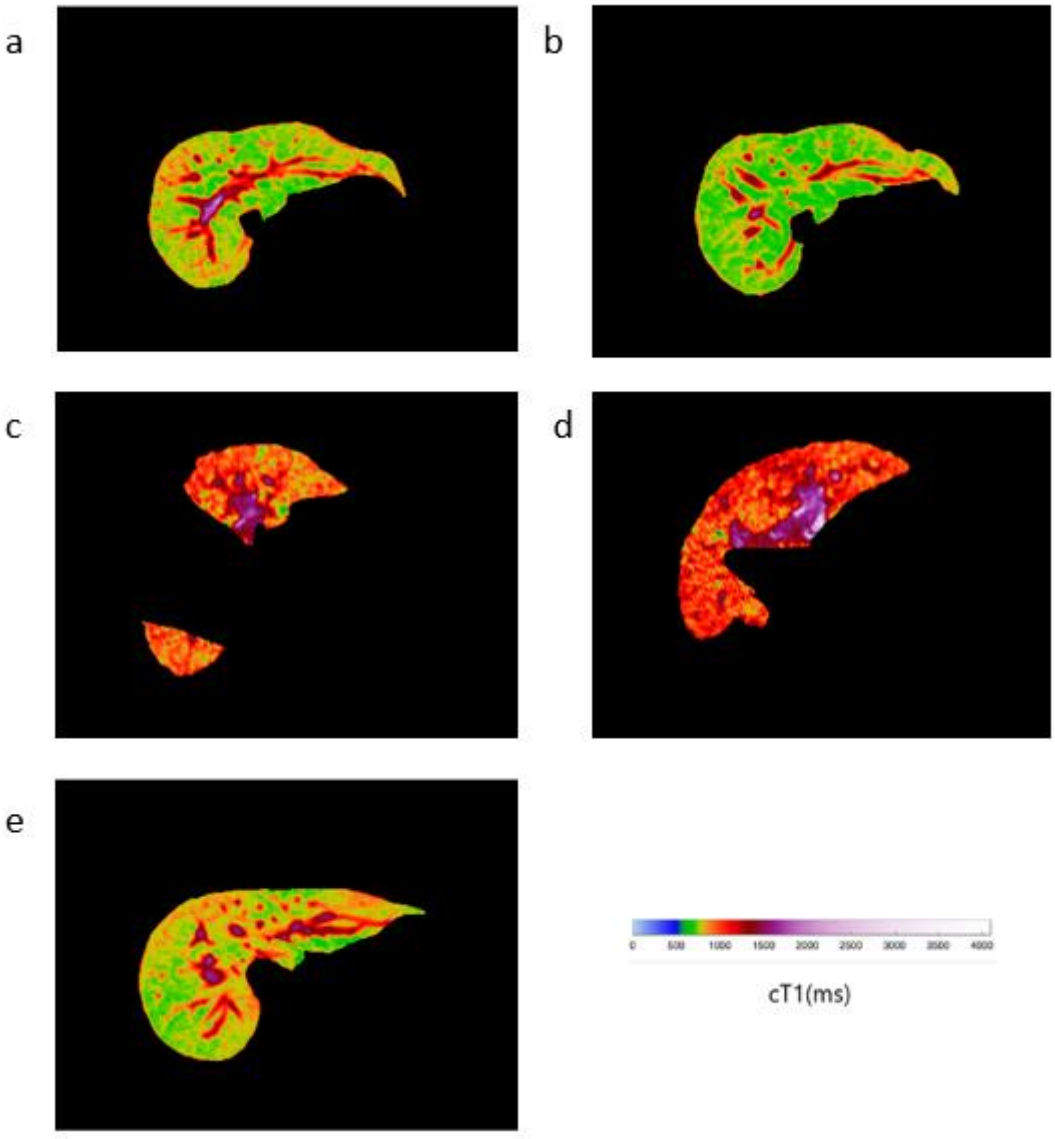
Table 43. Prediction of current/future clinically important scenarios in the MRI PBC cohort

	High risk Visit 1 (ALP/bilirubin study criteria)		*High risk at Visit 1 (Globe score)*		*Current Cirrhosis*		*Future Transplant Assessment*	
	AUROC (SE)	*p-Value*	*AUROC (SE)*	*p-Value*	*AUROC (SE)*	*p-Value*	*AUROC (SE)*	*p-Value*
MRI metrics (N=61)								
cT1 mode *	0.643 (0.072)	0.055	0.593 (0.096)	0.282	0.756 (0.067)	**0.003**	0.847 (0.103)	0.097
cT1 mean *	**0.696 (0.070)**	**0.009**	0.603 (0.098)	0.235	**0.783 (0.066)**	**0.001**	0.873 (0.076)	0.075
cT1 IQR *	0.665 (0.073)	**0.027**	**0.692 (0.080)**	**0.027**	0.748 (0.090)	**0.004**	0.737 (0.103)	0.257
Elastography								
Liver stiffness	**0.821 (0.054)**	**<0.001**	**0.799 (0.077)**	**<0.001**	**0.810 (0.077)**	**<0.001**	**0.864 (0.067)**	**0.034**
Serum Markers								
Platelets*	0.662** (0.071)	**0.029**	0.772** (0.075)	**0.001**	0.844** (0.070)	<0.001	0.768** (0.256)	0.301
INR*	0.552 (0.075)	0.484	0.585 (0.092)	0.313	0.656 (0.082)	0.065	0.503 (0.227)	0.987
ALT	0.834 (0.051)	**<0.001**	0.744 (0.087)	**0.004**	0.647 (0.084)	0.081	0.740 (0.194)	0.163
AST	0.892 (0.039)	**<0.001**	0.849 (0.066)	**<0.001**	0.719 (0.075)	**0.010**	0.893 (0.065)	**0.023**
ALP	0.978 (0.014)	<0.001	0.817 (0.063)	**<0.001**	0.743 (0.062)	**0.004**	0.864 (0.070)	**0.034**
Bilirubin	0.797 (0.056)	<0.001	**0.943 (0.034)**	**<0.001**	0.793 (0.073)	**0.001**	0.989 (0.013)	**0.005**
IgG	0.784 (0.060)	**<0.001**	0.668 (0.072)	**0.036**	0.667 (0.086)	0.048	0.650 (0.080)	0.385
MELD	0.729 (0.066)	**0.002**	0.901 (0.038)	**<0.001**	0.747 (0.077)	**0.004**	0.977 (0.022)	**0.006**
APRI Score*	**0.877 (0.043)**	**<0.001**	0.894 (0.060)	**<0.001**	0.831 (0.069)	**<0.001**	0.931 (0.045)	**0.012**
FIB-4 Score*	0.724 (0.065)	**0.003**	0.814 (0.062)	**<0.001**	**0.846 (0.071)**	**<0.001**	0.718 (0.198)	0.205
UKPBC score	0.872 (0.044)	**<0.001**	0.933 (0.052)	**<0.001**	0.828 (0.070)	**<0.001**	**1.000 (0.000)**	**0.004**
ELF	0.832 (0.052)	**<0.001**	0.855 (0.052)	**<0.001**	0.828 (0.067)	**<0.001**	0.842 (0.081)	**0.047**

*Analysis based on n=62 unless stated otherwise. Bold values are significant at p<0.05 with the best marker for each modality also being underlined. *n=61 due to missing data**Inverse relationship, i.e. a higher value of the marker was associated with a lower risk.*

Figure 20. Example colour-coded images of liver segmentation cT1 maps in MRI patients with PBC according to clinical risk group at Visit 1 and interim events/outcomes.

a) LAMP-121. Low risk group at Visit 1 with ALP 93, cT1 IQR 88ms.
b) LAMP-121. No change clinically during follow up with Visit 2 ALP 81, cT1 IQR 88ms.
c) LAMP-122. High risk group at Visit 1 with ALP 289, cT1 IQR 144ms.
d) LAMP-122. Interim liver transplant assessment with Visit 2 ALP 223, cT1 IQR 163ms.
e) LAMP-198. High risk group at Visit 1 with ALP 990, cT1 IQR 113ms. Interim liver transplant thus did not complete Visit 2.



The best predictive markers for each non-invasive modality (MRI, elastography and serum) were then compared in post-hoc analysis (Table 44). ALP was better at predicting study high risk status than both cT1 mean (p<0.001) and elastography (p=0.004). Bilirubin was significantly better at predicting high status via Globe score then cT1 IQR (p=0.011) but showed no advantage over elastography (p=0.053).

Table 44. Comparisons of ROC curves for the best predictors of current/future outcomes in the MRI PBC cohort

	Strongest Predictor			
Outcome	***MRI***	***Elastography***	***Serum Markers***	***p-Value***
High risk (ALP/bilirubin)	cT1 mean	Liver Stiffness	ALP	**<0.001**
High risk (Globe)	cT1 IQR	Liver Stiffness	Bilirubin	**<0.001**
Cirrhosis	cT1 mean	Liver Stiffness	Fib-4	0.414
OLT Assessment	cT1 mean	Liver Stiffness	UK PBC score	0.279

For each type of marker, the predictor with the greatest AUROC for the outcome of interest was identified from ***Table 14***. Comparisons only included those patients with data available for all three markers and the outcome of interest. Bold p-values are significant at p<0.05.

10.4.6.3 Effect of UDCA in PBC

Analysis was then performed to phenotype the UDCA-taking cohort to those not taking this medication. Markers of disease activity and severity were increased in the non-UDCA cohort, however mpMRI metrics demonstrated no significant differences (Table 45).

Table 45. MRI PBC cohort demographics at recruitment (Visit 1) based on UDCA use

Factor	On UDCA (n=58)	No UDCA (n=4)	p-value
Patient Characteristics			
Age (Years)	54 (30-81)	56 (36-62)	0.593
Gender (% Male)	4 (7%)	0 (0%)	1.000
Body Mass Index (kg/m2)	27(19-38)	31.0 (22.4-40.4)	0.090
White Ethnicity	56 (97%)	4 (100%)	1.000
UKPBC score			
UKPBC 5	0.81 (0.00-29.47)	13.00 (0.44-19.66)	**0.004**
UKPBC 10	2.67 (0.00-68.93)	35.89 (1.45-51.94)	**0.003**
UKPBC 15	4.91 (0.00-88.64)	54.19 (2.69-74.42)	**0.003**
Reduced survival on globe score	13 (22%)	3 (75%)	**0.049**
Transplant assessment during study	1 (2%)	1 (25%)	0.126
Markers of Disease activity & Severity			
ALP (IU/L)	140 (62-668)	595 (204-990)	**<0.001**
ALT (IU/L)	34 (10-225)	81 (23-216)	**0.008**
Bilirubin (µmol/l)	10 (3-58)	32 (6-67)	**0.002**
Platelets ($x10^9$/L)	230 (57 – 405)	254 (48-342)	0.939
MELD	6 (6-12)	8 (6-13)	**0.002**
IgG (g/L)	11.9 (6.8-28.8)	14.3 (10.5-23.2)	**0.205**
APRI	0.37 (0.12 – 5.26)	1.28 (0.35-2.66)	0.080
FIB-4	1.56 (0.54 – 15.09)	2.17 (1.15-14.51)	**0.032**
ELF	9.48 (7.24-13.13)	11.29 (9.72-14.61)	**0.009**
Liver stiffness (kPa, n=61)	7.2 (2.7-61.6)	30.7 (11.8-75)	**<0.001**
Cirrhosis	17 (29%)	1 (25%)	1.000
MRI Metrics (n=61)			
cT1 Mean (ms)	890 (729-1080)	932 (882-1070)	0.243
cT1 Mode (ms)	803 (629-1024)	848 (818-1000)	0.118
cT1 IQR (ms)	109 (76-215)	126 (94-144)	0.910

Data are reported as median (range), with p-values from Mann-Whitney tests, or as N (%), with p-values from Fisher's exact tests, and are based on n=62, unless otherwise specified. Bold p-values are significant at p<0.05.

10.5 Discussion

While rare, AILD is associated with ongoing morbidity and mortality. Clinical practice and treatment guidelines frequently diverge as a reflection of disease heterogeneity, lack of optimum treatment strategies, challenges in agreeing standards of care, a reluctance on the part of clinicians and patients to use liver biopsy, and an increasing recognition of the treatment burden for patients. This study aimed to investigate the utility of mpMRI in phenotyping AILD and its potential for use in risk stratification a real-world cohort of patients followed over a one-year period.

10.5.1 Common findings across all three cohorts

The study cohort demographics appear representative of AILD cohorts described in the literature and represent a broad spectrum of disease stage, ranging from early well-controlled disease to advanced liver disease requiring transplantation. Markers of liver disease severity and liver fibrosis were similar across the cohorts, indicating that recruitment was well-balanced but also suggesting that current treatments for all AILD are suboptimal.

As expected, female patients predominated the AIH and PBC cohorts, with younger and male patients more affected in PSC, as reflected in the literature. The wide age range observed within this study better represents the real-world patients affected by these conditions, compared to younger cohorts traditionally used within clinical trials. More of the PSC cohort had undergone previous liver biopsy than those with PBC, indicating ongoing concerns about diagnostic uncertainty using non-invasive means.

ALP was, as expected, higher within the cholestatic disease groups. Platelet count and transaminase levels were lower within the AIH cohort; this likely reflects the role of immunosuppressant treatment in suppressing liver inflammation while causing myelosuppression. Some AIH patients had especially low transaminase levels, potentially indicating over immunosuppression, or particularly deep remission. The high frequency of ongoing corticosteroid use in AIH indicates a reluctance to withdraw corticosteroids for fear of inducing an ALT flare, especially given the lack of appetite for repeat liver biopsy and without other validated options to assess underlying liver parenchymal inflammation. Given the associated short- and long-term sequelae of immunosuppressant overuse, it is important to prescribe the minimum affective dosages.

In this study, all cohorts had higher cT1 values than the 666ms (range 573-852ms) seen in healthy populations, an indication of the severity of disease and confirms that mpMRI metrics are capable of identifying abnormal liver tissue. In our cohort, PBC patients had a lower cT1 IQR than AIH and PSC patients ($p=0.013$) potentially indicating less heterogeneity within the liver; this is an interesting and new finding which is worth further study.

Baseline mpMRI correlated with numerous surrogate markers of disease activity, severity and fibrosis. Mean cT1 values closely resembled markers of liver tissue inflammation, such as ALT, AST and IgG and MRI markers of the heterogeneity of liver tissue structure (cT1 IQR) closely correlated with markers of disease severity, such as platelet count and bilirubin. Correlations were also seen with existing non-invasive markers of liver damage such as liver stiffness, ELF and MELD. As expected, cirrhosis was easily identified by standard blood tests, ELF and elastography. Similar differences in mpMRI parameters (cT1 IQR) were also observed in this study, suggesting that mpMRI technology could have utility in the multi-faceted assessment of liver disease.

On correlation analysis, the strengths and significances of associations between cT1/cT1 IQR and other surrogate biomarkers were lower when assessed at the follow up visit, compared to the analysis at baseline. This may be explained by the reduction in statistical power resulting from the smaller sample size at follow up. In addition, the exclusion of those with baseline flares may have introduced selection bias to the latter analysis, with the cohort not being representative of that analysed at baseline. Therefore, future analyses following the same consistent cohort over a longer time period might yield a better understanding of the changes associated with the correlation of these markers.

10.5.2 Disease cohort specific findings

10.5.2.1 PSC

The PSC cohort were more likely to be of non-White European ethnicity than patients with AIH and PBC; this is an interesting finding which may reflect the demographics of the local population. MpMRI was associated with the presence of both large duct PSC and cirrhosis; the predictive ability of mpMRI in this scenario was not inferior to that of existing markers such as platelets count, bilirubin or liver stiffness.

While small, the number of patients requiring transplant assessment within the short study period does confirms the high morbidity PSC creates and thus further confirms the need for improvements in clinical management. Transplant assessment was predicted by mpMRI (cT1 IQR) as well as elastography and serum markers such as platelet count; mpMRI was again not inferior to other markers. No marker was able to accurately predict future cholangitis, confirming the difficulty in predicting this event and the need for better understanding in this important area.

ALP cut offs are commonly used for entry to clinical trials; while ALP did associate with the presence of cirrhosis (thus predicting more severe disease), it did not predict future transplant assessment. A wider heterogeneity of liver tissue, represented by cT1 IQR was however predictive of this outcome and was not inferior to standard markers of fibrosis such as ELF, elastography, platelet count and bilirubin. This confirms widespread concern in the literature of how poor ALP is as a marker of disease and the need for better ways of risk stratifying patients with PSC; mpMRI may have future utility here.

Patients on UDCA tended towards a higher BMI (weight gain being a common side effect) yet lower bilirubin and other markers of disease activity. Given the ongoing contention around the efficacy of UDCA in altering long term outcomes in PSC, this is an interesting finding. However, the significance of this is unclear; it may be that higher risk patients have previously received little immediate benefit from UDCA treatment and have stopped it, or it might reflect differing policies regarding UDCA use in different centres, with more severe disease tending to be referred earlier to specialist units who may have less confidence in UDCA use. MRI metrics demonstrated differences in the UDCA taking and not taking groups in one metric only (cT1 mode), suggesting the groups may have similar underlying liver pathology.

The mpMRI profile of the PSC cohort was dissimilar to that seen in AIH and what has previously been observed in other liver conditions, such as NAFLD. This would confirm the complexity of liver disease assessment and re-iterate the need for disease-specific tools to more fully characterise the clinically relevant nuances of each disease.

10.5.2.2 AIH

As expected, serum liver tests were the best association with current AIH flare activity or other high-risk criteria. Clinical assessment of current AIH activity using serum biochemistry alone (specifically the most commonly used ALT, AST and IgG) did not identify many patients who developed a new flare event within 12-18 months. Given the unpopularity, risk and low uptake of repeated biopsies, these results suggest that the current non-invasive management of AIH is suboptimal. Interestingly no mpMRI metric nor ELF testing could identify those currently in the study high-risk group; liver stiffness did identify this, perhaps reflective of active inflammation causing stiffness rather than fibrosis.

Over a third of the AIH cohort in complete biochemical remission at Visit 1 experienced a future flare event, again confirming the unmet need in this area. CT1 has prognostic ability to predict future disease flares in these patients, with cT1 800ms giving a 19% risk of future flare, increasing to 76% at 1000ms. As elastography and ELF did not show similar prognostic capability, mpMRI has potential as a risk stratification tool to inform treatment titration, or even cessation, in patients with complete biochemical response.

This study also has highlighted AST:ALT as a more useful predictive test then other biochemical markers alone; this deserves further evaluation in larger studies. However, all markers were imperfect, highlighting and the unmet need remains for improved non-invasive markers that reflect underlying histological AIH activity and that can be used in the future to guide clinical treatment decisions. While AST:ALT was superior to cT1 in terms of overall predictive value for future flares, one was not statistically superior to the other. Initial attempts at combining these non-invasive variables have shown only modest improvements in predictive ability

above that of established serum markers. However, with larger prospective studies, further investigation may improve this.

10.5.2.3 PBC

The high-risk PBC cohort were younger than the lower risk group; this is supported in the literature where it is accepted that younger patients tend towards more severe disease. Markers of disease activity and severity were higher in the high-risk group, as expected. MRI markers also identified risk group and associated with the presence of cirrhosis, further indication that mpMRI is able to differentiate AILD phenotypes. Interestingly, ALP was associated with mean cT1 in PBC but not in PSC; this may be due to the extrahepatic nature of most PSC which may not be adequately assessed by mpMRI analysis primarily focussing on the liver parenchyma itself. An additional interesting finding was the reduced heterogeneity observed (via cT1 IQR) in PBC patients compared to those with AIH and PSC; this has not been described previously in the literature.

The high-risk PBC cohort were less likely to be taking UDCA; non-UDCA taking patients had more abnormal blood test results and more advanced liver disease than those on UDCA. Those not on UDCA had presumably not tolerated or responded to the medication thus would not have had the benefit of UDCA-associated response. However, some patients with grossly abnormal liver tests were still taking UDCA, potentially indicating clinical deterioration despite continuation of UDCA or perseverance with treatment despite non-response in case of some amelioration of disease trajectory. Variation in clinical practice without review of UDCA

response after 12 months of treatment or the previous lack of other therapeutic options may also be factors.

Due to the low volume of clinical outcomes in the PBC cohort, further in-depth analysis on the predictive ability of non-invasive markers to future transplant assessment was not possible. Of the three patients who subsequently underwent transplant assessment, one Visit 1 MRI was of insufficient quality, thus reducing analysis to just two patients and further reducing the power of the study.

Simple AUROC analyses suggested that mpMRI metrics were not predictive of future transplant assessment however ELF, liver stiffness and PBC Globe scores were. Further investigation over a longer time frame would add power to this preliminary analysis. ALP and bilirubin were highly predictive of high-risk status as would be expected due to both of the serum markers being large components of the definitions use for the high-risk groups.

10.6 Study strengths

This study was aimed to be a pragmatic real-world view of the utility of mpMRI in AILD, recruiting from standard clinic cohorts and without the strict limitations often placed on eligibility criteria in industry-led clinical trials. Thus, the results are more representative and applicable to the current AILD population. The study recruited patients from QEHB, a specialist liver centre with a huge catchment area so is not typical of a single centre study, given the wide range of patients seen there.

The study recruited the extremes of AILD, including patients with early mild disease and those with late stage disease requiring liver transplantation; this was similar across all three cohorts. Thus, this study accessed the breadth of disease in AILD, allowing for wider conclusions to be made about the results. Additionally, given the rarity of these three diseases, a study recruiting over 180 individuals is a big step forward in the understanding of these conditions, regardless of the mpMRI results.

10.7 Study limitations

While large numbers for rare diseases, the absolute numbers of some subgroups remains small, limiting some analysis, especially multivariable analysis. Overall, 15% of participants did not return for the 2nd MRI, which inevitably reduces the power of the analysis. As a result, the goodness of fit of the models may not have been optimal, and it is possible that there may have been some degree of overfitting to the data, especially since each model was based on less than 20 outcomes. Overall, the rate of clinical events within the 12-18-month follow-up

period was relatively low; a longer study follow up period may have allowed for more findings to be observed and analysed.

Given this was a real-world clinic cohort of patients with AILD, it was not felt appropriate to include a de novo liver biopsy in the study protocol, as it deviated from standard of care. Thus biochemical markers were used as surrogate markers for high and low risk disease. The limitations this brings to the study are acknowledged. Specifically, the lack of liver histology resulted in the inability to assess the correlations between cT1 and liver histology at both timepoints in the study. Given the significant time interval with intervening therapeutic treatment in all study cohorts, the amount of historic histological fibrosis was felt unlikely to reflect the current clinical situation at Visit 1 and thus was of limited value for this study.

10.8 Implications for practice and further research

Despite limitations, the results of this study are interesting and justify further prospective investigation of this technology in larger cohorts of AILD patients. Prospective studies pairing mpMRI techniques and biopsy in AILD (especially AIH) are justified, to enable further understanding of the associations between cT1 and liver inflammation and fibrosis in this population. Further investigation of mpMRI technology should involve a longer follow up period and additional MRI imaging at times of clinically significant events, such as during bacterial cholangitis, ALT flares or at initiation of new treatments, to further characterise the underlying changes.

While the results of this study are preliminary, it is possible that mpMRI results could be used now to aid in decision-making in clinical practice. An example of this would be to increase

confidence in decision-making when either the patient or clinician has no appetite for repeat invasive histological assessment, to justify increasing or maintaining medication in advance of a predicted flare event or to more quickly reduce immunosuppression where full response is observed, thus reducing the side effect burden). Successive mpMRI scans before and during new treatments for AILD, especially PSC given the lack of disease-modifying therapy, should be incorporated into clinical trials to further advance the understanding of the impacts of these treatments and of the disease overall.

A particular mpMRI feature of note was that associated with heterogeneity of liver texture (cT1 IQR). While this may reflect advancing cirrhosis with accompanying change in liver architecture, it deserves further investigation. Hepatic heterogeneity is inadequately considered by other means of liver disease assessment and thus demonstrates the potential for mpMRI to perform detailed whole liver fibrosis and inflammation assessment. The further development of mpMRI to quantify these changes may improve the understanding of AILD activity, disease trajectory and risk stratification.

This study suggests that changes in mpMRI results in these cohorts are reflective of different clinical phenotypes and might be further developed to give more detailed information about underlying liver disease than is currently available via existing non-invasive methods. Quantitative mpMRI appears to accurately reflect underlying AILD activity and fibrosis staging as well as quantifying the heterogeneous nature of specific diseases, such as PSC. By demonstrating an ability to identify those who will go on to experience AIH disease flares, mpMRI has shown promise in the phenotyping and risk stratification of individuals with high risk disease, who may not be identified using serum biochemistry alone.

This proof-of-concept study thus identifies mpMRI as a disruptive technology and justifies future prospective clinical trials in this area. There is the potential to develop this technology further to aid in clinical decision making, such as improved identification of patients at risk of deterioration and allowing earlier transplant assessment or alternatively for use in clinical trials. Together with other changes to patient management (such as the use of telemedicine), such advances in technology can be developed to better understand AILD and the long-term management of such patient cohorts, for patient benefit.

CHAPTER 6

FINAL DISCUSSION

11 CHAPTER 6: OVERALL DISCUSSION

This final chapter brings together findings from all four studies discussed in previous chapters, combining these to meet the overall thesis objectives. These were to advance the knowledge about the burden of PSC, from a patient and a health-care provider point of view, and to investigate what solutions evolving technologies may provide to alleviate some of this burden.

The objectives for this thesis (as defined in Chapter 1) were to describe:

1) The medical journey and healthcare resource use of patients with PSC
2) The personal experiences of patients with PSC, both of their disease and their healthcare
3) How use of telemedicine might impact upon healthcare experience for patients with PSC and other rare liver diseases
4) How advances in MRI technology might improve risk stratification in PSC and other AILDs

These objectives were approached using four different studies, purposely overlapping to provide complementary evidence for the research findings. The research methods were feasible and used existing clinical arrangements and infrastructure where possible for a real-life perspective into how PSC is managed in the UK. A summary of the different studies' impact upon the thesis objectives can be seen in Figure 21.

Figure 21: How the different thesis studies provide complementary evidence to meet the four thesis objectives

11.1 Summary of Findings

The results from this thesis demonstrate the costs of PSC, from a healthcare and patient perspective. All studies have highlighted the complexities involved in managing these patients, in particular the heterogeneity of disease, the lack of disease modifying treatment, difficulties in risk stratifying individuals and the variability of access to disease-specific care across the UK. Throughout the following discussion, importance is placed on the patient voice both to lend further weight to the quantitative findings and to add an additional dimension to the understanding of PSC.

To remove confusion when discussing the four studies, these will be referred to as the Cohort study (Chapter 2), Interview study (Chapter 3), Questionnaire study (Chapter 4) and MRI study (Chapter 5).

11.1.1 Corroboration with the published literature

This thesis corroborates existing literature that the burden of disease in PSC remains high. This is evidenced by poor long-term outcomes found in all four studies, further confirming the unmet needs in this cohort of patients. PSC patients experienced a high symptom burden, with frequent risks of hospital admission, hepatobiliary cancers and liver transplantation. Transplantation is high-risk major surgery with significant healthcare resource usage and the need for lifelong medication, close monitoring and with additional risks from recurrent PSC post-transplant and long-term immunosuppression.

All three quantitative studies observed higher rates of adverse outcomes and fewer asymptomatic cases, than that in the UK published literature[195]. This is likely due to the nature

of QEHB being a specialist centre, and thus would be expected to manage the sickest or most symptomatic of the PSC spectrum, or at least those more likely to be suitable for interventions such as clinical trials or transplantation.

This thesis has deliberately not placed emphasis on the burden of disease associated with other co-morbidities, in an attempt to isolate the burden of PSC itself. However, PSC often does not affect a patient in isolation and the impacts of co-morbidities (especially IBD) are likely to be substantial, further demonstrating the disproportionate burden of PSC relative to the small number of people affected.

The acknowledged difficulties in accurate risk stratification are further confirmed in this thesis. While commonly used in clinical trials to predict higher risk disease, ALP was not predictive of future transplantation or mortality in either the Cohort or the MRI studies. This again corroborates the ongoing need for better risk stratification and prognostic markers in PSC to reduce uncertainty for patients and clinicians.

Previously published findings of a high rate of UDCA use in PSC were again confirmed in this thesis, in contrast to international guidelines which do not recommend its use[9]. Previous studies have shown a reduction in ALP in patients taking UDCA but no long-term benefit to prognosis[24]; this was further observed in the MRI study where MRI markers of fibrosis and inflammation (which previously had correlated well with serum blood tests) in the UDCA-taking group were not statistically different to the non-UDCA group, again suggesting no benefit to UDCA at a functional level.

11.1.2 New findings & Added value

To more fully understand the impact of PSC and its related healthcare on patients, it is important to ask those affected. This patient voice is vital to understanding what is important to patients and how meaningful change might be achieved. This thesis specifically included in-depth interviewing of PSC patients to allow patients themselves to describe their experiences; this has not previously been investigated and adds a new and important dimension to the understanding of PSC patient experiences. The main themes of importance to patients found by this thesis are described below:

11.1.2.1 The personal burden of PSC and its management for patients

This thesis has demonstrated the personal impact of symptoms for PSC patients. Few patients remained symptomatic long-term, with most describing multiple symptoms and progression overtime. Patient descriptions of how these symptoms affected them, especially fatigue, are powerful and lend weight to the need for better treatments and management strategies. However, even in the absence of debilitating symptoms, the psychological burden of having a PSC diagnosis was still severe for most. The majority of interviewees described a fundamental change in their future trajectory and everyday life, regardless of their disease severity.

In addition, the time and financial burden of PSC-related healthcare from a patient perspective has been explored; this has not previously been demonstrated and would not be routinely considered by clinicians in daily practice or when re-designing a clinical service. Personal costs for accessing healthcare are high in PSC and patients described long journeys to visit their specialist. Patients are therefore forced to rely on non-specialist care for emergency

management or routine monitoring, or must continue to travel while also unwell. The personal costs (both in time and money) of repeatedly attending lifelong hospital follow up should not be underestimated when considering changes to patient management and this likely explains the appetite for exploring new techniques of accessing specialist PSC care, such as via telemedicine.

11.1.2.2 The uncertainties of living with PSC

Uncertainty was a key theme for patients within the Interview study, whether this be of their long-term prognosis, daily fluctuation in symptoms or of their healthcare. Much of this was due to the heterogeneity of disease seen in PSC with an unpredictable rate of progression and lack of disease-modifying treatment.

The clinical spectrum of disease has been demonstrated; patients in all four studies were observed to be diagnosed at a wide range of ages, with varying disease severity and disease course, and be located across the UK, often far from their hospital-based PSC treatment. Referral practices differed, potentially due to variations in local referral guidance but also likely related to individual clinician's personal experience in managing PSC and the expertise believed to be available elsewhere, as well as the uncertainty of efficacious treatment and monitoring strategies.

This heterogeneity is a challenge for clinicians to manage and the development of better ways of risk assessing patients would be of benefit to all. Such advances would enable clinicians to prioritise higher risk patients for more intensive monitoring, new treatments as they are developed and timely access to transplantation. At the same time, this would allow the

reassurance of lower risk patients and potentially increase confidence in managing these patients more locally, rather than at specialist centres.

The unpredictable nature of PSC means that patients may need intervention or specialist input urgently, and without notice. Current models of care do not lend themselves easily to such flexibility; few centres have "hotlines" for patients with liver disease to easily access care when they need to most. Particularly in cases of recurrent bacterial cholangitis, interviewees struggled accessing knowledgeable emergency care in a timely manner, with Emergency Departments found to be challenging places to convince non-specialists of the interventions needed.

11.1.2.3 Therapeutic relationship and the importance of the Specialist

In all of the cohorts described within his thesis, patients remained under specialist care rather than being discharged to their local services; this demonstrates the lifelong burden of disease seen at QEHB, and likely similar centres nationwide. This, along with the varying referral practices observed in the Cohort study, indicates a potential lack of expertise or confidence elsewhere to manage PSC appropriately. This is supported by the acknowledged inequality of liver services across the UK[46].

Newer changes to infrastructure, such as the "hub & spoke" model of de-centralising care, may provide patients attending non-specialist centres (the "spokes") easier access to the expertise traditionally only available within the "hub"; this can be effective in chronic liver disease management, however is not fully developed nationally[188]. Ongoing investment and education are therefore needed in hepatology services to ensure all patients have equal

access to informed and standardised evidence-based management for their PSC, with additional resources continuing to be aimed at finding new treatments.

A lack of confidence in the abilities of non-specialists to manage PSC was observed in this thesis and was a common perspective voiced by interviewees. Patients commonly knew more about PSC than their non-specialist doctors; these “expert” patients described having to be their own advocates when accessing non-specialist care but described the challenges of this when they felt so unwell. This is exacerbated by the input of multiple healthcare providers, corroborated by national HES data in the Cohort study (Chapter 2); this adds a further layer of complexity to managing this cohort given frequent difficulties with information transfer and communication between sites, as described by interviewees.

Patients demonstrated confidence in their PSC specialist and were often reluctant to relax this relationship, such as with the introduction of telemedicine. Interviewees were concerned by previous bad experiences and had little faith that anyone other than their specialist would be able to manage their PSC. The aforementioned controversies over UDCA use was just one example cited by interviewees of the uncertainties they faced with their medical management, undermining the trust they placed in their doctors and adding further strain on an already often fragile doctor-patient relationship. The particular importance of the doctor-patient relationship in PSC is understandable given the uncertainties in treatment and prognosis; this is likely under acknowledged by clinicians.

11.1.2.4 The potential role of telemedicine

Given the multiple challenges confirmed for patients in accessing timely PSC care and aforementioned complexities within the therapeutic relationship, investigation into the potential utility of telemedicine in this cohort was justified. Little evidence for the effectiveness of telemedicine in liver disease was found on scoping review, and none for PSC, justifying the subsequent questionnaire investigation into PSC patient attitudes to this technology. It was therefore not felt necessary to update the scoping review within the body of the thesis.

However, the ongoing Covid-19 pandemic has necessitated a rapid and widespread expansion of telemedicine interventions, likely resulting in new publications regarding the use of this technology. Given these changes, as well as the time taken to complete write-up of this thesis, it was expedient to re-visit the literature for an updated view of the evidence of telemedicine in this patient cohort. The scoping review was therefore updated using similar methods to those described previously, the aim of which was to find any new publications.

The full methods and results from the updated scoping review can be seen in Appendix N. In summary, nine new studies were identified, however, just five of these presented new data, the rest being expert opinion pieces. Three studies assessed the uptake of telemedicine initiatives during pandemic-related national lockdowns, which was unsurprisingly high. One study included quantitative questionnaire-based assessment of patient satisfaction; while most patients did express high satisfaction with their telemedicine experience in the short term, no in-depth investigation was done into patient experiences and their preferences for the future. One randomised control trial did investigate the efficacy of a telemedicine programme; this was in a highly selected population of obese NAFLD patients, with a discrete

online dietary intervention over just a few weeks, and during a national lockdown[189]. While this programme was successful, overall no new evidence for the long-term efficacy or popularity of telemedicine in chronic liver disease was found from this updated scoping review, especially outside of nationally mandated lockdowns or for AILD patients.

Given the recent expansion of telemedicine initiatives worldwide, it was surprising not to find more articles via this updated scoping review. More articles may be forthcoming as the pandemic recedes and clinicians can focus once again on research and evaluating their services. However, the search criteria were deliberately kept narrow to more reflect the populations studied within this thesis, which will inevitably have produced fewer results. The four studies presented within this thesis have repeatedly demonstrated the almost unique and unmet needs of the PSC population and the fragility of trust between them and their clinicians; this population are therefore more likely to struggle with telemedicine initiatives, especially in the longer term. It is probable that over time, more in-person consultations will be expected by patients and longer-term planning of outpatient services needs to consider carefully the impacts of retaining telemedicine initiatives for patients, clinicians, and the healthcare infrastructure.

New data on PSC patient perspectives of telemedicine has been presented within this thesis, via interviewing and questionnaire studies. A picture of the acceptance of telemedicine in PSC has emerged; while the majority were in favour, anxieties were also voiced that patients may not receive the same quality of care or have the same level of communication with their clinician as they would in a standard face-to-face clinic. This attachment to a physical therapeutic relationship with their clinician is likely a result of the previously described challenges patients experienced. Many interviewees described a loss of faith in the healthcare

system during their journey to a diagnosis and now that they had managed to access a specialist, were less willing to risk distancing themselves from them.

Additionally, if a patient is seen virtually, any tests routinely performed alongside in-person clinic appointments would instead need to be organised locally and the results transferred. Given patient accounts of how difficult negotiating the administration of their existing care can be, as described within the Interviews, it is likely that not all non-specialist centres would be able to organise these additional investigations and transfer the results in a seamless and timely manner. In order to reassure patients they are receiving the same care virtually; local agreements need to be in place to ensure all tests and communication of results can be organised. In the meantime, patients may find it more time efficient to make one longer journey for combined specialist appointments than risk multiple appointments closer to home or the increased potential for administrative confusion.

This may especially be of relevance to patients at QEHB (or similar centres) who are used to a "one-stop-shop" clinic approach, with most investigations completed the same day as seeing a PSC specialist. Despite appreciating the potential advantages of telemedicine, just two thirds of the QEHB PSC clinic cohort would be accepting of a virtual appointment (Questionnaire study). More would accept a mix of face-to-face and virtual appointments but stated that this would depend on their disease course and what was required from the consultation. A common view expressed by both interviewees and questionnaire respondents alike was that an in-person appointment was superior to a virtual one and thus the inconveniences of attending in person were "worth it". The aforementioned Parson's sick role[148] may have a role here; the duties of the patients to prepare for and travel to hospital to see their clinician are changed in telemedicine, thus potentially altering the therapeutic relationship and perceived efficacy of the consultation.

This thesis has therefore demonstrated previously unexplored complexities involved in setting up a telemedicine clinic in this cohort of patients; not all would accept a virtual appointment and additionally not all patients would be clinically suitable for virtual clinics or be technically able to access these. While not explored specifically within this thesis, one would suggest that those with the highest need for an in-person appointment from a medical point of view might be those with the most severe disease needing the most intensive monitoring. However, these patients are potentially the least physically able to travel due to their symptoms, especially fatigue. Additionally, the psychological distress experienced by many interviewees with milder disease may mean they might gain more satisfaction from an in-person appointment than they might from a virtual appointment, despite clinically needing it less.

Telemedicine is unlikely to be a long-term solution for most patients; in-person clinics will need to remain long-term either due to patient preference, a lack of access to the required technology, or due to clinical need. There will need to be strict criteria for the clinical appropriateness of a virtual appointment as well as flexibility between in-person and virtual clinics depending on how the patient progresses over time. Due to the lack of evidence for the safety and efficacy of telemedicine in PSC or chronic liver disease, repeated measurement of patient satisfaction and clinical outcome measures are needed once any virtual clinic is introduced to ensure patient satisfaction in the quality of care, as well as the quality itself, are not affected. Overall, a hybrid model of some face-to-face interactions interspersed with virtual consultations is more likely to be acceptable to both patients and clinicians.

This thesis demonstrates how telemedicine might be effective in improving some of the challenges posed by PSC. Key concepts of concern to patients have been identified when changing their outpatient management. These results were untainted by the recent pandemic and thus likely reflect a truer view of inherent patient opinion than is possible to gather now.

These opinions may well return once the pandemic has receded and the value of these results remains.

11.1.2.5 Risk stratification

The uncertainty of PSC is a common theme identified within this thesis. Improved risk stratification tools would allow more accurate assessment at individual level, and thus, facilitate more intensive monitoring in high-risk cases, or more reassurance in low-risk patients. This may allow for management in primary care for those at lowest risk, although given the complexities identified in the doctor-patient relationship, this is unlikely to be accepted by all patients.

Quantitative mpMRI values were observed to correlate with accepted surrogate markers of inflammation and of fibrosis in all three AILD cohorts; this included serum blood tests as well as transient elastography. MRI markers are thus able to correctly identify abnormalities within the liver and could have utility in the multi-faceted assessment of liver disease.

Some adverse events were able to be predicted using MRI parameters, for example, future ALT flare in AIH and impending liver transplant assessment in PSC. However, no superiority of MRI values was found compared to existing markers of inflammation and disease severity which are simpler (and cheaper) to complete. MRI assessment of fibrosis and inflammation in all three AILD cohorts was higher than in healthy controls from the literature[187]; this in itself indicates a need for more efficacious treatments, monitoring and risk stratification.

MRI findings of particular interest are not only the ability to quantify inflammation across the entire liver volume in a non-invasive manner (thus negating the many disadvantages of

percutaneous liver biopsy), but also the ability to assess the heterogeneity of the liver tissue, which was found to correlate highly with markers of fibrosis. Reduced heterogeneity was observed among PBC patients; this is a new finding and deserves further investigation. The heterogeneity of patient demographics, disease course and disease severity is further demonstrated in this thesis, exacerbating the challenges faced by patients and their clinicians.

While these mpMRI findings may not change patient management now, this remains a positive step towards a better understanding of AILD. As these non-invasive quantitative technologies evolve, utility is likely for the future real-world management of AILD and it is likely that they will become embedded in future standard patient management pathways, alongside other non-invasive markers. One potential use might be in identifying those at highest risk of needing imminent transplant assessment in PSC and thus monitoring more closely. Further prospective investigation into this technology is justified; this could include repeated imaging over a longer follow up period and during clinical events, such as during an episode of cholangitis. The addition of mpMRI techniques into upcoming clinical trials may also advance the understanding of the impacts of these treatments on the liver parenchyma, and contribute to the overall understanding of PSC.

11.1.3 Added value for non-PSC illness

Many of the challenges faced by PSC patients identified within this thesis are also observed in other chronic diseases. PSC has been demonstrated to fit recognised models of chronic illness which describe challenges with uncertainty, family relations, disrupted biography, managing medical regimes, and the importance of information[146]. While PSC patients remain a worthy cohort to study, other AILDs also demonstrate a great need for advancements in their management, especially in terms of accessing care and in risk stratification.

Patients with AIH and PBC were therefore included in two studies described within this thesis, with comparisons between all three diseases made where appropriate. These comparisons demonstrated similarities across all three diseases with few differences observed with in non-AILD patients (Questionnaire study). This suggests relevance of the thesis findings to other liver disease groups and those with other rare or chronic conditions. The MRI findings are of particular interest in the AIH cohort, with potential utility in increase confidence in AIH clinical decision-making when titrating immunosuppression and in preventing flare activity.

However, this thesis has demonstrated some aspects of PSC that are notable compared to other chronic conditions. PSC patients face the perfect storm of an uncertain and variable short-term quality of life, with a likely poor longer-term prognosis, all compounded by the lack of disease-modifying treatment and additional difficulties accessing knowledgeable medical care. It is important for clinicians managing PSC to be aware of this so the clinical management, communication and support can be better tailored to this cohort's needs. The particular challenges presented by PSC for patients and clinicians alike may mean that strategies that work in other disease groups (such as telemedicine) may be less successful in PSC.

11.1.4 Thesis Strengths

This thesis includes four studies woven together which not only demonstrate the clinical need in PSC, but also investigates how these may be answered. Using different research methods in overlapping studies has allowed for a more in-depth and multi-faceted investigation than a single study could have achieved. All research methods have potential flaws, therefore, using more than one method reduces the impact of these and allows more robust answering of the thesis objectives. The inclusion of such diverse research methods has had additional learning benefits for the researcher.

A further strength of this thesis is the inclusion of patient interviews, giving in-depth insights into patient experiences, something frequently overlooked in traditional quantitative research. Qualitative research methods were used to gain detailed patient-orientated views of the challenges they face; key areas of concern for patients have been identified.

The findings described within these studies agree in many places with the established literature (described in Chapter 1), suggesting the study cohorts do reflect the wider PSC population. While recruitment was mainly QEHB based, the inclusion of the HES dataset as well as interviewees from around the UK (who described similar experiences to QEHB patients) gives additional national insights and makes the results more widely applicable. While PSC does have some specific challenges not seen in AIH or PBC, the similarities suggest that the thesis findings are also more generalisable to other disease groups.

The studies included within this thesis were designed to be pragmatic and the objectives to be achievable; using the spectrum of patients seen in PSC clinics and recruiting via both NHS

and community channels. The strict inclusion and exclusion criteria seen in industry-led clinical trials can be seen as a pitfall when relating their findings to real patients in real clinics. The use of current genuine clinic cohorts within this thesis makes the findings more relatable to clinicians working in such clinics, whether they be PSC specialists or otherwise, as well as to patients. The spectrum of disease severity was also prioritised within this thesis; patients were deliberately recruited to demonstrate early and late disease in two of the studies (Interview and MRI studies). This has allowed for the heterogeneity of disease to be investigated and allowed those with milder disease to be heard equally with those who have more advanced disease.

Finally, AILD and PSC in particular remain rare diseases. To identify and recruit over 400 patients, including 186 into an MRI-based study, has produced substantial volumes of data on these cohorts. While the exact proportion of the UK's PSC population represented by this thesis is unknown, QEHB is a large hub for PSC patient activity so logic dictates a sizeable proportion of the whole UK PSC population were involved. A large dataset has been methodically collected of PSC (and AILD) patient experience, which had not previously existed.

This thesis has highlighted real-life challenges faced by patients and led to realistic suggestions for change that could improve experiences for not only PSC patients, but also those with other chronic diseases (see later sections). This research can only add to the understanding of these diseases and pave the way forward for more focussed research.

11.1.5 Thesis Limitations

All study designs have inherent weaknesses which can limit how the results can be generalised to wider patient populations. In this thesis, the majority of patients were recruited from just one centre, QEHB, which caters for its local population as well as being a tertiary referral and liver transplant centre. The findings are therefore more likely to be applicable to other tertiary centres than to district general hospitals or other non-specialist centres.

There is overlap between the cohorts studied; it would be hoped that all questionnaire respondents would also have been included within the cohort study, as would all of the PSC sub-set within the MRI study. It is likely that patients most interested in research could have been recruited to more than one of the studies, or possibly to all four. It was not possible to confirm this due to the anonymous nature of the questionnaires, however, one patient was known to have been recruited to both interview and MRI studies. Participants in the questionnaire study could have responded more than once, which could bias the results towards patients being more frequently followed up in clinic with potentially more unstable disease. This also applies to the MRI study, where more frequently attending patients may have been captured more easily.

The interviewees were recruited via PSC Support and mostly via online advertising, thus patients not part of this group or less confident online may have had less opportunity to be recruited. Non-English-speaking patients would have been disadvantaged to recruitment as the invitation letters and advertisements were all solely in English. While the interview cohort were purposively selected to reflect the breadth of patient experiences and demographics, no non-White participants volunteered for the study. These individuals were therefore under-represented in the interviews and further themes of importance to patients may have been

identified had they been included. This is especially the case given acknowledged health disparities and altered health-seeking behaviours observed in different ethnic groups[190] as well as suggestions that these populations may also respond less positively to telemedicine initiatives[191]. However, it is widely recognised that patients volunteering for research are self-defining and as a result of this racial disparities are commonly observed, with new NIHR guidance recently published on this[192].

While this thesis has investigated relatively large cohorts in the context of rare disease, some of the study subsets remain small. In particular in the MRI study, with just 62 patients recruited from each disease (plus some lost to follow up) and with small numbers of clinically significant events observed over a short study period, further multivariate analysis wasn't possible. The number of patients recruited for the Interview study was small however, qualitative research aims for saturation of data and does not focus on the absolute number of interviews undertaken[193]; data saturation was robustly achieved as described within the Interview chapter. There were more patients recruited to the interview study who were being managed by QEHB than by any other single centre; while this may reflect the dominance of QEHB as a specialist tertiary liver service in the UK, this must be noted before applying the findings to other centres.

This thesis was designed to recruit real-world cohorts of patients, which has added complications; the cohorts are less well defined and more heterogenous than those usually recruited to industry-led trials. Therefore, statistically significant findings may have been harder to observe. While justified, the where the lack of histological confirmation of the MRI findings, remains a disadvantage. It was a practical decision to make the questionnaires anonymous and thus gather a quick snapshot of the QEHB PSC clinic cohort without the need for ethical approval, this introduced difficulties in comparing the cohorts as the variables

collected were not common to all studies. In general, more standardisation of some baseline characteristics would have allowed further comparison between the cohorts to assess how representative they were to the wider PSC population, and to each other.

Missing data was observed within this thesis and meant that some assumptions needed to be made. The absence of mention of a symptom was taken to mean this symptom was not present; this may have been inaccurate and led to underestimation of the symptom burden in AILD. While retrospective electronic records at QEHB are comprehensive, data from ten years prior was also incomplete. Within the interview study, participants self-declared they suffered with PSC and described their experiences; no data was independently verified and recall of past events may be subjective.

That the researcher was medically qualified could have subconsciously introduced bias into the semi-structured interview analysis, as well as within the interviews themselves. This was minimised by the researcher being appropriately trained and the supervisory team providing a breadth of experience including specialist clinical, public health and sociological perspectives. It was not possible to perform all interviews in person given the distances involved, thus some were completed via telephone; these differing mediums could have affected the flow of the interviews and thus the final results. Telephone interviews are traditionally felt to be inferior than in-person interviews[194], however, it was justified to include telephone interviewing in order to recruit from a wider geography than was practical otherwise.

11.1.6 Generalisability to the wider PSC population

The thesis cohorts need to be representative of the wider disease population before the research findings can be applied elsewhere. By necessity and design, the studies discussed within this thesis targeted different populations, recapped below:

- The Cohort study (Chapter 2) included every patient with an ever confirmed diagnosis of PSC who had been seen in the QEHB liver outpatient department within the last 10 years (n=418).
- The Interview study (Chapter 3) included participants recruited nationally and who self-identified as having a diagnosis of PSC (n=18).
- The Questionnaire study (Chapter 4) recruited 101 participants seen at QEHB's PSC clinic, with a quarter having alternative diagnoses than PSC.
- Finally, the MRI study (Chapter 5) recruited 186 participants from QEHB AILD clinics; a third had PSC.

As the cohorts included such different demographics, recruitment methods and analyses, it is not possible to directly compare the groups. However, some estimation of how representative these cohorts might be of the wider PSC population where possible, is useful. Given this thesis was UK-based, comparison is made with UK literature where possible, and in cases where this is absent, the next most recent European-based data is used. Similarities between the thesis cohorts and national PSC cohorts are evident (Table 46).

The prevalence of PSC in the UK is unknown; some studies have estimated the UK PSC cohort using a reported prevalence of 5.6 per 100,000[195] with a UK population estimated at 66.8 million people[196], indicating that approximately 3740 people may have PSC in the UK. UK-PSC, the national research collaboration has had over 2000 individuals partake in their genetic

studies to date[197]. However, one UK-based study using HES data found a prevalence of just 1258 cases of PSC nationally between 1998 and 2014[195]. The latter appears surprisingly low and further demonstrates the difficulties found when using national data sets.

All four studies described within this thesis observed higher rates of adverse outcomes and fewer asymptomatic cases than the UK literature[195]. The Cohort Study found higher rates of liver transplantation than the other thesis studies, however this was over a 10 year follow up period and does reflects the published longer-term prognosis of PSC[8]. The cohort study described a younger cohort at PSC diagnosis than observed elsewhere; this may be due to QEHB seeing tertiary referrals who might be expected to have a more aggressive disease course, be more eligible for clinical trials or be better candidates for liver transplantation.

Two of the thesis studies (Questionnaire and MRI studies) included non-PSC patients; similarities and differences to these cohorts with PSC patients have been highlighted throughout and suggest that the thesis findings could also be relevant to other liver disease groups. Of the non-PSC patients included within the studies, all had diagnoses of rare liver diseases, most of which was auto-immune in nature, and thus there lies the potential for significant overlap in patients' experiences. The demographics of the PSC cohorts did differ from other AILD patients being generally younger and more likely to be male. This reflects the literature, and suggests that the experiences faced by PSC patients may be subtly different to that of other AILD patients. It is of patient benefit for clinicians to be aware of this.

Overall, there are enough similarities between the thesis study cohorts and national cohorts to conclude they are indeed fairly representative; thus the results generated from this thesis may be applicable to the wider PSC patient population and beyond.

Table 46: Comparison of the different study cohorts described within the thesis with national published data

	UK cohort (literature)	*QEHB Clinic (Ch2)*	*Interviews (Ch3)*	*Questionnaire (Ch4)*	*MRI (Ch5)*
Cohort size	3740 (approx)	417	18	101	186
Proportion with PSC	All (confirmed)	All (confirmed)	All (self-reported)	72 (71%, self-reported)	62 (67%, confirmed)
Recruitment source	Hospital Episode Statistics (UK-wide)	QEHB (Informatics)	PSC Support (UK-wide)	QEHB (PSC clinic)	QEHB (AILD clinics)
Demographics					
Median age at diagnosis (range)	57 years[195] (6-93)	40 years (18-84)	51 years (23-72)	n/a	n/a
Ethnicity White	n/a	360 (88%)	18 (100%)	PSC: 64 (87%) All: 86 (85%)	PSC: 46 (76%) All: 161 (87%)
Male	63%	270 (65%)	10 (56%)	PSC: 45 (60%) All: 54 (54%)	PSC: 37 (60%) All: 53 (29%)
Disease severity					
Cirrhosis	6.4%[195]	208 (50%) (at first clinic attendance)	7 (39%) (to date)	n/a	PSC: 21 (34%) All: 64 (34%) (to date)
Transplant assessment	n/a	178 (43%) (over 10 years)	4 (22%) (to date)	PSC: 11 (15%) All: 13 (13%) (to date)	PSC: 4 (5%) All: 6 (3%) (In 12-18 months)
Asymptomatic	40%[198]	66 (16%) (over 10 years)	2 (11%) (to date)	PSC: 8 (11%) All: 14 (13%) (to date)	n/a
PSC specific metrics					
Co-morbid IBD	54%[195]	276 (67%)	11 (61%)	n/a	50 (81%)
On UDCA	n/a	245 (59%) (over 10yrs)	9 (50%) (to date)	n/a	24 (39%) (at time of recruitment)
Large duct PSC	89.8%[195]	339 (82%)	16 (89%)	n/a	54 (87%)
Cholangitis	40%[195]	133 (32%) (over 10 years)	12 (67%) (to date)	35 (47%) (to date)	8 (13%) (In 12-18 months

Data are reported as median (range) or as N (%). Liang et al was used as a comparator where possible as this is the most recent UK study available; where this study did not provide the data, the next most recent study available online was used. N/A – unavailable in the literature at this time.

11.1.7 The Effects of COVID-19

As previously discussed, data collection was completed for this thesis prior to the pandemic. This worldwide event has resulted in major changes to healthcare provision relating to this thesis that must be recognised. This includes social distancing, mask-wearing and increased adoption of home or hybrid working, along with increased use of online platforms for business and pleasure. Of particular relevance is the rapid and widespread expansion of the use of telemedicine in healthcare[199], including at QEHB, where three of the thesis studies were based.

This sudden switch to mostly virtual consultations was out of necessity to maintain some non-urgent care for people with chronic medical conditions, while at the same time maintaining social distancing and reducing risks for everyone involved. Patients and clinicians had little choice but to accept this, despite previous any concerns about the effects this method of consultation might have on quality of care or communication[200].

Social distancing is especially important in chronic health conditions which give higher risks of complications from Covid-19. This includes chronic liver disease and initially those with cirrhosis or on immunosuppressant medications were advised to shield completely[201]. This would have a particular impact upon the AILD cohort, especially the AIH and PSC-IBD patients given the additional concern around immunosuppression on top of liver disease. The prognosis of covid-19 in the presence of cirrhosis remains uncertain, with initial studies demonstrating increased mortality[202], but more recent studies refuting this in all but advanced cirrhosis[203]. It is therefore logical to have observed a high level of initial enthusiasm from clinicians and patients alike for alternatives to traditional face-to-face consultations[204].

However, despite the ongoing pandemic and safety rationale for delivering healthcare at a distance where possible, there is now considerable backlash from a public frustrated by ongoing disruption to normal services[205]. At the time of writing (October 2021), much routine outpatient care at QEHB remained remote. However, the expectation is that at the pandemic recedes, more patients will be again invited to attend appointments in person[206]. With government guidance now advising a reversal of the 2020 universal virtual triage policy[207], decisions are needed as to how much telemedicine to retain, both in primary and secondary care, and for whom. The challenge will be in deciding how much telemedicine to retain long term, to suit patients, clinicians and NHS Trusts alike.

Given the modifications made in healthcare delivery, it is inevitable that the patient experience of telemedicine may be different now, to when the thesis studies were completed. However, while experiences of telemedicine in practice may have affected attitudes in the short term, the insight into patient perceptions described in this thesis remains untainted by the pandemic and thus reflects true background patient opinion, which is likely to resurface overtime. The results from this thesis, therefore, will continue to have merit as the pandemic recedes and healthcare providers make plans for how much telemedicine to retain in the longer term.

11.1.8 Improving PSC patient experiences

Through asking patients directly within this thesis (via interviews and free-text questionnaire responses), numerous opportunities for improvement have been identified that could improve PSC patient experiences now, while new treatments and technologies are in development. These are discussed below:

11.1.8.1 Information

Providing patients with good quality information and sign-posting them to peer support early on after diagnosis was important to interviewees. Clinicians need to avoid advising unselected internet searches; this thesis has demonstrated the harm this can do to patients, as outdated and inaccurate information is usually found. Signposting patients to approved sources of information is feasible, requiring no new infrastructure and minimal cost; peer-reviewed pamphlets are freely available online from The British Liver Trust and from PSC Support.

Patients also wanted information that was tailored to them and their individual stage of disease. More widespread use of existing risk scores may be useful for patients to view their trajectory, as far as is feasible given the uncertain prognosis in PSC. Further development of disease-specific risk scores and improved methods of monitoring progression are needed. Allowing patients access to their own medical records would be a start; while some centres do this, this is not yet universal.

The lack of accepted treatments or monitoring strategies for PSC, as well as the disproportionate provision of liver services across the UK[46], has led to variations in the medical management of patients with PSC. This has not gone unnoticed by patients, as demonstrated

by interviewees. This further undermines the already fragile doctor-patient relationship and adds to the anxieties patients face when they observe other patients being treated differently. The development of evidence-based management pathways that all PSC patients can expect to be offered would help to standardise care.

Interviewees demonstrated that lay knowledge of liver disease remains poor. Given the rising burden of lifestyle-related liver disease internationally, more education of the lay public is needed about the importance of a healthy lifestyle in the prevention of liver disease. At the same time, this must be sensitive and a balance made to educate rather than stigmatise other liver disease patient groups.

11.1.8.2 Accessing the right care at the right time

Interviewees described difficulties in accessing medical care, especially emergency care when they were less able to advocate for themselves due to being unwell. The fluctuating nature of PSC makes scheduling of useful follow up challenging; there is no predicting when patients would best benefit from an appointment or need expert advice. Flexibility in accessing outpatient clinical care would be useful, albeit challenging to organise in the real world. Helpline access, similar to those successfully run nationally in IBD, would allow for more responsive management of this notoriously unpredictable disease.

The ideal would be having patient clinical information accessible to patients and their clinicians nationally; realistically disjointed NHS administrative systems do not allow this and so any such system would need to be patient held, at least for now. For patents suffering recurrent cholangitis, a personalised hospital admission plan or patient passport (including

personal and disease-specific information and signposting to validated resources) might aid non-specialist medical staff provide appropriate and timely treatment, especially in emergency situations.

More difficult is to ensure the equality of PSC care nationally. Liver service provision is unequal across the UK[46], although it is improving. Many patients still travel long distances to access PSC care, as evidenced in the Cohort, Interview and Questionnaire studies. While using telemedicine may improve access to some, this is not universally popular with patients. Importantly, clinician perspectives to telemedicine have not been studied within this thesis and must be examined before the complexities involved can be fully appreciated.

Expansion of hepatology services nationwide is needed and incoming changes to training with more hepatology exposure[208] may well mean improved knowledge of rarer liver diseases going forward. Over time, this would hope to improve the knowledge and management of all liver conditions and help equalise access to liver services across the UK, regardless of the use of online platforms or virtual clinics.

Most interviewees felt that a specialist should be involved in the long-term care of every PSC patient, however some felt they got relatively little out of this interaction yet at significant personal inconvenience. Not all PSC patients may want or need to be seen in a specialist centre, especially those with mild disease, and some non-specialists may have extensive prior experience of managing PSC. Clear referral and discharge pathways are needed nationally to streamline this and allow access to more specialised services if required, without unduly overburdening them.

Going forward, a new PSC diagnosis could herald an initial specialist appointment, potentially using telemedicine. Subsequent management could then be via specialist units (for advanced

or symptomatic disease or those eligible for clinical trials) or potentially in non-specialist services or even primary care, provided agreements are made as to how to monitor and when to re-refer. Research opportunities should be available to all patients and infrastructure needs to evolve to incorporate this into routine clinical practice.

11.1.8.3 Changing attitudes of clinicians

In general, more individualised care is needed for optimum management of every patient. As well as more accurate risk stratification methods, clinicians need to discard the traditional medical models of disease and become more responsive to the needs of each individual in order to protect the therapeutic relationship. In the absence of new treatments, a key management goal in PSC is to make daily life as tolerable as possible and is a key priority for patients. This means re-assessing priorities for treatment and managing expectations; it is vital that doctors focus on what matters most to the patients, and not be blinded by blood tests or scan results, which can mean little to patients themselves.

While patients are not always correct, doctors need to be more accepting of the expert patient advocating for themselves and embrace this partnership rather than rebel against it; this has a lasting impact upon patients and their trust as evidenced by interviewees in this thesis. A shift needs to occur where doctors are more open to the knowledge of their patients and learn to work with them as expert partners; medical school training on this would be a start. Equally, patients need to work with clinicians to aid in the transfer of information and agree to fulfil their part of agreed management plans. This balance will be different for each patient-clinician team and will need co-operation and understanding from both sides.

11.1.9 Implications for further research

Whilst recognising the methodological limitations inherent in the constituent study designs, the key findings reported in this thesis add value and provide new evidence-based insights into patient experiences of living with PSC. Further work is needed to further develop non-invasive methods of risk-stratifying these patients to accurately predict progression at the individual level; this may be via qualitative MRI techniques however further longitudinal research is needed with larger cohorts before these can be used routinely in clinical practice.

Telemedicine may have a role in equalising access to specialist care however is a complex balance between what is needed to safely clinically manage the patient and what the patient needs to feel supported. Telemedicine is likely to have an ongoing role in streamlining routine outpatient management, but must be tailored to the individual patient and ensure no detriment to either clinical outcomes or to patient trust in the medical team. Given the particular importance placed on the doctor-patient relationship in PSC, identified by interviewees, it is likely that telemedicine might work best for those with an already established face-to-face clinical relationship, or for one-off specialist consultations while a more local clinician continues the ongoing management. Going forward, clear pathways are needed as to whom is suitable for virtual clinics alongside robust infrastructure to ensure monitoring at a distance does not affect patient outcomes and repeated measures of patient satisfaction.

11.2 CONCLUSION

This thesis presents four studies which form a sizeable body of evidence as to the patient experience of PSC, what challenges these patients face and how this might be improved using incoming technological advances. The inclusion of qualitative research methods is novel in the context of PSC and lends weight to the research findings. The challenges in the optimal medical management of PSC have been confirmed; that is, managing a widely heterogenous cohort with unpredictable progression and troublesome symptomology without efficacious disease-modifying therapy or accurate risk stratification methods.

Telemedicine is one potential method of improving access to care in PSC, however, patient attitudes to this are complex. While not suitable for everyone, telemedicine does have place in disrupting traditional medical care and is likely to improve experiences for some patients with PSC, along with many other chronic diseases. However, which patients will benefit most from this technology is uncertain and convenience must not be prioritised unduly over quality of care.

The further development of risk stratification methods in PSC may also aid patients come to terms with their disease profile, help clinicians prioritise those for transplantation, and help develop new treatments. While mpMRI shows potential utility and could be used to supplement existing end-points in clinical trials, more research and development is required before the widespread use of this technology in clinical practice can be recommended.

In conclusion, this thesis has confirmed the great clinical need in PSC, added to the body of knowledge of this rare disease, and highlighted multiple areas of particular importance to patients, both with PSC and other chronic liver conditions.

"It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change" (Charles Darwin)

APPENDICES

12 Appendix A. QEHB PSC cohort study Proforma & Variables list

Table 1: Data collection proforma for QEHB Cohort study

Patient Demographics	Date of birth	
	Gender (Male =1, Female =2)	
	Ethnicity (free text)	
	Body Mass index (kg/m2)	
Patient relationship to QEHB	QEHB the patient's local hospital (Y=1)	If not, where is (free text)
	Referral source (GP, Gastroenterologist, Surgeon, Hepatologist)	
	Referral reason (diagnosis, transplant, ongoing management)	
	Diagnosis made by QEHB (Y=1)	
	Time from diagnosis to QEHB clinic (if diagnosis made elsewhere)	
Cumulative QEHB activity	Number of liver clinics	
	Frequency of liver clinics (to the nearest 3 months)	
	Number of hospital admissions	
	Number of abdominal MRI/CT/US scans	
	Number of ERCPs	If any, number that were therapeutic
	Number of colonoscopies	
	Number of liver biopsies	
	Date of diagnosis	
PSC disease details	Reason for diagnosis (symptomatic = 1, asymptomatic =2)	
	Time from start of symptoms/investigations to diagnosis (nearest 3 months)	
	Where diagnosed (QEHB = 1, Other = 2)	
	How diagnosed (MRCP, Liver biopsy, ERCP)	
	Aetiology (large duct = 1, small duct = 2)	
	IBD co-morbid diagnosis (Y=1)	
	Ever symptoms (Y=1)	If yes, describe (free text)
	Ever UDCA (Y=1)	If yes, dose (mg)
Blood test results	At first & last QEHB liver clinic	ALP, Bilirubin, Albumin, ALT, Creatinine, Sodium, UKELD, INR, platelets

Appendix A: Description of Variables for QEHB PSC Cohort Study

The dataset metrics were collected individually from the electronic records, in the manner described below. In all metrics, where the data was not available, this was coded as unknown.

1) Subject demographics

The data extracted by the QEHB informatics team included basic demographic information already input into the electronic case notes as detailed below:

Gender – This was self-reported and categorised as male, female or unknown/other

Patient age – This was self-reported and calculated and rounded to the nearest year.

Height – As measured by clinic staff at the initial QEHB clinic appointment (or within 6 months if not available at first clinic) and rounded to the nearest centimetre.

Weight – As measured by clinic staff at the initial QEHB clinic appointment (or within 6 months if not available at first clinic) and rounded to the nearest 100 grams.

BMI – Using the above described Height and Weight measures and using the standard formula weight (in kilograms) divided by height (in metres squared).

Ethnicity – This was self-reported and used the standard Office for National Statistics classifications for ethnicity; categories were White, Asian/Asian British, Mixed, Black/ African/Caribbean/Black British and Other. Where this was available electronically, this result was used. Where this was not disclosed, the clinical letters were interrogated.

Employment – This was self-reported. This was not routinely reported within the electronic case notes so the clinic letters were analysed for any mention of occupation status at any time; where this was mentioned more than once during the subject's follow up and had changed, the first answer was taken. The categories were employed full time, employed part time, unemployed, student and retired.

2) PSC-specific metrics

Date of PSC diagnosis – This metric was found after interrogation of the clinic letters and investigation reports. Where this was clearly stated (for example via MRCP, or liver biopsy date), then this date was used. Where only a year was available, 1st July of that year was used, as the midway point through that year. If the information available could not identify the date of diagnosis to within a year, this metric was left as unknown.

Reason for diagnosis – The clinic letters were used to assess the reason the subject initially underwent the investigations that led to the PSC diagnosis. Categories were symptomatic, incidental or unknown.

Symptoms – All available clinic letters were analysed for any mention of symptoms during the follow up period; these were accumulated and thus represent the entirety of symptoms experienced during the follow up period. If no symptoms were reported at any time, this was coded as asymptomatic. Specific symptoms were jaundice, pruritus, fatigue, cholangitis, abdominal pain, ascites/oedema, weight loss/sarcopenia, encephalopathy, variceal bleeding and other; each category was listed as present/not present.

PSC phenotype – the clinic letters and investigation reports were analysed for evidence of small or large duct PSC. Large duct PSC was defined as having an abnormal MRCP or ERCP demonstrating biliary stricturing; small duct PSC had normal imaging but consistent changes on histology (such as periductal fibrosis)[129]. The categories for this variable were large duct, small duct and unknown.

Co-morbid IBD – The clinic letters and investigation reports were analysed for evidence of IBD with the categories of present, absent or unknown.

UDCA status & dose – The electronic notes were interrogated for mention of UDCA usage. Where this was not found, it was assumed the patient was not taking this drug. Where

applicable, the dosage of the UDCA was calculated using the subjects' weight at the closest time point to the dose described in the clinic letter; if these were not within twelve calendar months of each other the dose was recorded as unknown. If the dose changed over time, the largest of the doses was recorded.

3) **QEHB metrics**

Location of the subject's primary treatment centre –A combination of the subject's postcode and clinic letters were used. If the patient did not currently live in a Birmingham ("B") postcode area, it was assumed that QEHB was not their natural primary treatment centre, unless the clinic notes suggested the patient had moved out of the area since referral. Any subject with a "B" postcode was assessed if they were referred from another secondary care operator (then QEHB was deemed not to be the primary centre) or directly from their GP (then QEHB was deemed to be the primary centre).

Time of diagnosis to first QEHB clinic appointment - This was calculated using the date of the first QEHB clinic appointment and the date of PSC diagnosis. This was rounded up to the nearest three months to allow for variations in clinic waiting list times.

Referral reason/source – The referral and clinic letters at QEHB were used to identify the source and reason for the referral . Categories for this variable were referral for diagnosis, second opinion, ongoing management, transplant assessment, cholangiocarcinoma assessment, ERCP assessment, for consideration of clinical trials, at the patient's request and transition from Birmingham Children's Hospital. When more than one reason was indicated within the case notes, the Investigator made a judgement on which appeared to be the most pressing reason for referral.

4) Severity of Disease

Cirrhosis at first QEHB clinic – All available clinical information was analysed to decide whether cirrhosis was present, using data from within 12 months of first QEHB appointment. Indications for the diagnosis of cirrhosis were via histology, the presence of portal hypertension (as below) or imaging/blood tests consistent with cirrhosis (e.g. abnormal synthetic liver function or an irregular liver edge on imaging). The categories were cirrhosis present, absent or unknown.

Portal Hypertension at first QEHB clinic – All available clinical information was analysed to decide whether portal hypertension was present, using data from within 12 months of first QEHB appointment. Indications for this was the presence of varices, ascites or encephalopathy, or a combination of a large spleen with a low platelet count. The categories were portal hypertension present, absent or unknown.

Blood test results at the first QEHB clinic – Results from the date of the first QEHB clinic appointment were analysed, or the next available if taken within 12 months. The list of blood tests recorded along with normal reference values are seen in Appendix B.

Most recent blood tests – These were the last blood tests available electronically, either before the date of death/transplantation, or immediately before the end of the follow up period.

5) Outcomes

Liver transplantation– The electronic record was interrogated for evidence the patient had undergone liver transplant. If the surgery date was not available, the date of the nearest clinic letter was used instead; categories were transplant completed, not completed or unknown.

Liver transplant assessment – Clinic letters from the assessment clinic was interrogated for evidence the patient had ever undergone a transplant assessment. The categories were transplant completed, not completed or unknown.

Hepatobiliary cancer – Clinic letters and investigation reports were trawled for evidence of any cancer diagnosis; the date of diagnosis was calculated using date of the histopathology report, where available, or the date of the nearest clinic letter. The categories for this variable were cholangiocarcinoma, hepatocellular carcinoma, colon cancer and Other (with free text) and each was coded as being present/absent during the whole study period.

Death – The electronic case notes indicate automatically if a patient has died. When this was the case (or when additional review of the case notes indicated this), the cause of death was assessed using scanned death certificate information or using detail from the most recent clinic letters to calculate if PSC was the most likely cause of death or not. Thus, the categories for this were dead and alive, with causes of death recorded initially in free text form. These free text responses were then sub characterised into the following groups, native liver failure, graft liver failure, cancer, sepsis and related multiple organ failure, other and unknown.

Alive/ongoing follow up – On interrogation of the case notes, where a patient had no evidence of death, liver transplantation, discharge or transfer to another liver centre then they were counted as alive and under ongoing follow up. The category for this variable was yes or no.

6) QEHB Portal Activity Summary

Within the QEHB electronic case notes there is an automated activity table detailing all hospital admissions, outpatient appointments by specialty and procedures, along with attendance or did-not-attend (DNA) status. These tables were interrogated to accumulate hospital activity from the date of first QEHB PSC clinic appointment until the end of the study period, date of death or date of liver transplant surgery. The below metrics were derived:

Number of clinic appointments –Liver clinic appointments only were manually counted; other specialist appointments (including gastroenterology) were excluded as falling outside the scope of the study.

Did Not Attend Appointments – This was manually counted using the activity table, only liver clinic appointments were counted toward this total rather than all clinics.

Follow-up frequency – The last two calendar years of appointments during the follow up period (or prior to death or liver transplant) were analysed and a frequency calculated. This was rounded to the nearest three months due to variability in clinic waiting list times. The categories were 3 monthly (or more frequently), 6 monthly and 12 monthly (or longer).

QEHB Inpatient hospital admissions – This was manually calculated and confirmed using the hospital discharge letters. Elective day case procedures were not included.

Numbers of investigations –All liver-related investigations were manually accumulated from the date of first QEHB clinic to the end of follow up. The categories were ERCP, Endoscopic Ultrasound (EUS), Liver biopsy, MRCP or MRI Liver, CT Liver and abdominal ultrasound scans. All other completed MRI and CT scan reports were interrogated further to assess if these were ordered primarily due to the PSC management or for another condition entirely; if the latter then these were excluded from the analysis.

7) Hospital Episode Statistics Data - variables

The following variables were pulled directly from the HES system:

Number of hospital admissions – The total number of hospital admissions per patient and sub characterised this as those at QEHB or elsewhere, and if this was coded as elective or emergency.

Total length of stay per patient – Total number of inpatient days per patient over the entire study period; no further breakdown was available.

Total admissions with PSC diagnosis coded as main reason for admission –the total number of hospital admissions where the primary code for reason for admission was PSC; no further breakdown was available.

Inpatient treatment speciality – The HES extract differentiated admission speciality according to the following groups; Colorectal Surgery, Liver Surgery, Upper GI Surgery, Gastroenterology, Liver, and Other.

Liver transplant – If a liver transplant had been recorded within the study period and if so the date of this (most likely the date of coding rather than of surgery); if no code then it was assumed the patient had not undergone transplantation.

Number of outpatient appointments – The total number of outpatient appointments over the study period, subcategorised into QEHB appointments and those elsewhere; no further breakdowns were available.

Number of non-attendances for outpatient appointments - The total number of outpatient non-attendances over the study period, subcategorised into QEHB appointments and those elsewhere; no further breakdowns were available.

Total numbers of procedures – The total number of procedures undertaken per patient, over the study period. The categories were matched to the QEHB dataset. No further breakdown was available for types of imaging, indication, location or results of these tests.

13 Appendix B. Commonly used serum blood tests with normal reference ranges at QEHB

Test	Role in liver disease	Normal reference range
Albumin	Synthetic liver function	35-50 g/L
Alkaline Phosphatase (ALP)	Cholestasis	30-130 U/L (males), 30-103 U/L (females)
Alanine transaminase (ALT)	Hepatic inflammation	5-41 IU/L
Aspartate aminotransferase (AST)	Hepatic inflammation	5-43 IU/L
Bilirubin	Synthetic liver function, cholestasis	1-17 umol/L
Immunoglobulin G (IgG)	Hepatic inflammation (AIH)	5.40-16.10 g/L
International Normalised Ratio (INR)	Blood clotting, synthetic liver function	0.9-1.2
Platelets	Low may indicate portal hypertension	50-450 $x10^9$/L
AST to platelet ratio index (APRI) [103]	Composite score, indicator of liver fibrosis	>1.0 = 76% sensitivity, 72% specificity for cirrhosis >0.7 = 77% sensitivity, 72% specificity for significant fibrosis
Fibrosis 4 (Fib-4) [104]	Composite score, indicator of liver fibrosis. Uses age, AST, ALT and platelet count	<1.45 = no/mild fibrosis on liver biopsy, 1.45-3.25 = moderate fibrosis, >3.25 = severe fibrosis/cirrhosis

Enhanced Liver Fibrosis (ELF)[105]	Composite serum marker of liver fibrosis	Suggests cut-offs are: <7.7 = excludes significant fibrosis (high sensitivity) >9.8 = identifies moderate fibrosis (specificity 98%) >11.3 = identified cirrhosis (specificity 97%)
Transient Elastography (TE)[109]	Ultrasound-based assessment of liver stiffness an indicator of fibrosis	Cut-offs vary depending on liver aetiology, active inflammation is a confounder <7kPa = likely no or mild fibrosis >12.5kPa = cirrhosis is likely
Model for End Stage Liver disease (MELD) [39]	Composite score, predicts 1-year risk of death after events such as variceal bleeding or surgery Uses creatinine, bilirubin, INR, sodium and any recent history of renal dialysis	Possible range 6-40, Score <9 = 2% mortality Score 10-19 = 6% mortality Score 20-29 = 20% mortality Score 30-29 = 53% mortality Score 40+ = 71% mortality
UK End-stage Liver disease (UKELD)[40]	Composite score, predicts 1-year risk of death after events such as variceal bleeding or surgery. Uses INR, bilirubin, creatinine and sodium	Possible range 40-79. A UKELD score of 49 indicates a 9% one-year risk of mortality, and until 2019 was the minimum score required to be added to the liver transplant waiting list in the UK. UKELD 60 = 50% 1-year mortality

14 Appendix C. Topic guide for interview study

Introduction to the Interviews (for the interviewer)

The aim of this interview is to explore your experiences of having PSC and of your hospital care. Please give as much detail as you can about your experiences and feel free to talk about anything you feel is important.

As the interviewer, I must make sure not to influence what you say therefore I will not say very much, except to ask another question or prompt you for more information. Please do not me offended by this, I am definitely listening and taking in everything you say.

If there is anything you prefer not to talk about please let me know; you can decline to answer any question if you so wish. If you feel uncomfortable or upset in any way or want me to stop the tape for any reason please let me know.

Please try not to use the names of specific people, for example, say “my hospital doctor” rather than “Dr Smith” or “my husband” rather than “John”. Do not worry if you do mention specific people as these names can be removed later.

Does that make sense? Do you have any questions? Shall we start?

Section 1: Experience of Diagnosis

Can you tell me about how you found out you had PSC? What tests were needed?

Can you talk me through the moment you were given your diagnosis? How did you feel?

What happened after you were given your diagnosis? How has your life changed since having PSC?

Section 2: Experience of symptoms

How does PSC affect you on a day to day basis? Can you describe what symptoms you experience?

How do these affect your daily activities? Work? Social life? Family life?

What would you say is the worst thing about your diagnosis?

Can you talk me through your management for your PSC?

Section 3: Knowledge of prognosis

What have you been told about how PSC will affect you? (Now/in the future)

How does that make you feel?

What is your understanding of the long-term problems that can occur with PSC?

Have your plans for the future changed due having PSC? If so, in what way?

Section 4: Impact on family/friends

Do your family know that you have PSC? How do they feel about your diagnosis? Do they understand what PSC is? What was it like telling them?

Do your friends/work colleagues know that you have PSC? How do they feel about your diagnosis? Do they understand what PSC is? What was it like telling them?

How has your diagnosis affected your personal relationships? Romantic? Family? friends? Work colleagues?

Section 5: Experience of medical management

Can you talk me through your journey since you were diagnosed?

Can you tell me more about who currently manages your PSC and where this is based?

How do you feel about going to your hospital appointments? What it is like?

What is the best/worst thing about your care for your PSC?

What would be your priorities for your future care?

Section 6: Experience/Attitude towards future telemedicine

Can you tell me your understanding/experience of telemedicine or virtual clinics?

(followed by the below standard explanation of what a virtual clinic is)

How would you feel about this new type of appointment starting in the future?

How do you think this might affect how you are managed?

How might this affect how you feel about your appointments??

Can you think of any advantages/disadvantages to this sort of appointment?

Is this something you would consider? What factors might affect your decision?

Standard explanation of telemedicine & a virtual clinic

Telemedicine is using telecommunication technology to perform medical procedures or appointments. This can take many forms such as telephone appointments, using remote technology to monitor blood pressure or blood sugars, or doing virtual clinics.

A virtual clinic is when the patient and doctor carry out the normal clinic appointment but rather than being face-to-face in the same room, such as by using a video link over the internet. This means the patient and doctor can be many miles away from each other yet still be able to talk to and see each other.

This sort of clinic appointment is a possibility for future care for many people, particularly those who may travel long distances to see their doctor.

15 Appendix D. PSC support advertisement for interview study

RESEARCH PARTICIPANTS NEEDED

Who is eligible to take part?

All patients with PSC are eligible to take part in this research. Ideally we are looking for patients in or near the West Midlands area, however if you live further afield you will still be considered so please do get in touch.

What is the research about?

The purpose of this research is to find out more about the experiences of people who have PSC. We are particularly interested in finding out more about your experiences of having PSC and your experiences with different types of healthcare professionals in different settings.

What is involved?

You will be asked to take part in a face to face interview with the researcher. This is likely to last between 1 and $1^{1/2}$ hours. You can choose to be interviewed in your own home or at the University of Birmingham

Who is undertaking the research?

This research is being undertaken by researchers at the University of Birmingham and is supervised by Professor Gideon Hirschfield.

If you are interested in taking part in this research or would like more information please contact:-

Dr Katherine Arndtz (Clinical research fellow, NIHR Liver Biomedical Research Unit)
Email: [redacted]
Tel: [redacted]

16 Appendix E. Patient information sheet & consent form for the interview study

PARTICIPANT INFORMATION SHEET FOR THE INTERVIEW STUDY

Dear Participant

You are invited to take part in a research study for patients with Primary Sclerosing Cholangitis (PSC). Before you decide whether to take part in this study it is important that you understand why this research is being done and what you will be asked to do. Please take time to read the following information and discuss it with others if you wish.

What is the purpose of this research? The purpose of this research study is to explore your experience of living with PSC. We are particularly interested in your experience of being seen by doctors in different health care settings. The information gained from this research will be used to make recommendations for new ways of managing PSC and will offer insights into the experiences of patients with PSC. The overall goal of the research is to improve our understanding of what matters most to you.

Why have I been invited to take part? You have been invited to take part as you have PSC.

Who is doing this research? This research is being undertaken by a team based at the University of Birmingham. Dr Katherine Arndtz is conducting this study as a basis for her postgraduate degree. This research is taking place under the supervision of three senior clinicians/researchers based at the University of Birmingham. Dr Gideon Hirschfield is a Senior Lecturer at the Centre for Liver Research and an Honorary Consultant Hepatologist at the Queen Elizabeth Hospital Birmingham. Professor Jayne Parry is a Professor of Policy and Public Health in the Institute of Applied Health Research. Dr James Ferguson is also Consultant Hepatologist at the Queen Elizabeth Hospital Birmingham.

What does the research involve? This study involves one face to face interview with the researcher. The interview will be recorded on tape and some written notes will be taken. The interview will take between 1 hour to 1.5 hours approximately. In most cases the interview will take place at the University of Birmingham, in your home or at your place of work. There may also be a possibility of having you interview over the telephone if you prefer.

Do I have to take part in this research? No. It is up to you to decide whether or not to take part. If you decide to take part, you will be given a copy of this information sheet to keep. You will also be asked to sign a consent form. You can change your mind at any time and withdraw from the study without giving a reason.

What are the benefits of taking part in the study? Taking part in this study may not help you directly but the information that is gained from the study will help to increase our understanding of PSC and how it is currently managed. Information may be used to develop new care pathways for patients.

What are the disadvantages of taking part? Some people can find it difficult to talk about their condition. If you find it difficult to talk about a specific aspect of your disease, then you can request not to answer these questions. You can ask for the interview can be stopped at any point.

What happens if I change my mind and no longer want to be involved? Once you have agreed to take part in the study, you are entitled to change your mind about taking part in the study. You can do this up until two weeks after the interview has taken place. You can do this by contacting the study team and letting them know that you wish to withdraw. You do not have to give a reason. If you choose to withdraw, the information collected up to that point including recordings, written notes and transcripts will be destroyed.

Will I get to see the results from this research? You will be given the option to receive a summary of the research findings when it is completed.

Will I be paid for my involvement? You will not be paid for your involvement. However, you will be reimbursed for any travel expenses that you may incur if you are interviewed at the University of Birmingham.

Will my involvement be confidential? Your personal details will be anonymised and will not be available to anyone outside the research team. You will be assigned a code number that will be used on all paperwork, stored data and in any publications that arise from this research. Direct quotations from interviews may be used in publication in an anonymised form. The interview will be recorded on audio tape and then transcribed (typed out word for word) onto a computer by an external company. No identifiable information will be recorded on the tape and the transcriber will be bound by a confidentiality agreement. All paperwork related to the study and any physical recordings will be stored in a locked cabinet in a secure place within the University of Birmingham. Any electronic data stored on computer will be protected by a password. This data will be stored for up to 10 years. Only members of the direct research team will have access to this information.

In the event that information is disclosed during the study period, which in the opinion of the research team, may pose a risk to the safety of the participant or another individual then it is the obligation of the research team to pass this information on to the relevant parties.

How will the information collected be used? At the end of the research, a report will be written which will form part of Dr Arndtz's research thesis. The results may also be published in medical journals and may be presented at conferences. The written reports and

presentations may include anonymous quotes from your transcript. All published information will be anonymised and no participant will be identifiable from any publications.

Who has approved this study? This study has been reviewed and approved by the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (Reference ERN_16-0130)

How is the study funded? This research is funded with support from the National Institute of Health Research (NIHR) Birmingham Liver Biomedical Research Unit and the Queen Elizabeth Hospital Birmingham Charity.

Contact details for further information

Please do not hesitate to contact us if you need further information.

Chief investigator: Professor Jayne Parry

Research fellow: Dr Katherine Arndtz

Email:

Telephone:

CONSENT FORM FOR PARTICIPANTS FOR THE INTERVIEW STUDY

Participant number: _____

Please initial each box

I confirm that I have read the information sheet dated 20th December 2016 (version 1.0.) for the above study.	☐
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
I understand that my participation is voluntary and that I am free to withdraw up to two weeks following my interview without giving any reason and without my medical care or legal rights being affected.	☐
I understand that the information collected may be used to support other research in the future, and may be published. All information obtained and/or published will be anonymised.	☐
I consent to direct quotations from my interview being used in publications in an anonymised form	☐
I agree to take part in the above study	☐

…….. ……..
……..

Name of Participant Date(dd/mm/yyyy) Signature

…… ……
……..

Name of person taking consent Date (dd/mm/yyyy) Signature

17 Appendix F. Interview study sample transcript with initial coding

Sound file: **Interview 018**

Appendix F. Interview study sample transcript with initial coding

Verbatim

I: Er, okay. So it's the 16th of March and it's participant number 018. Er, so I will just ask you to think back and tell me how it all began.

IV: So I, my baby was 10 months' old and I'd spent, we were abroad, we were living abroad and I'd spent all of that time, I was like an ex-pat wife so I had no worries. You know, all this ladies that lunch sort of social life [laughs]. It was very nice and easy but I was knackered and I thought it was because I had the amazing non-sleeping baby. She literally woke up every hour or hour and a half for like a year or two and, er, so I, I was on my knees. I was so tired. I remember I'd be talking to other mums and, and like my eyes would be glazing over and I wouldn't be concentrating on what they were saying but I put it all down to the baby. I already had ulcerative, ulcerative colitis but, and I'd had colonoscopy when I was diagnosed but it kind of like was all, like, left, you know. And then I just started, one time, one day I just got really, really ill. I got a really bad sore throat. My glands were all up so I thought I'd better go to the doctors. So I went to the doctors and they, they were going through my medical history and they're like, 'Hmm, you should have a colonoscopy again soon and we'll do some bloods'. 'Cause it was all private healthcare they'll do every test they can think of. And then they got the bloods and then they said, 'Oh, we need to refer you to someone because you've got', it must have been because I had, erm, raised blood tests. So went to a nice hepatologist in Singapore and he, he sat me down and he said, 'Right. Yes, you've got raised whatever it was so how much do you drink?' And I, I was thinking, 'Ooh, not that much really'. I've sometimes had a drink on a Sunday, 'cause he said, 'You need to cut back on that'. And then I believe him. I was like [mmm], 'Ooh, yeah. Better have then. I must be drinking too much'. And I, but I was having at the most like three glasses or something. And, erm, but still I, I was like, 'Ooh, that must be, I must be, you know, gosh, like that'. And, er, and then he said, 'We're going to, you're going to do a colonoscopy. Erm, no, you've going to have an MRI scan', so he obviously

Commented [KA(al1]: Co-morbid IBD, diagnosed first

Commented [KA(al2]: Alcohol, stigma

1

Sound file: **Interview 018**

thought there was something going on and he had obviously decided it was [0:02:30] related because I went for this scan probably about two days later, all private. Anyway, in, in there and, erm, no. So somehow I knew that he was trying to decide whether I had PSC or not before I went for this scan 'cause I Googled it and I'm like, so I learned quite a lot in that bit of Googling. I was quite worried. Yeah, they said it's, it's either, they thought I had coeliac disease or PSC 'cause I remember we had this weekend where it was going to be one of the two and I don't know if that was before or after the MRI scan. And, erm, so I, I, in this MRI it took literally an hour and a half and I was in this MRI scan trying to think [sighs], 'Are they, have I got PSC or not? They're obviously looking. Oh, it takes a long time'. Didn't even know that was a long time. And this Chinese, they're quite frank people. They're not [laughs], they don't, they don't mince their words and she goes, 'Oh yeah. Erm, I keep, every time I look I can, I can, I keep seeing, erm, blockages in your bile ducts. I can't get a clear picture of your bile ducts like this'. And I'm in the scanner 'cause they brought me out at one point and, after about an hour and then I went back in so they brought me out to say keep seeing blockages or there's some blockage and it does, there's something in your bile ducts so we can't get a proper picture. And I knew enough by this point to know that I had blockage in my bile ducts so probably did have PSC or something. I hadn't thought as far as, like, bile duct cancer luckily. So I was really upset waiting and they told me this while I was having the scan. It wasn't like a hepatologist it was the scanner so I had already figured it out. And then, erm, when we had the, the next appointment with the hepatologist when he went through the results he went, 'Oh, I'm very sorry to tell you you've got primary sclerosing cholangitis'. And then he, like, had a pause and then he went, 'I'm so sorry. You've got such a young family. You need to go back to the UK to your family'. I'm like, 'What?' And he, and I remember thinking what does he mean? Does he mean I'm dying and he's just not said it? Does he mean, is he being, is it like some sort of Chinese, erm, they like their families or something and like 'cause I'm not so well I should get, I just didn't know what he meant. So I Googled a bit more and I found a few websites and one said you've got 12, average mortality or survival of 12 years so I kept looking. I kept looking and then I found one that was NHS Cheshire and it said

Commented [KA(al3]: search for information, internet searching

Commented [KA(al4]: mode of diagnosis

Sound file: **Interview 018**

I had five years to live and I was like, obviously you go on the worst-case scenario and I'm like, 'Oh my God'. And the worst thing was just thinking, 'My, I've got a baby. You know, I'm not going to, I might not even see her go to school'. So it was just, it was just awful because literally I thought I'd been diagnosed with a disease and there's no cure and you die quite soon and that's all I could think of. And then everyone in my family, or my immediate family all started Googling and found out all this stuff and I was just like, 'I don't want to know anymore. I'll just go on a need to know basis'. And, erm, oh my God [laughs]. So, erm... I'm sorry.

I: Do you want us to pause?

IV: I'm all right. Oh my God, I am actually all right. And then, erm, my husband found Roger Chapman online and he was just amazing. He, so we were still abroad and he, he was just like, 'Yeah, don't worry. There is, this is a thing, primary sclerosing cholangitis. I can', erm, I don't know what he said, it was just very reassuring but so then we did. We did check. Matt changed his job and we came back to the UK and then I started pestering the PS, I found the PSC support group. In fact, I think Roger was the one that, that told us about it so then I started pestering them [laughs]. 'Can I help you? What can I do, what can I do?' And eventually they let me help. That was good and that was really good, finding them, 'cause then I, I started to find out more information. So I had this cloud thinking, 'I am going to die. Am going to die'. And it, it just so happened that about [sighs] a month after we'd got back to the UK to live there was a conference, PSC one, and I went there and I couldn't believe it. I met people that had had transplants and they were okay, 'cause that's the other thing. You read this information about transplants and it always describes it in terms of five-year survival or 10-year survival or 90-day survival [mmm] and it's all you can think is that that's how long you've got. Like you don't realise that that's a standard measure of time. But then I met someone and they'd had theirs for like eight years and they were doing fine. I'm like oh my God. And Roger Chapman's going, 'Yeah. Just live your life, it's going to be fine'. So, so that whole, that whole period of just how I, how it all, I got diagnosed and how I felt was just horrendous and that's probably why I'm, I do what I do now with the support group 'cause everybody goes to

Commented [KA(al5]: search for information, online resources, poor prognosis found

Commented [KA(al6]: existential crisis, poor prognosis, effect on family

Commented [KA(al7]: existential crisis, poor prognosis

Commented [KA(al8]: prognosis, transplant

Sound file: **Interview 018**

it and it's, erm, I don't know. I just, just thinking about it, it was awful. And, erm, but yeah, came back to the UK. Started seeing Roger Chapman, that was good. I live quite a long way away so I drove, we drive two and a half hours to go and see him for my appointments and he said I was, you know, just live your life normally. Don't do anything different. Do whatever you want. And, erm, that's my… So then we moved again. Then we moved up north so then I started getting my, erm, treatment from Manchester. So I got an experience of hepatology where they don't have experience of PSC. So I'd get my letters and the, the top of the letter it said, 'Viral hepatitis clinic'. And I, I didn't know what viral hepatitis was at that point so if I did I would have been doubly offended I think. Erm, but I thought, 'Why am I in the wrong clinic?' And that made me not feel so confident and, er, so I never used to like that but I let that go 'cause that's NHS admin [mm-hmm]. And the doctor, he used to say things. So I read a lot about PSC and I had access to scientific papers because I still had my old university log-in and, erm, so I could get, get a lot of it. And I felt like I knew more than him and [laughs] this doctor, he would say things that were, they just didn't sit right with me about what, or research that I'd read and he didn't know about it so I just didn't really have much confidence in him. But it didn't matter 'cause I was all right. There wasn't anything, you know, my bile ducts were fine, all, everything was all right. Erm, and then I moved, oh, one time he wrote to me and said my PBC was okay so he'd put a different disease in [laughs] so that was a bit confusing. Erm, and then we moved down here and I came back to Oxford for my care and I had different doctors then and it's just a completely different story because what, you know, whatever test, you know, 'Can I have a [0:09:56] scan?' 'Yeah, we'll sort that out'. Or they were just really, really organised and good about it. I didn't have to fight for every single test and I'm not even one of those patients that wants to have loads of tests. I just want the minimum. Erm, and, erm, that's it. That kind of brings us to now and it, I've had a few, few times where I've had cholangitis [mm-hmm] and the first time that was really worrying because that, I thought that that meant my PSC was progressing so I was really worried about it. Erm, but luckily the doctor straight away said it's not. It, you just, your PSC goes up and down, up and down so I was, that was okay but it's just, it's so hard and people don't realise how, it's like being hit by a…

4

Commented [KA(al9]: Administrative difficulties with healthcare

Commented [KA(al10]: Professional patient, imbalance of information, doctor/patient relationship

Commented [KA(al11]: Symptom – cholangitis, anxiety over progression/prognosis

Sound file: **Interview 018**

[0:10:44-0:10:55 – outside interruption].

IV: So where was I? Oh yeah, cholangitis. So I, I, it, it was awful. Like I wanted to scratch my skin off with a fork the first time. Erm, then I got, again that was, that was really lucky because I had found a hepatologist, actually my first hepatologist when I lived in Essex was a private one that Roger had recommended and, erm, so I was able to get on antibiotics really, really quickly so I didn't have to go in hospital, which was really good, but that feeling of your skin being, it was like, it was just like extreme sunburn I felt. Really horrible. Erm, and, and I've had that a few times actually now but I know the signs. The last time I had it just about a year ago I felt it all coming. I did feel it. I felt, I started feeling itchy, didn't feel too good. I knew what it was so I went to the GP because I have, erm, antibiotics at home for it and I started taking them. Then I looked at the sell-by date and it had been a couple of years and they were, they'd gone past and I thought I'd better go and get some new ones. So I took, I got the GP and he sat there and he said, I said, 'Oh, I'm having a flare-up of cholangitis. Can I just get new antibiotics?" And he went, 'There's no such thing as a flare-up. Erm, you don't get that'. And he, he sort of got pedantic over the, my terminology. And I, and it's so hard to, erm, advocate for yourself when you've got a doctor that is talking to you like they know better than you and I'm thinking I wrote the leaflet on bacterial cholangitis. I know what it is, I've had it before and he honestly didn't believe me. And he went out of the office. I think he Googled it 'cause he came back in and he went, 'Oh, yeah, you can have it. Have the antibiotics'. And he was amazing after that and he went, 'Right. I'm going to arrange for you to have an ultrasound. I want you to come back in, erm, five days and we're going to do another test and we're going to see', and he just switched to, it was like a different person. But that initial appointment when I said, 'I can feel myself getting it, getting it', and he went, 'Yeah, you', what did he say? He said something like it's not, you don't get flare-ups and, and if you did have it you wouldn't be sat here like this. And I was thinking no, I could feel it gradually getting [mmm], you know, I just want to catch it early please. He was really, really good. Erm, but they didn't arrange me, for me to have a follow up so then I was going to, they told hepatology, he was in contact with them but they didn't, this is Oxford and they didn't arrange for me to have an MRI

Commented [KA(al12]: Symptom - itch

Commented [KA(al13]: Symptom - itch

Commented [KA(al14]: Professional patient, imbalance of information, doctor/patient relationship

Sound file: **Interview 018**

scan and I just happened to be in a taxi with Roger Chapman 'cause he'd already retired and he said, 'You need to have an MRI scan if you've had a cholangitis attack so you need to ask for one'. So I got one eventually six months after my [laughs] initial cholangitis. So it doesn't go smoothly. Even if you're, you know the signs, you feel confident about what's going on it still doesn't go smoothly. If, if it takes one doctor that's confident in their view it's so easy for them to overpower you and I feel sorry for patients that do go appointments and they are worried about something and the doctors dismiss it like they'll dismiss the pain or they'll say, 'Itching, yeah. That's, that's okay, that's normal'. And yeah. So but I, I'm kind of fake really because, you know, I'm here 11 years on now and, erm, I'm, touch wood, I've not got all these, this, this, my liver's pretty good at the moment so I'm not like other people but it's what I see other people through. It's awful I think, especially when you see the younger ones. The younger, like younger men and they come on the forums and they are, they start to have really sudden and extreme symptoms and they've got families to care for and they start having to reduce their hours at work and you, you almost can see their, you can see and you know what's going to happen and they're going to be the ones needing transplants and it's horrible to watch that. But yeah, I think I've got off lightly at the moment [laughs].

Commented [KA(al15]: Professional patient, imbalance of information, doctor/patient relationship

Commented [KA(al16]: Feeling lucky not severe disease

I: Yeah. Erm, and apart from, so in between the cholangitis do you have any symptoms at the moment?

IV: Erm, I get, I just get like pain in my, my liver, like really, like a knitting needle. It's like someone poking with something sharp in there and I get tired, I get really tired. Erm, so if I do something one day then the next I just feel wiped out. Or I get, get to about seven o'clock at night and I feel like I just want to go bed. I'm really tired. And we've got used to it now as a family so for a long time we still used to try and go out at night or go to, you know, you go to the cinema on a Saturday night or a Friday night. We used to still try and do that and I'd be sat there in the cinema and I've fallen asleep at people's houses and things like that. And, erm, now we just do everything in the daytime. We just have, find ways round it. And you know what, even what I'm doing is I gave up my work and I just do PSC support full-time voluntary but part of that is

Commented [KA(al17]: Symptom - pain

Commented [KA(al18]: Symptom - fatigue, effect on activities, coping

Sound file: **Interview 018**

because I genuinely don't think I could get to do a 9 to 5 job in an office or whatever every day so this, I can do it when I'm feeling all right. But I've got other conditions as well. I get a lot of migraines. I get probably like eight or nine a month and that's like, that is worst than the PSC 'cause it's so frustrating. You're there and you can't do anything. I can't speak properly when I've got that, or right, properly. I think I can but what comes out is dribble [laughs]. Mmm.

I: Okay. And how has it kind of affected your trajectory of your life kind of overall? You said you, you gave up work.

IV: Yeah. Erm, I was just about to say and then he came down but my husband, he just point blank said, 'We're not having any more children because a) I don't want to put you at risk, b) I don't want them to not have a mother'. I was like, 'No, but I really want one and Roger said live your life properly', so that was a big, for him, for my husband, it was just like no, cannot do it and that was no. So that's changed 'cause I think we would have had more than one child. Erm, certainly my career, I wouldn't, you know, that's gone but actually I really like what I'm doing now so that's good, erm, apart from the public speaking part, don't like that. I only do that to get a cure [laughs]. Erm, yeah. I think just like my social life's taken a bit of a downturn. Some friends get it and I see them in the day but other ones I think have drifted away and they're the ones that want to go out drinking at night and want to do things and I think it's just not compatible and we've kind of grown apart. Don't know whether that happens normally to people in life anyway. Erm, I've not got a pension. I used to have when I worked but I've never followed it up 'cause in my mind I just think there's no point. I kind of should probably re, re-address that now 'cause I think I'm, I'm sort of defying those statistics [mmm] that I read initially but I went for a long time thinking actually I'm not even going to bother at all with a pension. Erm, and it affects other stuff 'cause Matt was, he works for a cyber security company and ideally we'd be living in America and we just can't [mmm] go at the moment 'cause I just don't think there'd be an insurance policy that could cover what potentially could happen [mmm] for me with the transplant. So it's got, it's affected a lot of things, erm, in, in our lives but you kind of make the best of it and you just make decision based on the

Commented [KA(al19]: Effect on family relations, disrupted narrative/trajectory

Commented [KA(al20]: Effect on friendships, social life

Commented [KA(al21]: Effect on travel, holidays

Sound file: **Interview 018**

information you've got. So who knows whether we would have done those things anyway [mmm]. So yeah. What else do you need to know? I'm sure I had loads to say.

I: You, you've said loads. You've, I mean just thinking of the questions going tick.

IV: Shall I tell you about the colonoscopies 'cause we have to that, I've, 'cause I've got ulcerative colitis and I do have them every year now and I think there are quite a few people like me and I think this needs investigation because the, the actual prep, the drink, when I drink that now it goes down and then a few minutes later it comes back up, erm, to the point where I have to have a sip every few minutes of the bowel prep. So it takes a glass that you, that is one, that'll be one of the [0:19:39] or Citromag [mm-hmm]. That'll take about two hours to drink and it doesn't, you know, they don't, they don't really work effectively and I've not had an effective bowel prep for years, not one where they go excellent. Not had one of those and I think, I think there's quite a few people with PSC that have this and it's getting worse every year [mmm]. So that is, that's just another thing that you have to go through. Clearly you want to have it so that you can be checked for cancer or cells that are changing but it's horrible. It's horrible. That drink is horrible. I don't mind the, the actual day although it gives me a migraine as well. You go, you go for the colonoscopy and you know they give you the sedation but they want to keep talking to you and you're just thinking no, just let me relax. Stop talking to me. And they're going, 'Come on. You all right, my love?'

I: Yeah. Wakey-wakey.

IV: Yeah. I know.

I: Yeah, no that's true. Mmm.

IV: I wish they would sort the bowel, well they might do 'cause I've had a, I had an appointment. Luckily my hepatologist is amazing and she arranged for me to have an appointment with like the chief gastro and the [redacted] and he's looking into an alternative way of having the prep so I'm waiting to find out about that but amazing.

Commented [KA(al22]: Unpleasant investigations, monitoring

Commented [KA(al23]: Personalized medicine

Sound file: **Interview 018**

I'll do anything not to have that drink 'cause it's, it's just rubbish. It comes back up and it doesn't work properly and then there's the risk you get to hospital and they make you have more [laughs].

I: Not what you want.

IV: No.

I: Okay. And you mentioned friends and that sort of telling them and what's all that dynamic like?

IV: Erm, I kind of don't really talk about it anymore. When I first got diagnosed I felt as though, like compelled to make a big announcement to everyone 'cause it was a big deal for me. Actually it's not a big deal for everyone else so, so you kind of do this like ah, I've got this disease and, and people, it goes over people's heads unless they're talking to you and then they ask you about it and it's a total and utter conversation stopper 'cause if you tell them the truth, it's a bile duct disease, it's autoimmune, there's no cure. You know, it can lead to transplant, they don't know what to say. They actually don't know what to say. They either react just to the word liver disease, doesn't matter that you say autoimmune and you almost get a knowing look. I have had this where from mums at school that I think they think I'm an alcoholic. I'm sure they think I am [laughs]. Or, or it kind of freaks them out that you've got an incurable disease and because it's not like cancer they can't, it's like they can't give you sympathy. It just freaks people out. If it, if it, if it had that word in it I think, that's how I think people should react to it. It's like oh, you, you know, what are you dealing with? What can we, how can we help you? [Mmm]. But they don't. They just, they'd go oh. Oh, you're dying or like, you know [mmm], you know what I mean? It's a real conversation stopper so it's easier not to talk about it. And I don't, I don't drink anymore and I think that's quite difficult, especially for the young people and for me. It, it's almost socially unacceptable not to drink unless you're pregnant or unless you're driving and I find if I'm driving, if I am out at night 'cause that's when you are expected to drink, if you, if you're not drinking you're expected to drive or [mmm] it's a good excuse. I get so tired I'm not very good at driving at night like that.

Commented [KA(al24]: Effect on friendships, poor lay knowledge

Commented [KA(al25]: Alcohol, stigma

Commented [KA(al26]: Effect on friendships, anxieties about cancer

Commented [KA(al27]: Alcohol, stigma

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So I've tried, I've done it a few times. My husband knows now, he just drives at night if we do ever go out at night but that's, that's a, difficult. And people are constantly talking about alcohol and how drunk they're going to get and, and I want to say to them, 'You should look after your livers', and I don't 'cause I know I'm harping on about it. And now it's to the point where I put posts on Facebook, organ donation and all this, and like the only people that like those posts are the people that have got PSC, not, not actually any, okay, a few of my closer friends will, will click like but I think it's only 'cause they just feel sorry for me. Like what's she saying that again for? So I put, occasionally if I do, I post that like I'll pop a puppy picture on afterwards and that's all like, that's easy for people to deal with. They like that and, erm, you know, they can click like and carry on and it's not heavy for them. So I don't think people understand though. They don't understand. They either think that you're worrying over nothing and they'll say, 'Oh, don't worry. It's not, you know, you might be one of the, you know, the ones, the lucky ones', or whatever and I don't think anybody's, I know I've said I think I'm quite lucky 'cause I'm doing all right but I don't think anyone is lucky with PSC. Mmm. So yeah, not, not, not really. And when I worked I didn't really talk about it then either because you don't want them to think that you're an ill person. And sometimes you, it is hard. You drag yourself into work, you're feeling really, really tired and then someone will be moaning about a cold and you think, 'Okay'.

I: You've got no idea.

IV: Yeah. No idea, exactly. Exactly. You can't, you can't, what can you say? You can't take away other people's worries and things that they've got even if they are what you consider to be minor. But you'd just wish they'd, I don't think, I don't think people really understand what it's like. I mean although, unless you do explain it in full they generally, I think they definitely think that you drink or there's, 'cause it's liver disease you've done something and I don't think that's fair for anybody. Even people, because this is what happened recently. I had an ultrasound, this is last year, and the person that did the ultrasound, they wrote on it, 'Yeah, there's fibrosis and in the absence of a diagnosis this is fatty liver disease', and that's what they wrote. The GP

Commented [KA(al28]: Alcohol, stigma

Commented [KA(al29]: Poor lay knowledge, effect on friendships

Commented [KA(al30]: Lucky not got severe disease

Commented [KA(al31]: Effect on work

Commented [KA(al32]: Alcohol, stigma

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got it and took PSC off my diagnosis and put fatty liver disease, this is in January, and I happened to go back for an appointment in October just before [0:25:59] and she went, 'Right. You've got fatty liver'. I'm like, 'What? No, I've not. I've got PSC'. 'No, you've got fatty liver'. I'm like, 'What do you mean? Where have you got that from?' And she went, 'Oh, erm, yeah, you've, there's a test in January, you've got fatty liver disease'. And I'm like, 'Why', in my head I'm like why has nobody told me? How have I managed to get a disease that I could have prevented and it is the most awful feeling in the world to think that something's happening to you that you could have done something about. And then this GP was going, 'You need to lose some weight', like this. That's all the information she gave me. So I went away. Oh, and then she did my blood pressure and it was about, it was like 108. It was really, it was the highest it could be and she went, '[0:26:47]'. Yeah, exactly. And then she went, 'Are you stressed?' And I, I was because I had all this stuff to do, I was, I had two presentations that week in Washington and I was already stressed. And, erm, so she did this blood pressure three times over the appointment and each time it was like off the scale. She went, 'You've got hypotension as well as fatty liver disease'. I'm like ah, oh my God, oh my God. So she goes, oh, I'd gone to get something different for my migraines 'cause they were getting worse and I wanted to be able to get them more controlled and the, the GP had referred me to a specialist in Oxford, got the appointment and the specialist wrote back and said, 'We're not giving an appointment because she's already got a confirmed migraine diagnosis so we need her to try some different drugs', which I thought was a bit off 'cause I've got all these other conditions. I thought it might be better for someone to listen. So I, that's why I was at the GP to say I'm going through this letter, which drug can I have? So she gave me [0:27:50] because that lowers your blood pressure and so I was like okay. So I didn't dare take that for a week [mmm] 'cause I was going to America. And, erm, yeah, so that was awful. So I had to keep going back for a few weeks to have my blood pressure done again and the, is it ECG it's called? [Yeah]. Whatever it's called, the heart thing, and they came back normal. Every time I've been in they've all been normal and, erm, I did try and lose weight a bit and started doing more exercise and I was thinking I'm sure I, I can't, how have I got fatty liver disease? Why have I not

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been told about this? Why did nobody tell me in January? And I said to the hepatologist one time, 'Why did nobody tell me?' And she went, 'That's because', er, I said, 'Why has my hepatologist not told me?' 'Cause I had an appointment in April with them since [mmm], since this January test and she said, 'Oh, hepatologists don't deal with that, fatty liver'. Okay. Erm, but why, why has nobody said anything if I could do something about it? Anyway, so I, I emailed my doctor, my hepatologist in the end, big long email saying this, this is, this date this happened, blah, blah, blah. And then she, she was so good. She replied back that night and said, 'Look. I've just been through your electronic records, so not your full ones but your electronic and there's no evidence to suggest you've got fatty liver disease so this has come somehow from the doctor so I'm going to write them a letter and explain what we know [mmm] and then when we see you we'll check more but you've', and I knew I'd had fibrosis scans that had come back really good and it's just really... So, so I haven't got fatty liver disease and it took a little bit of a battle with the GP to get them to change my diagnosis on the system back to PSC [laughs]. It was ridiculous and I don't know what it is. And the other thing is until recently every year we had to, I had to phone up for my flu injection 'cause they didn't have PSC down as a chronic liver disease or it didn't count [mmm] so I had, had to chase that up. But my GP's been a nightmare really to be honest. This is a different one to the one that got really good with the cholangitis. It's a different lady.

Commented [KA(al33]: system failings

Commented [KA(al34]: system failings

I: In what way you said that your new GP's not very good?

IV: This is, so the one when I had cholangitis and he said you haven't got it 'cause there's no flare, no such thing as a flare, that was a guy. He was, he was only there for a few weeks on call or something and then this new one, this, so you go to a big practice and you see a different one every time and this one is a lady and she went, 'I'm going to put myself as your named doctor because you've got like migraines and things like that so I know what's going on', and then like this story unfolder with, with her deciding that I had, well I think maybe one of the reception admin [mmm], one of the admin had just seen that message from the ultrasound and made the wrong assumption [mmm]. I'm sure that's how it started and then she was just working from

Commented [KA(al35]: lack of consistency

Sound file: **Interview 018**

what was on her screen but it was one of those conversations the first time when it was, it was like what? What are you saying? So it was, so she's not, she's good in that she thinks she's helping, you know, helping my fatty liver [mmm] although if I had fatty liver disease I wouldn't want to be told like that and be told to go and lose weight. I'd want more information and how do I do it, what exactly do I need to do 'cause it's, in my mind it's a bit more serious than going on Slimming World or something [mmm]. Er, so she didn't give any of that. Erm, so, and with the PSC [sighs] I think, I think it's just a reflection of the fact people don't understand it. If you can be diagnosed with PSC for 10 years and then the GP can think that it's okay to take it off the system and refuse to put it back on kind of I think it's a reflection of what they, what they know. So, but then I guess it's all, was all based from a mistake. It was, it's just horrible when you think they, they genuinely, this is a new level of not understanding your liver disease [mmm]. And I don't even expect my GP to have a lot, a great deal of understanding. I just expect them to be there for the, the routine things and it, and I, also what, the other thing that's, I'm on a roll now, what is the other thing that's really annoying is that whenever the GP arranges a blood test I'll go and have it done. Then I have to phone up and get it and you phone up and they'll, they, literally they're like guarding the blood tests. 'Which ones do you want? Which results do you want?' Like this and you have to say [0:32:42] and [mmm] just name the one, you get the results. But the JR Hospital can't see the results that the doctor's got. And then the JR, they'll do their results and I'll have no way of getting them unless they actually write to me and tell me them and the GP certainly doesn't see them. So my last letter from my hepatologist, 'cause I'm trying to get on some of her research and she said, 'Ah, need to just, we need to just arrange another blood test 'cause you've not had one for a year'. I'm thinking, 'I have. I've had two' [mmm], 'cause I spoke to you that time when I wanted to come off [0:33:16] [yeah] and she was brilliant. She said, 'Right, we'll do a blood test the day you come off it and then one three months' later and we did all that. 'Cause the GP was doing something I don't think one person has seen the whole picture. So [laughs], so that makes it hard. I think you just have to be, accept that you've got to be on the ball with PSC and I'm not particularly on the ball to be honest. I really only chase my bloods up when I know I've got the next

Commented [KA(al36]: system failings

Commented [KA(al37]: system failings

Commented [KA(al38]: self advocating

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appointment and I need to have them to take. I wouldn't do it out of efficiency [laughs]. I'm probably the worst example [laughter]. I tell all these people to do that and I'm not, I don't [laughs].

I: It sounds like you've had to do a lot of the work here to, you know, get things sorted out and stuff.

IV: Yeah, but it [sighs], I don't know what it's like in Birmingham because they, I understand that they've got this lovely system where you can, everybody can see it all and, erm, you don't have to chase things up and someone will get, you get a letter and then automatically you get the, all the tests sorted out for the same day and you know you're going to get your blood test in a few days later and it all works really nicely and predictably. And I think for me I, and this is so three, four different hospitals now for PSC and different GPs 'cause we have moved about a lot and it's, it's like everybody has a different, slightly different system and every PSC doctor you see, not unless, no, if they're in the same clinic it tends to be the same but if they're in a different hospital they have a different way of doing it and a different way of explaining it and a different outlook on it. So you never, you know, if you do move you don't quite know what, what to expect and what's, what's going to happen and how it'll all work with your GP and some people have got amazing GPs that, that are really good. They know that they're in the middle. They're like the main point of communication and they coordinate all the other diseases [laughs]. Then you've got this situation where it's all patchy and no one talks to each other and you're never quite sure. 'Cause I, I was given some tablets one time and I Googled whether I should have them or not 'cause I think I got them without instructions and then, and then I, I, I felt like I perhaps shouldn't be having them. And then I didn't care have them 'cause then I thought well maybe they don't, that, that looks like there's an interaction 'cause I take [0:35:43]. I was like [mmm] better not have them. So you end you end up like not really trusting anything unless you're sat in front of your hepatologist so yeah. That was why I really wanted to see a specialist about the different migraine tablets so that would have been much better to have just to be able

Commented [KA(al39]: system failings

Commented [KA(al40]: need for specialist

Sound file: **Interview 018**

to go through those [mmm]. As it was, that [0:36:03] brilliant so [laughs] that's worked wonders.

I: Fair enough, yeah. Yeah, no, that's difficult, isn't it. And you mentioned Birmingham and, er, high-tech [yeah] kind of blood test system and stuff and I know that you know about the, the virtual clinic and [yeah] the video clinic [yeah] and stuff. What's your opinion on all of that?

IV: I think it, that that's the way to go and that virtual clinic, I remember having a conversation a year or so before they applied for the funding saying, 'Wish we could do it like this', because people, if you've got PSC you want to see a specialist, you want to see somebody that actually understands what's happening or understands if, if something is changing with you, whether or not that's something that needs to be acted on or if it's okay to ignore. And if a specialist tells you it's okay to ignore then you can be confident that you can ignore it. If a gastro or somebody that you don't think really knows about PSC tells you to ignore it you worry and you think maybe I, maybe they're wrong or they don't understand me and it's really… But if you live more, you know, a few hours away from a centre like Birmingham and you, and you're like me and you're fairly asymptomatic, it's a long way to go just for a five-minute appointment where you look at your blood test, do an ultrasound and you say everything's all right. You know, driving a five-hour round trip [mmm] seems pointless yet you want to do it because you want to have confidence that the person looking at your tests knows that they're okay or knows that they're not okay. And so the virtual clinic, if it, at the moment it's just limited to West Midlands but if other centres started to do that it would be brilliant because people with PSC wherever they lived would get the experts looking at their tests and results. And, you know, it might mean that some people get referred for transplant at the right time because we see it that, we see people on our forums and they're starting to get symptoms and things are starting to get a little bit messy and complicated and they're going in and out for ERCPs and they're still at local centres. And you just think that, that, surely that should have a PSC specialist and then suddenly it all comes in a rush and they're being [mmm] assessed for transplant. And I think it would be better for everybody if

Commented [KA(al41]: telemdicine

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they were referred earlier and I think the experts, the ones at the transplant centres, are probably the ones that recognise the signs more than a gastro or even someone with an interest in liver. If they've not got many PSC patients then, you know, we can't expect them to know what the optimum time to refer someone is for [mmm] transplant. You really can't so, and a lot of patients, we all seem to resign ourselves to symptoms and it's a bit worrying sometimes because on our different forums you see that oh, I've got this, this and this. I've got a sudden itch, severe pain and I'm getting a bit jaundiced, it's all come on all of a sudden and people go, 'Oh yeah, that's PSC for you'. And we're going, 'You need to go and see a specialist. You need to let your consultant know. They want to know'. But people…

Commented [KA(al42]: specialist

[0:39:27- 0:40:55 – outside interruption].

IV: Where was I? I feel like I'm just moaning.

I: No. It's stuff that's interesting.

IV: That virtual clinic, I, yeah, I think that's amazing. I would love it if more patients could have access to that, not just the West Midlands ones [mmm]. So I want that to be a success [yeah]. So do, I do tell James to update me [laughs].

I: Oh right. And do you think, you know, there's obviously those advantages to it. Do you think there's any disadvantages to it?

IV: I'm, yeah, a little bit because you're not physically in front of someone so that doctor can't actually feel your liver 'cause when I go for my appointments they poke around or you might need to have an ultrasound or an actual test. So I don't know whether the virtual clinic would be, it might mean you need less of those tests because you're getting a better appointment, that might be a good thing but to me it's slightly, I'd slightly worry that it might mean that people might get less tests that they need but that's the only thing. I don't know if, there might be disadvantages in that people don't know how to do Skype and they need a lot of guidance on it 'cause whenever I set up calls with sometimes my trustees, erm, it, the, every time Skype does an update you waste so much time [mmm] waiting for people to figure it all out and get online. So

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that's a disadvantage but I think that's a, a small blip. That's not a disadvantage of the actual system, that's just a disadvantage of what technology we've got available at the moment. Erm, and if you can, if you can see someone on the screen and the, and the doctor can see you then that surely is partly quite good apart from you don't get a feel of your liver. Erm, and sometimes you, you might be less nervous on the phone than when, apparently I've got white coat syndrome. So [laughs], so yeah, no wonder my blood pressure goes up [yeah, yeah] but when I am in hospital, I didn't know I had but I just some, the doctor said I had it. Maybe a lot of people get that and so if you, at home if you're more relaxed you might remember to say everything that you need to say. You might have a list written down of questions, which I understand is encouraged anyway [mmm] for people to think what questions they've got. So I think there's a, there's loads and loads of advantages and especially for the asymptomatic people with PSC. You know, and if they're seeing specialists virtually and they get referred to transplant centres at the right time because they're seeing specialists virtually then that's, that's a win win. And obviously when you are at that stage when you've got advanced liver diseases you are going to have to be face to face I think. Probably going to get a lot more tests so, but yeah, I think it's really good.

Commented [KA(al43]: telemdicine

I: Fantastic. Just looking through my list [laughs]. You've answered it all. Erm... I guess just, I mean obviously talking about kind of the future and, and, erm, man, management of PCS, you know, what, what would you want to happen with your management? What would be kind of your ideal scenario?

IV: Erm, for, for now or for when I started getting more symptoms?

I: Whenever.

IV: Erm, okay, if money was no object I would really like to have my hepatologist appointment with the gastroenterologist at the same because I think sometimes our ulcerative colitis and our IBD gets a little bit overlooked. And this, this seems to even apply to, to people that are seen by gastroenterologists [laughs]. So it's almost like we, they just want to focus on the PSC part and okay, there's no treatment or cure so

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we, doesn't really matter what we do with you guys. And you have milder colitis anyway so there's that kind of feeling. So I, it would be really good if you could perhaps not even every appointment but have the, the two specialities there talking to you in your appointment. It'd be great if you could have all the tests done on the same day so if you get out of sync slightly, like I have done this time, I'm going to be going three times. I'll be going one for my ultrasound, one for I don't know, something, there's something else, oh and one's for research appointment, so I'll be going twice. And, and normally they can get that arranged for the same day. I'd really like it if I could phone up and get those appointments easily, not have to phone lots of different departments just to get like coordinated [mmm]. That's quite difficult. Erm, I'd like to feel that I could be on the end of a phone to someone. So I, okay, I kind of am very familiar with what all the symptoms are going to be but if I put myself in the shoes of somebody that's not and they're fairly newly diagnosed it's great to be able to come on our forum but actually at the end of the day sometimes you need somebody with some medical knowledge at the end of a phone even if you're early PSC [mmm]. Like the transplant patients seem to have that and I think it'd be great if, in an ideal situation if we could all have somebody that knows about PSC on the end of a phone, especially times when people go into A&E. That's difficult for people 'cause quite often people have no clue what PSC is and they're battling against feeling very worried about themselves else they wouldn't be in A&E and somebody to, you know, talking to them saying, 'We don't, you know, there's nothing wrong with you', or, 'We can't do anything'. So if there was a way of contacting some specialist at that time, that would be really, really good. Erm, I think [sighs], I think [sighs] this is probably an issue for the support group and the doctors. I think we need better information about PSC and I believe there's a reluctance to give information about PSC because there's no, there's not a lot of evidence about what the best care is. There's not really [mmm] that much. I've sat on the PSC guidelines and there's no consensus between the doctors most of the time. In fact, you quite often get two camps. And so people are not being cared for consistently and it's not always because the doctors have got a lack of knowledge compared to the ones with knowledge. There's doctors out there that have got a little bit of knowledge or they've

Commented [KA(al44]: lack of effective treatment

Commented [KA(al45]: system failings, navigating, self-advocating

Commented [KA(al46]: conflicts with medical staff, doctor/patient relationship, poor lay and medical, knowledge

Commented [KA(al47]: lack of effective treatment

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got a different opinion and so the care's completely different everywhere. We, we had, erm, a question last week about pain relief and literally people were yeah, you mustn't have ibuprofen with PSC. Next post, you must never have paracetamol with PSC but ibuprofen's okay. And people have been told all these [mmm] different, different options that they can have so I think that we need to do better information and I think that the, the doctors need to do better medical information 'cause people, if you're a patient you can't really tell the difference between a doctor not having the answers because there aren't any and a doctor not having the answers because they just don't know them, if that makes sense [yeah]. So yeah. And, you know, and I, if I didn't have to have colonoscopies that'd be brilliant. And also if you could, you know, we've got, we've got this disease and then we've got these cancers and I moan and I joke about colonoscopies but I get it. I have them and I will carry on having them even though I don't like them. But we have bail duct cancer and that's much worse, yet there's no way of doing surveillance for it. That's pretty hard, you know, and there's, there's, there's one blood test that will tell you and there's this CA19-9 and, but that's not actually a good marker [mmm] for bile duct cancer and anyway it goes up and down with PSC. Probably causes, when it goes up it definitely causes a lot of anxiety yet not having that test causes a lot of anxiety 'cause they'll get a pain and they'll think, 'Have I got it? Have I not got it? Is something being missed?' So, you know, an ideal, ideal clinic would be everybody knowing what they're doing about your conditions as they're connected and that you could be surveyed properly for cancers in a way that's meaningful. So that's, yeah, that's what I'd like. So are you going to fix that, yeah? [Laughter].

Commented [KA(al48]: importance of information

I: No, so yeah, really good point.

IV: And then if you could make your appointments more easily and change them that'd be a really added bonus because that is, that's probably one of the hardest things is it's like this wall of admin to get through and it's difficult. I, I've been put down as DNA a few times at the Manchester Hospital because they kept cancelling the appointments so [laughs] I got told off by the doctor one time. I'm like, 'No, you kept cancelling it'. So there's some admin systems that leave a lot to be desired [mmm],

Commented [KA(al49]: administrative difficulties, navigating, self-advocating

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okay]. And every appointment, if they told you what research there was going on or they knew about it so you, you'd automatically think to, have part of the conversation would be about research opportunities in every appointment would be really good. Yeah. And if they asked, if the, the doctors proactive, when they go oh right, how are you, like this you kind of get side-tracked into the questions that they lead on and they're like, they're just like medical questions that they ask you but they don't say, 'Are you, you know, are you tired? Is that fatigue?' You know, and then maybe if you really are then they could do some tests, other tests. So I'd like if they would not only ask about the liver things about but asked about, ask, ask us about our like softer symptoms like pain, fatigue. Erm, it, they would probably ask, you would, you would tell them about that but it's not so easy to bring up pain and fatigue in a [mmm], in a, a busy appointment.

I: I think I've exhausted all my questions [laughs]. Is there anything else that you wanted to say that we've not talked about or…

IV: I don't, I don't, no.

I: …that is important?

IV: So I guess, I guess I've, the main thing is I wish there were more doctors that were interested in PSC and I know we're trying to stretch the ones that we do have for everybody and that's kind of impossible. So I guess the, a way of addressing those is to have better information for doctors and for patients, erm, and for them to understand us more but we're trying, we're working on that I suppose but yeah. I think, I'm trying to think what, I mean I've talked from my perspective mainly but there's a lot of, I'm trying to think now what generally people think. I think there's a lot of people who have their pain dismissed and it's quite excruciating for some people and they need, they do need something stronger than what they're given. Erm, there are a lot of people that have got itch that goes, they just think, they just accept it and don't do anything about it or they'll try the first line of the first drug like [0:53:01] and then it doesn't work but they just carry on on it and they don't go back to the doctor and say, 'It's not working properly'. Erm, and they might not see the doctor again for

Commented [KA(al50]: keen for research

Commented [KA(al51]: mismatch doctor and patient priorities

Commented [KA(al52]: inequality of care, need for specialists, improved patient information

Sound file: **Interview 018**

six months but [mmm] they don't go back and say it's not working, can I have the next one. So there's a lot of people with those, and I don't know that the doctors, they know that, that the other drugs work differently and maybe you could try one of those [mmm]. And it's not Birmingham clearly but it's the, the more local hospitals that do this. Erm…

I: I guess maybe if the, the quality of life, you know, if they had a PSC specific one I guess in the future if that's' done before every clinic visit [mmm] if it asks about some [yeah] maybe. I don't know [yeah] whether that's like a trigger of [yeah] [0:53:51].

IV: It'd be good, wouldn't it, if there was an app of the quality of life measure and people literally just did it while they were waiting [mmm] and then it would feed in automatically to the computer in the doctor's office and they can look at last time's scores as well and they would see, see the trend that [mmm] maybe even the patient's not perceived. That'd be amazing, wouldn't it? We need to make an app.

Commented [KA(al53]: measuring what is importance to patients

I: Between your, your half with the cyber security and my half with this IT NHS we can [0:54:22].

IV: Yeah. Yeah.

I: Erm, no, I was just thinking but yeah. I mean something like that, you know, when that does come in might [mmm] be that kind of trigger that perhaps people need and if they're not that [yeah], if they're not as familiar with it, with PSC, it, it gives them that [yeah] trigger of actually itch is a thing you need to sort out.

IV: Yeah. And it's, you know, you're on a medicine and it's still not worked. We talked about, we went, we applied to the MRC for this grant last year and we didn't get it. This was with Newcastle and, erm, part of it was a patient passport but it was a passport that was on a platform and it was to help patients navigate their appointment and I suppose you would, to simplify it it was like, it would be like an electronic flowchart that this is happening. Do this, do this, do this but it would empower the patients to ask questions, the right questions about their care. So I'm feeling fatigued. Can you do a blood test for thyroid, or whatever and find out, you know, exclude other

Commented [KA(al54]: patient passports

Sound file: **Interview 018**

things or treat the other things. Oh, I've not had a colonoscopy for four years. Perhaps I should have one. Erm, and so we didn't, the, the grant was a big one. That, that was just a little patient part of it but [mmm] I think that, I still think that, for PSC patients I think that would be brilliant. It would really, really work for the ones that are not seen in the big hospitals. I mean if we could like link it up virtually, wouldn't it be good if you could do things like that and then those results would go to the doctor even if you didn't have an appointment and someone was monitoring those results and they would go [yeah] we need to see that person sooner.

I: Some red line that…

IV: Wow. Yeah. Yeah, that would be really good.

I: They have that in, erm, one of the Birmingham hospitals is a big kidney disease centre [yeah] and every kidney function test for anyone at that centre that drops below a certain point, a, a, like a referral's made or a ping goes somewhere…

IV: Really?

I: …that goes, 'Uh-oh'.

IV: Yeah, that's good. That's really good. If only we had the evidence and the heart, and, and rules that you can make properly for PSC. If we did it we'd have to, it would have to be quite general at first until we started getting better evidence to then feed into guidelines and make actual recommendations and rules.

I: Mmm. It's that, yeah, it's that evidence base, isn't it.

IV: Yeah. And what you're doing and what Eleanor's doing will go a long way to starting to build up evidence once they're out. I was talking to Eleanor about her, what she's been finding actually yesterday and she said it's really interesting and you've probably picked up on it as well that she said that people have got really good coping strategies for everything. So there's the issues but they're actually figuring ways out to, of having coping strategies for different things. She didn't say what any were but I

Sound file: **Interview 018**

thought that was interesting [mmm]. There's about a million papers to be written from stuff like this.

I: Erm, fab. Anything else you can think of?

IV: I don't think so.

I: Don't think so?

IV: I don't think so.

I: Okay. Well fab. I'm going to stop the tape.

18 Appendix G: Scoping review summary tables & reference databases

Stage 1: Re-applying the Cochrane review search strategy

Table 1. Summary of included article characteristics

Author	Population	Aim & Intervention	Findings
Paneroni et al 2015 (abstract)	Italy 36 subjects (18 test, 18 control)	This study was a home-based telemedicine programme of COPD compared to standard outpatient face-to-face care, including some video and telephone calls.	22% of telemedicine patients found the technology unfriendly. Both programs improved symptoms and lung function ($p<0.005$) with no difference between the intervention groups.
Jelcic et al 2014	Italy 27 subjects (7 test, 20 control)	This study looked at the effectiveness of cognitive therapies via telemedicine in patients with Alzheimer's disease, compared to an in-person rehabilitation programme.	The mean MMSE score improved significantly in both intervention groups; other neuropsychiatric markers were unaffected.
Sorkneas et al 2013	Denmark 266 subjects (132 test, 134 control)	This study investigated patients with COPD in the week after their hospital discharge and whether the addition of daily nurse-led video consultations to the standard of care improved outcomes.	No differences were found in mortality, or re-admissions between the intervention groups.
Aguilera et al 2014	Spain 457 subjects (368 test, 89 control)	This study investigated telemedicine in the diagnosis of dermatological complaints, including video consultations, compared to standard management.	Interobserver agreement was good between the groups but was affected by image quality ($p<0.01$) and diagnostic confidence ($p<0.01$).
Selman et al 2015	UK, USA 15 subjects (7 test, 8 control)	This study evaluated the acceptability of tele-yoga in COPD and heart failure compared to education via qualitative interview.	The intervention was acceptable to patients however poor online streaming was a problem. No formal comparison of groups was undertaken.

Hsu et al 2016	USA 40 subjects (20 test, 20 control)	This study investigated an online diabetes programme (including virtual consultations) in patients new to insulin compared to standard clinic visits.	The intervention group achieved a lower HbA1C and required less input from clinicians ($p<0.05$) however required additional training to use the online system.
Ringbaek et al 2015	Denmark 281 subjects (141 test, 140 control)	This study investigated additional video consultations in severe COPD, compared to usual care	No differences were observed in mortality or hospital admissions between the groups ($p>0.05$). The intervention arm experienced less severe exacerbations ($p<0.001$) and fewer outpatient attendances ($p<0.001$)
Scalvinia et al 2015	Italy 200 subjects (100 test, 100 control)	This study compared post-surgery cardiac rehabilitation in-hospital compared to a home-based programme which included daily video conferencing.	Outcomes and fitness in the two groups were found to be comparable.
Boman et al 2014	Sweden 38 subjects (19 test, 19 control)	This study investigated remote cardiology consultations alongside robot-assisted echocardiography.	The time from referral to specialist consultation was reduced ($p < 0.001$) and patient satisfaction was high.
Zenaro et al 2014	Italy 84 subjects (42 test, 42 control)	This study compared verbal consultation vs telemedicine-assisted consultation for paediatric fractures.	The telemedicine group received an orthopaedic management plan more quickly, and required fewer hospital appointments than the control group ($p<0.001$).
Bull et al 2014	USA 26 subjects (13 test, 13 control)	This study investigated virtual consultations and video motor assessments in Huntington's disease.	Motor assessments were reliable in both groups and patients were interested in this technology.

Westra et al 2015	Netherlands 31 subjects (16 test, 15 control)	This study compared video vs face-t-face consultations after plastic surgery.	Patients were less satisfied with online consultations but were able to be seen quickly remotely than in person.
Rasmussen et al 2015	Denmark 374 subjects (193 test, 181 control)	This study investigated face-to-face vs video consultations in the management of foot ulcers.	Wound healing (p=0.42) and need for amputation (p=0.59) were similar on both groups; the telemedicine group encountered higher mortality (p< 0.005).
Corner et al 2014	USA 5 subjects (no control)	This study analysed the effects of a new video-conferencing programme for children with obsessive compulsive disorder.	All subjects completed their treatment, experience symptom improvement and parents were satisfied with the programme. There was no control group.
Choi et al 2014	USA 121 subjects (43 tele, 42 in person, 36 telephone support)	This study compared standard face-to-face consultations in depressed adults to a new telemedicine-based therapy programme or telephone therapy.	Depression and anxiety scoring in the telemedicine group was lower than for those who underwent telephone therapy; this was maintained over 6 months follow -up.
Khatri et al 2014	Canada 18 subjects (8 test, 10 control)	This study investigated group-based cognitive behavioural therapy either in-person or via video link.	Qualitative analysis of both groups identified similar concerns. Outcomes were comparable in both groups (p<0.05)
Viers et al 2015	USA 55 subjects (28 test, 27 control)	This study investigated face-to-face vs video consultations for patients post-prostate surgery.	No significant differences were found between groups in terms of satisfaction, waiting time and patient-clinician face time. The telemedicine group have lower travel distances and costs than the control group.

Yuen et al 2015	USA 52 subjects (26 test, 26 control)	This study compared in person or tele-health programmes in the treatment of PTSD.	Both groups improved similarly, with no difference in patient satisfaction scores.
Greenwood et al 2015	USA 90 subjects (45 test, 45 control)	This study compared a telehealth intervention in type 2 diabetes with usual care.	The telehealth cohort have more improvement in their HbA1C than the control group (p=0.005).
Fortney et al 2015	USA 265 subjects (133 test, 132 control)	This study investigated remote consultations vs usual care in PTSD.	The telemedicine cohort experienced higher improvement in disease-specific scoring than the control arm; this was sustained at 12 months (p<0.05).
Richter et al 2015	USA 566 subjects (286 test, 280 control)	This study compared telephone vs video counselling in smoking cessation.	At 12 months, abstinence rates were similar between groups (p=0.406). Telemedicine was however, costlier than telephone counselling.
Sathiyakumar et al 2015	USA 24 subjects (11 test, 12 control)	This study investigated video clinics vs face-to-face consultations in orthopaedics.	Patient satisfaction was similar between groups (p=0.74) however telehealth consultations were quicker (p=0.01).
Rosenbeck et al 2015	Denmark 37 subjects (no control)	This study investigated a new video conferencing intervention in post-COPD hospital discharges. There was no control group.	Improvements were seen in disease-specific assessment scores and no adverse events were recorded; the programme was potentially profitable.
Isseta et al 2015	Spain139 subjects (69 test, 70 control)	This study compared in-person vs telemedical consultation in the follow up of patients with obstructive sleep apnoea on CPAP.	Outcomes were similar in both groups. The telemedicine intervention was more cost-effective however required more patient consultations.

Stage 2: ***Relaxing the Cochrane criteria with a liver disease focus***

Table 2: Summary of included article characteristics

Author	Population	Method & Intervention	Findings
Kaur K, et al 2015 (abstract)	UK 10 subjects	This study was a questionnaire exploring opinions of future Skype follow-up after liver cancer surgery.	60% expressed an interest in the Skype clinic however only 40% had the required access. Cost analysis suggested Skype consultations were reliable and could run at 1.6% of in=person clinic costs.
Rossaro L, et al 2008	Australia 103 subjects	This study was a retrospective analysis of an established telemedicine service for HCV in rural communities.	This service was found to be effective; there was no control group.
Shukla S, et al 2014 (abstract)	USA 49 subjects (25 liver)	This study was a questionnaire on satisfaction of a new tele-gastroenterology video clinic; there was no control group.	Difficulties travelling to specialist centres was cited by 65% of patients. 98% of patients were happy that the quality of care they received via video was the same as face-to-face and 92% found this new clinic more convenient.
Talal A, et al 2016 (abstract)	USA 22 patients	This study was a telephone questionnaire of satisfaction of an established video conferencing clinic in the treatment of HCV patients; there was no control group.	82% found the remote consultation more convenient and over 95% were as satisfied compared to previous in-person clinics.

Scoping Review Reference Database

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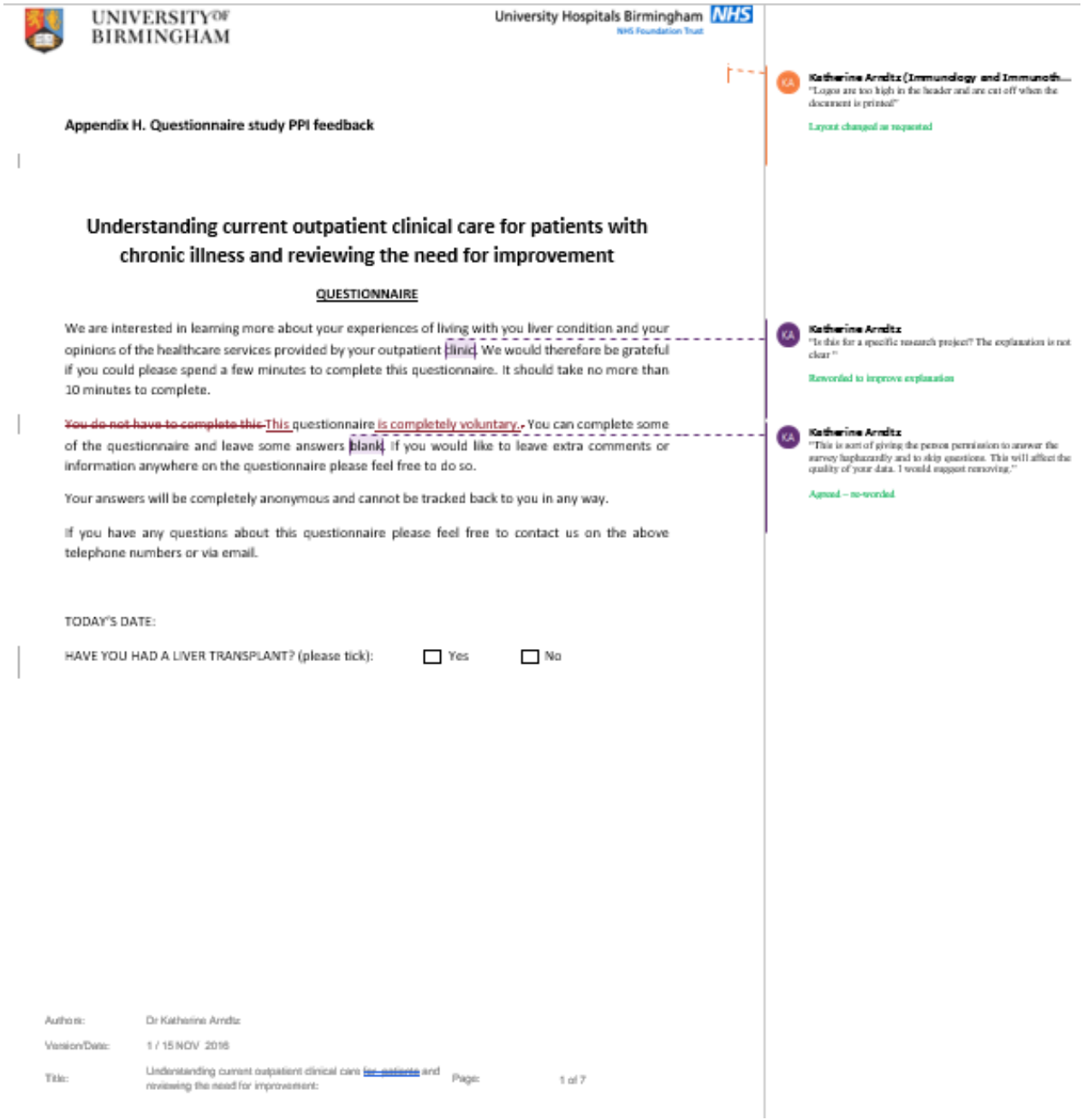
19 Appendix H. Questionnaire study PPI feedback



UNIVERSITY OF BIRMINGHAM

University Hospitals Birmingham NHS
NHS Foundation Trust

Appendix H. Questionnaire study PPI feedback

Understanding current outpatient clinical care for patients with chronic illness and reviewing the need for improvement

QUESTIONNAIRE

We are interested in learning more about your experiences of living with you liver condition and your opinions of the healthcare services provided by your outpatient clinic. We would therefore be grateful if you could please spend a few minutes to complete this questionnaire. It should take no more than 10 minutes to complete.

~~You do not have to complete this~~ This questionnaire is completely voluntary. You can complete some of the questionnaire and leave some answers blank. If you would like to leave extra comments or information anywhere on the questionnaire please feel free to do so.

Your answers will be completely anonymous and cannot be tracked back to you in any way.

If you have any questions about this questionnaire please feel free to contact us on the above telephone numbers or via email.

TODAY'S DATE:

HAVE YOU HAD A LIVER TRANSPLANT? (please tick): ☐ Yes ☐ No

Author: Dr Katherine Arndtz
Version/Date: 1 / 15 NOV 2016
Title: Understanding current outpatient clinical care for patients and reviewing the need for improvement
Page: 1 of 7

KA **Katherine Arndtz (Immunology and Immunoth...**
"Logos are too high in the header and are cut off when the document is printed"
Layout changed as requested

KA **Katherine Arndtz**
"Is this for a specific research project? The explanation is not clear."
Reworded to improve explanation

KA **Katherine Arndtz**
"This is sort of giving the person permission to answer the survey haphazardly and to skip questions. This will affect the quality of your data. I would suggest removing."
Agreed – re-worded

Q1) How old are you? (please tick)

Under 18 ☐ 18-20 17-20 ☐ 251-340 21-30 ☐ 351-440 31-40 ☐ 451-540 41-50 ☐
551-640 51-60 ☐ 651-740 61-70 ☐ 75+ 71-80 ☐ 81+ ☐

Katherine Arndtz
"17-20 overlaps with <18"

Age ranges now changed in final version to line up with standard hospital policy for questionnaires

Q2) What is your gender? (please tick)

Male ☐ Female ☐ Transgender ☐ Prefer not to say ☐

Prefer to self describe Other ☐ ..... please specify.....

Katherine Arndtz
"This can be a touchy subject, therefore advise not using the word 'other', suggest 'prefer to self describe' or something similar. Also some people may not want to answer this question"

Changed

Q3) What is your employment status? (please tick)

☐ Full time employment Student ☐ Unemployed
☐ Part time employment
☐ Self-employed (Full time)
☐ Self-employed (Part time)
☐ Work - full time ☐ Student
Work - part time
☐ Retired
☐ Full time carer
☐ Unemployed
☐ Other (please specify).....

Q4) If you are in employment, how have you organised to be here today? (please tick)

☐ Booked leave (paid)
☐ Booked leave (unpaid)
☐ Not booked leave, my hours are flexible
☐ I am unemployed
☐ Other (please specify).....

Katherine Arndtz
"Unnecessary as should only answer if in employment - also omits retired"

Wording improved in final version to make it clearer and retired added as an option

Q5) Where do you live?

Please state only the first part of your post-code (e.g. B15 or SE25)

.....

Q6) How did you get to the clinic today? (please tick)

☐ Walked ☐ Public transport ☐ By car
☐ Other (please specify).....

Katherine Arndtz
"Would probably also include taxi as one of the options."

Added taxi in as an option in final version

Q7) How long did it take you to get to the clinic today (from home or work)? (Please tick)

☐ Under 30 minutes ☐ 30-60 minutes ☐ 1-2 hours
☐ 2-3 hours ☐ 3+ hours
☐ I booked overnight accommodation

Q8). What costs have you had in relation to your appointment today (please tick all that apply)?

☐ Travel costs e.g. fuel, taxi, public transport (please circle) and please detail approximate cost:
£ _____
_____

☐ Parking, please detail approximate cost: _____

☐ Accommodation, please detail approximate cost: _____

☐ Other, please detail _____

Q9) Has anyone else come with you today? (please circle one)

☐ Yes ☐ No
If yes, please specify who (e.g. partner, parent, friend).....

Q10) How often do you use any of the following:

Smart phone
Never ☐ Only when I have help ☐ Every day ☐ Every week ☐ Fortnightly ☐
Monthly ☐ Every other month ☐ Every 6 months ☐ Once a year ☐

Computer
Never ☐ Only when I have help ☐ Every day ☐ Every week ☐ Fortnightly ☐
Monthly ☐ Every other month ☐ Every 6 months ☐ Once a year ☐

Laptop
Never ☐ Only when I have help ☐ Every day ☐ Every week ☐ Fortnightly ☐
Monthly ☐ Every other month ☐ Every 6 months ☐ Once a year ☐

Tablet
Never ☐ Only when I have help ☐ Every day ☐ Every week ☐ Fortnightly ☐
Monthly ☐ Every other month ☐ Every 6 months ☐ Once a year ☐

KA **Katherine Arndtz**
"...and include approximate cost"
Added into final version

KA **Katherine Arndtz**
"Why is this circled rather than ticked as the others are?"
Changed to tick in final version

KA **Katherine Arndtz**
"Suggest changing the layout of these questions. Quite squashed and difficult to read. Also too many options re frequency."
"To be consistent, should say "Please tick"
Change wording and improved layout

KA **Katherine Arndtz**
"Would specify desktop computer to distinguish from laptop (which of course is a computer itself...)"
changed

Q11) —Thinking about your consultation with your health care professional, how would you rate the following (please tick):

	Poor	Fair	Good	Very good	Excellent
1. How long you waited to get an appointment	○	○	○	○	○
2. Convenience of the location of the appointment	○	○	○	○	○
3. Getting through to the office by phone	○	○	○	○	○
4. Length of time waiting for the appointment	○	○	○	○	○
5. Time spent with the physician/health care professional you saw	○	○	○	○	○
6. Explanation of what was done for you	○	○	○	○	○
7. Technical skills (thoroughness, carefulness, competence) of the physician/health care professional you saw	○	○	○	○	○
8. The personal manner (courtesy, respect, sensitivity, friendliness) of the person you saw	○	○	○	○	○
9. The visit overall	○	○	○	○	○

Katherine Arndtz
"Would include a "Not applicable" column - eg people may not have tried to phone."
"Why has this changed from boxes to circles?"

This rating scale comes from a validated research tool and therefore unfortunately we cannot alter to add more columns. We have changed the wording to only tick if it applies to you which will hopefully help with this concern.

Is this primarily aimed at patients with PSC, if so do not need **Others please specify**. If not put other conditions down as well? To make it easier.

Katherine Arndtz
Other diagnoses added in final version

Q12) What is your liver diagnosis? (please tick)

☐ Primary Sclerosing Cholangitis (PSC)

☐ Other (please specify)……

Q13) When were you first diagnosed? (please tick)

☐ Under 1 year ago ☐ 1-5 years ago ☐ 6-10 years ago
☐ 11-20 years ago ☐ 20+ years ago

Q14) Where were you diagnosed? (please tick)

☐ Queen Elizabeth Hospital, Birmingham
☐ My local hospital (please specify).....)
☐ By my GP
☐ Other (please specify).....)

Q15) Why were you diagnosed? (please tick)

☐ Abnormal blood tests found by accident or when investigating another condition
☐ To investigate my liver symptoms

Q16) How long did it take for you to be diagnosed, from either the start of symptoms or the first abnormal blood test if you did not have any symptoms? (please tick)

☐ Under 6 months ☐ 6 months-1 year ☐ 1-2 years
☐ 2-3 years ☐ Over 3 years

Q17) How were you diagnosed? (please tick **ALL** that apply)

☐ Blood tests ☐ Liver biopsy ☐ Ultrasound
☐ MRI scan ☐ Endoscopic tests/ERCP ☐ I'm not sure
☐ Other (please specify).....

Q18) Do you have inflammatory bowel disease such as ulcerative colitis or ~~Chron~~Crohn's disease?~~?~~ (please tick)

☐ Yes ☐ No ☐ I am awaiting tests
☐ ~~I am n~~Not~~not~~ sure

Q19) What symptoms of ~~your~~your liver disease do you currently experience and how frequently? (please tick **ALL** that apply and circle the frequency)

☐ I have no symptoms

☐ Itching daily/at least once weekly/at least once monthly/less than monthly

☐ Tiredness/Fatigue daily/at least once weekly/at least once monthly/less than monthly

☐ Pain daily/at least once weekly/at least once monthly/less than monthly

☐ Fevers/chills daily/at least once weekly/at least once monthly/less than monthly

☐ Other (please specify) .....
daily/at least once weekly/at least once monthly/less than monthly

Q20) Is University Hospitals Birmingham your local hospital? (please tick)

☐ Yes ☐ No

If we are not your local hospital, please state where/when you were referred from, when and why:-

Name of Hospital: .....

Year referred to UHB: .....

What is the reason that you were referred? (Please tick **ALL** that apply)
☐ Diagnosis
☐ Specialist liver management
☐ Second opinion
☐ Transplant assessment
☐ Consideration for clinical trials
☐ I'm not sure
☐ Other (please specify).....

Q21) Approximately how often do you have an appointment for your liver condition at UHB? (please circle one)

☐ Around once a year ☐ Around every 6 months ☐ Around every 3 months
☐ Other (please specify).....

KA **Katherine Arndtz**
"Previously called "Queen Elizabeth". Should use consistent naming."

Agreed, changed

KA **Katherine Arndtz**
"Again inconsistent naming "

changed

Q22) Apart from seeing the doctor, do you usually have any other appointments/procedures the same day?

☐ No, I just see the doctor
☐ Yes, I have my blood tests taken
☐ Yes, I usually have an ultrasound scan
☐ Yes, I have something else done (please specify).....

Many thanks for taking -the time to fill in this questionnaire.

Please return it to the reception desk

KA **Katherine Arndtz**
"Which reception desk? Outpatients or main reception? You should be as clear as possible"

There will be boxes at both desks

20 **Appendix I. Final Questionnaire study proforma**

University Hospitals Birmingham NHS
NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

Dr Katherine Arndtz
Liver Unit
Queen Elizabeth Hospital Birmingham
B15 2TH
Email [redacted]
Tel: [redacted]

Understanding current outpatient clinical care for patients with chronic illness and reviewing the need for improvement

Questionnaire

We are interested in improving your experiences of your outpatient care in areas that matter most to you. To do this we need to learn more about your experiences of living with your liver condition and your opinions about our outpatient clinic. We would therefore be grateful if you could please spend a few minutes to complete this questionnaire. It should take no more than 15 minutes to complete.

You do not have to complete this questionnaire; it is completely voluntary. Your answers are completely anonymous and cannot be tracked back to you in any way. If you have completed this questionnaire before, you do not need to complete it again.

If you have any questions about this questionnaire please feel free to contact us on the above telephone numbers or via email.

Today's date:

Have you had a liver transplant? (please tick): **Yes** ☐ **No** ☐

Part 1: About you and you experience in clinic today

Q1) What is your age group? (please tick)

0-15 years ☐	16-17 years ☐	18-24 years ☐
25-49 years ☐	50-64 years ☐	64-74 years ☐
75-84 years ☐	85 years or over ☐	

Q2) What is your gender? (please tick)

Male ☐ Female ☐ Transgender ☐

Q3) To which of these ethnic groups would you say you belong to? (please tick)

White/British ☐	White/European ☐	Caribbean ☐
African ☐	Chinese ☐	Indian/Pakistani ☐
Bangladeshi ☐	Mixed ☐	

Q4) What is your employment status? (please tick)

☐ Student ☐ Unemployed

☐ Self-employed (Full time) ☐ Self-employed (Part time)

☐ Work - full time ☐ Work - part time

☐ Retired

☐ Full time carer

☐ Other (please specify)……

Q5) If you are in employment, how have you organised to be here today? (please tick or leave blank if you are unemployed)

☐ Booked leave (paid)

☐ Booked leave (unpaid)

☐ Not booked leave, my hours are flexible

☐ Other (please specify)……

Q6) Where do you live? Please state only the first part of your post-code (e.g. B15 or SE25) _____ _____ _____ _____

Q7) Thinking about your consultation with your health care professional today, how would you rate the following (please tick all that apply to you):

	Poor	Fair	Good	Very good	Excellent
1. How long you waited to get an appointment booked	◯	◯	◯	◯	◯
2. Convenience of the location of the appointment	◯	◯	◯	◯	◯
3. Getting through to the office by phone	◯	◯	◯	◯	◯
4. Length of time waiting for the appointment to start	◯	◯	◯	◯	◯
5. Time spent with the physician/health care professional you saw	◯	◯	◯	◯	◯
6. Explanation of what was done for you	◯	◯	◯	◯	◯
7. Technical skills (thoroughness, carefulness, competence) of the physician/health care professional you saw	◯	◯	◯	◯	◯
8. The personal manner of the person you saw (e.g. courtesy, respect, sensitivity, friendliness)	◯	◯	◯	◯	◯
9. The visit overall	◯	◯	◯	◯	◯

Part 2: About your liver condition

Q8) What is your liver diagnosis?

☐ Primary Sclerosing Cholangitis (PSC) ☐ Primary biliary cholangitis

☐ Alcohol related liver disease ☐ Auto-immune hepatitis

☐ Other (please specify……..)

Q9) When were you first diagnosed? (please tick)

☐ Under 1 year ago ☐ 1-5 years ago ☐ 6-10 years ago

☐ 11-20 years ago ☐ 20+ years ago

Q10) Where were you diagnosed? (please tick)

☐ Queen Elizabeth Hospital, Birmingham

☐ My local hospital (please specify……)

☐ By my GP

☐ Other (please specify…….)

Q11) How long did it take for you to be diagnosed, from either the start of symptoms or the first abnormal blood test if you did not have any symptoms? (please tick)

☐ Under 6 months ☐ 6 months-1 year ☐ 1-2 years

☐ 2-3 years ☐ Over 3 years

Q12) Have you ever been admitted to the Queen Elizabeth Hospital due to your liver condition?

☐ Yes ☐ No

If yes, how many times?.....

Q13) Have you ever undergone assessment for liver transplantation?

☐ Yes ☐ No

Q14) What symptoms of your liver disease do you currently experience and how frequently? (please tick)

	Daily	Weekly	Monthly	Less than once per month	Never
1. Extreme tiredness/fatigue	◯	◯	◯	◯	◯
2. Itching	◯	◯	◯	◯	◯
3. Poor memory or concentration	◯	◯	◯	◯	◯
4. Pain	◯	◯	◯	◯	◯
5. Fever/chills	◯	◯	◯	◯	◯
6. Other (please describe) …… ……	◯	◯	◯	◯	◯

Part 3: About your Outpatient appointment

Q15) Is the Queen Elizabeth Hospital Birmingham (QE) your local hospital? (please tick)

☐ Yes ☐ No

If we are not your local hospital, please state where/when you were referred from, and why:-

Name of Hospital:……

What is the reason that you were referred? (Please tick **ALL** that apply)

☐ Diagnosis
☐ Specialist liver management
☐ Second opinion
☐ Transplant assessment
☐ Consideration for clinical trials
☐ I'm not sure
☐ Other (please specify)……..

Q16) Approximately how often do you have an appointment for your liver condition at the Queen Elizabeth Hospital? (please tick one)

☐ Around once a year ☐ Around 6 months ☐ Around 3 months

☐ This is my first appointment ☐ Other (please specify)……..

Q17) How did you get to the clinic today? (please tick)

☐ Walked ☐ Public transport

☐ By car ☐ By Taxi

☐ Other (please specify)……

Q18) How long did it take you to get to the clinic today (from home or work)? (Please tick)

☐ Under 30 minutes ☐ 30-60 minutes ☐ 1-2 hours

☐ 2-3 hours ☐ 3+ hours

☐ I booked overnight accommodation

Q19) Has anyone else come with you to your appointment today? (please tick one)

☐ Yes ☐ No

If yes, please specify who (e.g. partner, parent, friend)…….

Q20). What costs have you had in relation to your appointment today (please tick **all** that apply for you **AND** for anyone who attended with you)?

☐ Travel costs e.g. fuel, taxi, public transport (please circle) and please detail approximate cost: £_____

☐ Parking, please detail approximate cost: £ _____

☐ Accommodation, please detail approximate cost: £_____

☐ Other, please detail approximate cost……£ _____

Q21) Overall, what are your feelings about attending your liver outpatient clinic?

a) Please tell us about the positives:-

……
……
……
……
……
……
……
……

b) Please tell us about the negatives:-

……
……
……
……
……
……
……
……
……

Q7) Some possible future improvements to your outpatient clinic experience may involve the use of technology. Please tell us how often you use any of the following (please tick the most relevant box for all options) :-

	Never	Only when I have help	Every day	Every week	Every 2 weeks	Monthly	Every other month	Every 6 months	Once a year
Smart phone	○	○	○	○	○	○	○	○	○
Desktop Computer	○	○	○	○	○	○	○	○	○
Laptop	○	○	○	○	○	○	○	○	○
Tablet	○	○	○	○	○	○	○	○	○

Part 4) Future possible changes to your hospital appointments

Medicine is changing and some hospitals are introducing different ways of seeing patients instead of in the traditional outpatient's clinic. Please read the description below of one possible future change and answer the following questions: -

A "Virtual Clinic" is when an appointment takes place between a health professional and a patient who are in two different places, by using the internet. The people involved in the appointment can see and speak to one another and ask any questions as normal, however the patient does not need to travel to the hospital.

Q23) If this type of appointment should be introduced at the Queen Elizabeth and if it were to be offered to you, would you be interested in some or all of your appointments being changed to the virtual clinic, instead of face-to-face at the hospital? (please tick)

☐ Yes for **all** of my appointments
☐ Yes for **some** of my appointments
☐ No
☐ Unsure

Please explain your answer, giving reasons why you would/would not like to change your appointment type

……
……
……
……
……
……
……
……

Many thanks for taking the time to fill in this questionnaire.

Please return it to the reception desk where there is a box provided

21 Appendix J. Demographics of questionnaire study free-text responders

Number	Age (years)	Gender	Ethnicity	Diagnosis	Frequency of Symptoms	Is QEHB the local hospital	Travel duration to QEHB	Frequency of Technology use	Would they accept a virtual clinic?
1	50-64	Female	White	PSC	daily	No	2-3 hours	daily	yes
2	25-49	Male	White	PSC	less than monthly	No	3+ hours	daily	yes
3	25-49	Male	White	PSC	monthly	No	1-2 hours	daily	no/unsure
4	50-64	Female	White	NON-PSC	weekly	Yes	<30 min	never	no/unsure
5	25-49	Male	White	PSC	less than monthly	No	30-60min	daily	yes
6	25-49	Female	Mixed	PSC	daily	No	1-2 hours	daily	yes
8	50-64	Male	White	PSC	monthly	No	30-60 min	daily	yes
9	25-49	Male	White	PSC	less than monthly	No	2-3 hours	daily	yes
10	50-64	Male	White	PSC	daily	No	1-2 hours	daily	no/unsure
11	25-49	Male	White	PSC	never	No	30-60min	daily	yes
12	18-24	Female	White	PSC	daily	No	1-2 hours	daily	yes
13	64-74	Male	White	PSC	less than monthly	No	1-2 hours	daily	yes
14	25-49	Female	British/Asian	PSC	daily	No	30-60 min	daily	yes
15	25-49	Male	White	PSC	never	No	2-3 hours	daily	yes
16	25-49	Male	White	NON-PSC	daily	No	2-3 hours	daily	yes
17	25-49	Male	White	PSC	daily	No	2-3 hours	daily	yes
18	18-24	Female	White	PSC	weekly	No	1-2 hours	daily	yes
19	64-74	Male	White	PSC	weekly	No	2-3 hours	never	no/unsure
20	64-74	Male	White	NON-PSC	never	No	1-2 hours	never	no/unsure
21	25-49	Male	White	PSC	weekly	No	1-2 hours	daily	yes
22	50-64	Female	White	PSC	weekly	No	30-60min	weekly	no/unsure
23	64-74	Male	White	PSC	weekly	No	3+ hours	daily	no/unsure

24	25-49	Male	White	PSC	daily	Yes	<30 MINS	daily	yes
25	50-64	Male	British/Asian	PSC	never	No	30-60min	daily	yes
26	25-49	Male	White	PSC	monthly	Yes	<30 min	x	no/unsure
27	64-74	Male	White	PSC	daily	No	30-60 min	daily	yes
28	50-64	Male	White	PSC	daily	No	1-2 hours	daily	yes
29	64-74	Female	White	PSC	daily	No	x	daily	yes
30	18-24	Male	White	PSC	daily	Yes	<30 min	daily	yes
31	75-84	Male	White	PSC	daily	No	30-60	daily	no/unsure
33	25-49	Male	White	PSC	monthly	Yes	<30 min	daily	yes
34	50-64	Female	British/Asian	PSC	less than monthly	Yes	<30 min	never	yes
35	25-49	Male	White	PSC	less than monthly	No	1-2 hours	daily	no/unsure
36	25-49	Female	White	PSC	daily	Yes	30-60min	daily	no/unsure
37	64-74	Female	White	PSC	less than monthly	No	30-60min	daily	yes
38	25-49	Female	White	NON-PSC	less than monthly	No	2-3 hours	daily	yes
40	25-49	Male	British/Asian	NON-PSC	daily	Yes	30-60 min	daily	yes
41	75-84	Female	White	NON-PSC	monthly	No	1-2 hours	daily	no/unsure
43	25-49	Male	White	NON-PSC	monthly	No	2-3 hours	daily	yes
45	25-49	Female	British/Asian	PSC	daily	1	30-60 min	daily	yes
46	18-24	Male	White	PSC	never	No	2-3 hours	daily	yes
47	16-17	Male	White	PSC	less than monthly	No	30-60 min	daily	yes
48	25-49	Female	White	NON-PSC	daily	No	>3 hours	daily	yes
49	25-49	Female	White	NON-PSC	daily	No	1-2 hours	daily	unsure
50	25-49	Male	White	NON-PSC	daily	No	3+	daily	yes
51	25-49	Female	White	NON-PSC	daily	No	3+ hours	daily	Unsure
52	50-64	Female	Black/Caribbean	PSC	daily	Yes	<30 min	daily	no/unsure
53	25-49	Male	White	PSC	weekly	No	3+ hours	daily	yes
54	25-49	Male	White	PSC	monthly	No	30-60 min	daily	yes
55	75-84	Female	White	NON-PSC	daily	Yes	30-60 min	2 weekly	no/unsure

56	50-64	Female	White	PSC	never	No	1-2 hours	daily	no/unsure
58	25-49	Female	Mixed	NON-PSC	less than monthly	No	<30 min	daily	yes
59	75-84	Female	White	NON-PSC	less than monthly	Yes	<30 min	never	yes
60	50-64	Male	White	PSC	weekly	No	<30 min	daily	yes
61	50-64	Male	White	NON-PSC	daily	No	1-2 hours	daily	yes
62	25-49	Female	White	NON-PSC	never	Yes	<30 min	daily	no
63	50-64	Female	White	PSC	daily	No	30-60 min	daily	yes
64	18-24	Male	Black/Afro-Caribbean	PSC	weekly	Yes	30-60 min	daily	yes
65	50-64	Female	Black/Afro-Caribbean	PSC	never	No	30-60 min	daily	no/unsure
67	18-24	Male	White	PSC	daily	No	30-60 min	daily	yes
68	25-49	Male	White	PSC	daily	No	3+ hours	daily	yes
69	50-64	Female	White	NON-PSC	less than monthly	Yes	<30 min	daily	no/unsure
70	18-24	Male	White	PSC	monthly	No	30-60 min	daily	yes
74	18-24	Male	White	PSC	daily	No	2-3 hours	daily	yes
75	25-49	Female	White	PSC	weekly	No	30-60 min	daily	yes
76	18-24	Female	White	PSC	daily	No	30-60 min	daily	yes
78	64-74	Male	White	PSC	never	No	30-60 min	daily	yes
79	25-49	Male	White	PSC	weekly	No	2-3 hours	daily	yes
80	50-64	Female	White	NON-PSC	daily	No	1-2 hours	daily	yes
81	18-24	Female	White	NON-PSC	daily	No	3+ hours	daily	no/unsure
82	25-49	Male	White	PSC	daily	No	1-2 hours	daily	yes
83	25-49	Male	White	PSC	daily	No	1-2 hours	daily	yes
84	50-64	Female	White	PSC	daily	No	1-2 hours	daily	yes
85	18-24	Female	White	PSC	daily	No	1-2 hours	daily	no/unsure
86	75-84	Male	White	PSC	daily	No	30-60 min	never	no/unsure
87	25-49	Female	British/Asian	PSC	daily	Yes	<30 min	daily	yes
88	25-49	Male	Mixed	PSC	less than monthly	No	1-2 hours	daily	yes

89	18-24	Male	White	PSC	daily	No	30-60 min	daily	yes
90	18-24	Female	White	PSC	daily	No	30-60 min	daily	no/unsure
91	18-24	Male	White	PSC	monthly	Yes	30-60 min	daily	yes
93	25-49	Female	White	PSC	less than monthly	No	2-3 hours	daily	yes
94	18-24	Female	British/Asian	NON-PSC	less than monthly	No	2-3 hours	daily	no/unsure
96	64-74	Male	White	PSC	monthly	No	3+ hours	never	no/unsure
98	25-49	Female	White	PSC	less than monthly	No	1-2 hours	daily	yes
99	18-24	Male	White	NON-PSC	never	No	3+ hours	daily	yes
100	64-74	Male	White	NON-PSC	never	No	30-60 min	daily	no/unsure
101	50-64	Male	White	PSC	daily	Yes	30-60 min	never	no/unsure
103	64-74	Male	White	PSC	less than monthly	No	1-2 hours	daily	no/unsure

22 Appendix K. MRI study protocol

The MRI study described within this thesis is described within this full protocol as the Longitudinal Assessment of MRI in PSC extension study (LAMP extension, found in 6.4 and Appendix 2 below)

LiverMultiscan™ – Replacing liver biopsy

Summary

Title:	LiverMultiscan™ – Replacing liver biopsy
Protocol version:	8.0
Date:	28 October 2016
REC: Reference:	West Midlands – Black Country Date favourable opinion granted: 9 January 2014 Ref: 14/WM/0010 (IRAS reference: 140543)
UKCRN Portfolio ID:	15912
ISRCTN reference:	ISRCTN39463479
Chief Investigator:	Professor Gideon Hirschfield MA MB BChir MRCP PhD Professor of Hepatology/Honorary Consultant Hepatologist Centre for Liver Research NIHR Biomedical Research Unit

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	2 MRC/University of Edinburgh Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh 3 Department of Cellular Pathology, University Hospitals Birmingham NHSFT 4 Department of Imaging & Medical Physics, University Hospitals Birmingham NHSFT 5 Centre for Cardiovascular Science, University of Edinburgh 6 School of Biosciences, University of Birmingham
Sponsor: Sponsor's reference:	The University of Birmingham RG_13-260
Funding body 1: Section of project funded Funder's reference: Funding body 2: Section of project funded Funder's reference:	Innovate-UK (formally known as Technology Strategy Board) CALM, MURAL, LAMP and volunteer parts of the study 101679 NIHR Rare Diseases Translational Research Collaboration Extension to the LAMP study N/A
NHS R&D Office: NHS R&D reference:	University Hospital Birmingham NHSFT R&D Department RRK4966

Signatures

This protocol has been approved by:

Chief Investigator: Dr Gideon Hirschfield Date:

Sponsor's Representative: Dr Sean Jennings Date:

NHS R&D Representative: Dr Chris Counsell Date:

Contents

Update history

Version 1.0	24 September 2013	
Version 1.1	28 October 2013	Minor changes following discussion with JF.
Version 2.0	30 October 2013	Changes to section 8 “analysis” following input from JH.
Version 2.1	25 November 2013	Minor changes to sections 7.3 and 7.5.6
Version 3.0	28 November 2013	Addition of volunteers to protocol. Updates to section 1. Addition of section 2. Other very minor changes to wording throughout.
Version 4.0	29 January 2014	Amendment to extent to include whole liver slice assessment
Version 5.0	15 April 2014	Amendment to include breath sampling from CALM study patients in Edinburgh
Version 6.0	19 June 2015	Amendment to include serum sampling from volunteers for metabolomic profiling
Version 7.0	25 August 2015	Amendment to extend the LAMP study
Version 8.0	28 October 2016	Minor changes to LAMP extension inclusion criteria, minor changes to PIS wording and addition of Dr Arndtz

Background

Chronic liver disease is a major contributor to ill health in western society and is the 5th biggest killer in England and Wales.(1) In the UK it is the only major cause of death that is currently increasing in incidence.(1) This increase is expected to continue over the next decade due to the increase in harmful alcohol consumption and the dual epidemic of obesity and type two diabetes leading to an explosion in the prevalence of non-alcoholic fatty liver disease (NAFLD).

Chronic liver disease encompasses many different aetiologies but the common end point of almost all liver diseases is fibrosis. Early stages of fibrosis are asymptomatic but progression leads to advanced fibrosis, which is known as cirrhosis. Cirrhosis involves grossly altered liver architecture, impairment of liver function and the risk of serious complications such as variceal haemorrhage and hepatocellular carcinoma (HCC).

The identification of severe fibrosis or cirrhosis gives prognostic information, targets the screening for complications and helps identify those who would benefit from liver transplantation. There is some evidence that the degree of fibrosis gives prognostic information even at earlier stages.(2, 3) The degree of fibrosis gives not only prognostic information but helps to plan treatment. Notable examples of this are determining the duration of treatment in hepatitis C and the timing of treatment in hepatitis B.

There is clearly a need to identify those with hepatic fibrosis and to do so at an early stage. At present the gold standard for the assessment of chronic liver disease is liver biopsy. This is invasive, unwelcomed by patients and carries a risk of significant complications. There is also considerable sampling error, with a standard liver biopsy looking at only 0.002% of the liver. This is particularly relevant with inhomogeneous diseases such as primary sclerosing cholangitis (PSC). There is a need to develop reliable, non-invasive methods of assessing patients with chronic liver disease.

Current non-invasive techniques for assessing liver fibrosis include blood markers, transient elastography (TE) and magnetic resonance imaging (MRI). Conventional blood tests (LFTs) have little if any correlation with different stages of fibrosis.(4) Combinations of tests into 'biomarker panels' have been shown to predict advanced fibrosis(5) but their sensitivity is inadequate to diagnose early stage fibrosis.(4) TE is an ultrasound based technique that correlates well with liver biopsy, particularly at higher levels of fibrosis.(6) The usefulness of TE is limited due to the fact that it is operator dependant and has significant inter- and intra-observer variability. Currently the cut-off values for liver stiffness require further validation.(6) It also cannot be used in those with ascites and its reliability is poor in the obese.(7, 8) MRI techniques such as magnetic resonance elastography (MRE) and magnetic resonance spectroscopy (MRS) have shown promise but are as yet unproven with trials to date being small and using populations that limit the generalisablility of results.(9, 10)

In recent years, exhaled breath analysis by commercially available e-Nose systems has been increasingly studied as an alternative non-invasive method to diagnose and classify many human diseases.(11, 12) An e-Nose is built of an array of chemical sensors that react to the different fractions of the volatile organic compounds which, when combined, give a 'breath print' specific for a disease. Elucidating the role of this technology in assessing liver disease is an exciting new avenue in clinical research.

Metabolomics is the study of metabolism and the chemicals (metabolites) involved in those processes. The profile of these metabolites is known as the metabolome and is unique to each individual. Defining

the metabolome in the serum has the potential to be used as a non-invasive technique for staging liver disease.

This project aims to assess a novel MRI technique called LiverMultiscan™ for the staging and long term monitoring of chronic liver disease. LiverMultiscan™ is a technique that combines MR imaging with MRS to quantify fibrosis, fat and iron in the liver. Pilot study data has shown that LiverMultiscan™ has excellent correlation with liver biopsy in the detection of fibrosis, fat and iron.(13) It is the first non-invasive test to differentiate early stages of fibrosis.

In summary, chronic liver disease is a major public health problem throughout the western world and, at present, the available tests to stage the disease are lacking in sensitivity. This study will assess LiverMultiscan™ with the aim of improving the diagnosis and staging of liver disease in a safe and non-invasive manner.

Objectives

Primary

To investigate the ability of LiverMultiscan™ to accurately diagnose hepatic fibrosis, siderosis and steatosis when compared to liver biopsy.

To investigate whether LiverMultiscan™ can characterise primary sclerosing cholangitis (PSC) or related autoimmune liver conditions and correlate with disease progression and/or regression.

To investigate the ability of LiverMultiscan™ to diagnose and stage heterogeneous liver damage.

Secondary

To assess the correlation of LiverMultiscan™ with other non-invasive markers of hepatic fibrosis such as transient elastography, blood biomarkers, serum metabolomics and metabolic profiling based on a sample of patient's breath

Study design

Overview

The main part of the study will be known as Comprehensive Assessment of the Liver with MRI (CALM). There will also be a subset of patients with PSC or related autoimmune conditions who will be in a sub group study known as Longitudinal Assessment with MRI in PSC (LAMP). There will also be a second subset of patients who are on the liver transplant waiting list. These patients will be in a sub group study known as MUlti-Regional Assessment of the Liver (MURAL). These studies are outlined below.

We will also invite healthy volunteers to have one or more of the following investigations: LiverMultiscan™, Fibroscan, blood tests, blood test for metabolomics profiling or to provide breath samples. Volunteers will not be required to undergo a liver biopsy. Volunteers will be recruited from staff and colleagues within the investigators' institutions. We will exclude those with a known liver condition and/or contraindication to MRI. Also excluded will be people with type two diabetes or other features of the metabolic syndrome and those with regular alcohol consumption in excess of 21 units/week for men and 14 units/week for women.

Volunteer scans will be used to develop the use of LiverMultiscan™ at the sites involved in the study. This will ensure that the MRI protocol is functioning correctly on the MRI systems used. This data will also be used to ensure data generated on the two different MRI systems used in CALM are comparable to each other and to data generated in previous studies.

Comprehensive Assessment of the Liver with MRI (CALM)

Participants: 150 (approximately 75 Birmingham, 75 Edinburgh) adult patients referred, as part of their routine care, for percutaneous liver biopsy to investigate known or suspected liver disease at either Queen Elizabeth Hospital Birmingham or the Royal Infirmary of Edinburgh

This study will investigate the ability of LiverMultiscan™ to predict liver biopsy histology. All patients who are booked for a liver biopsy to assess suspected or known liver disease as part of their routine care will be invited to take part. This includes both inpatients and outpatients. It also includes patients who have had a liver transplant.

Participants will have an MRI scan with LiverMultiscan™, blood tests and a Fibroscan prior to their liver biopsy. They may also be asked to submit breath samples. The MRI, blood tests and Fibroscan will be done in the two weeks before the biopsy. The MRI results will be compared to the histology, Fibroscan, blood tests and metabolic profile of patient breath samples.

Longitudinal Assessment with MRI in PSC (LAMP) (PSC sub set)

Participants: 30 adult patients with PSC or related autoimmune liver diseases

The monitoring of disease progression or regression in patients with PSC or related autoimmune liver diseases is difficult due to a paucity of reliable tests. This sub-section of the study will investigate if LiverMultiscan™ combined with an MRCP can be used to monitor PSC or related autoimmune liver diseases. Participants will be invited to attend for two MRI scans with LiverMultiscan™ and MRCP 18 months apart. Patients will also have a Fibroscan and blood tests at each visit. Throughout the study, participants will continue with their routine standard of care.

Extension to the LAMP study (Longitudinal Assessment with MRI in auto-Immune Liver disease - LAMILD)

Participants: 180 adult patients with autoimmune liver disease (AIH, PSC, PBC)

Autoimmune liver disease comprises three distinct clinical entities (autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis). Current techniques to characterise these three conditions are relatively crude and lack the ability to accurately predict risk of future adverse events. The LAMP study has highlighted the potential for LiverMultiscan to characterise autoimmune liver disease. This extension to the LAMP study aims to assess the ability of LiverMultiscan to phenotype autoimmune liver disease, characterise difference between the three diseases and assess disease severity.

This study extension will take highly characterised patients from the specialist autoimmune liver disease clinics at the Queen Elizabeth Hospital. Patients within these clinics will be invited to take part in the extension of the LAMP study.

Study investigations will be the same as for those in the initial LAMP study. Additional details regarding the LAMP extension are contained in appendix 2.

MUlti-Regional Assessment of the Liver (MURAL)

Participants: 20 adult patients active on the transplant waiting list at Queen Elizabeth Hospital Birmingham excluding those with polycystic liver disease.

This study will investigate the ability of LiverMultiscan^{TM} to predict liver biopsy histology in multiple regions of the liver. All patients who are active on the transplant list will be invited to take part.

Participants will have an MRI scan with LiverMultiscan^{TM}, blood tests and a fibroscan prior to their liver transplant. The MRI results will be compared to the histology, fibroscan and blood tests.

Exclusions

Unable or unwilling to give fully informed consent

Any contraindication to MRI. This includes but is not limited to 1st or 2nd trimester of pregnancy, cardiac pacemaker and severe claustrophobia

Liver biopsy targeted at a distinct liver lesion

Patient interventions

Non-clinical

Written and fully informed consent will be taken by an investigator fully trained in taking consent including good clinical practice (GCP) training. An MRI safety questionnaire will be undertaken to ensure that MRI is safe for the participants and there are no contraindications.

Demographics and anthropometrics

Age, sex, race, medical history, height (metres), weight (Kilograms), calculation of body mass index (BMI) (weight / height^2), hip circumference(at the maximum circumference over the buttocks (cm), waist circumference at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (cm), calculation of waist:hip ratio (waist circumference / hip circumference).

Blood tests

The majority of the blood tests required for this study are part of participants' routine care. Those attending for biopsy require blood tests before their biopsy to check on blood clotting. Additional blood will be taken at the same time as these clinically necessary tests. This will reduce the number

of needles and therefore the impact of the study on participants. LAMP participants and healthy volunteers will require blood tests when they attend for their MRI scan. These will be taken by an appropriately trained member of the study team.

The required tests are the same for CALM, LAMP, LAMP extension, MURAL and volunteers. These are listed below.

Haemoglobin (Hb), Platelet count, Prothrombin time (PT), Activated partial thromboplastin time (APTT), Sodium, Urea, Creatinine, Bilirubin, Alkaline phosphatase (ALP), Gamma glutamyl transferrase (gGT), aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Albumin, Immunoglobulins (Igs), Ferrritin, Transferrin Saturations, Lipid profile, Enhanced liver fibrosis (ELF) test, Plasma and serum for storage.

Blood biomarkers of fibrosis such as AST:platelet ratio index (APRI) and AST:ALT ratio will be calculated from these results.

In addition some volunteers will be asked to give blood for metabolomics profiling. Patients are required to fast for 6 hours prior to blood tests.

Fibroscan

A Fibroscan is generally performed as part of all patients' routine care prior to a liver biopsy. If there is no Fibroscan result from the two weeks prior to the participant's biopsy a Fibroscan will be performed by an appropriately trained member of the research team. The test is safe and painless. It is taken with the patient lying supine with their right hand behind their head. The participant will be required to fast for at least 3 hours prior to their Fibroscan. The following measurements will be taken:

Transient elastography (TE) using the M probe if skin capsule distance (SCD) < 2.5cm.

TE using the XL probe if SCD is >2.5cm and ≤3.5cm

Fibroscan not possible if SCD >3.5cm

Continuous attenuated parameter (CAP) will be measured and recorded if available.

The number of attempts, the success rate and the IQR:mean ratio will be recorded to determine the quality of the Fibroscan examination.

MRI

Participants will undergo a non-contrast MRI scan of the liver lasting approximately 25 minutes. This will include a T1 map, T2* map and proton spectroscopy (MRS). For those in the LAMP sub-set an MRCP will also be performed. This will add approximately 20 minutes making the total scanning time approximately 45 minutes.

The values for T1, T2* and MRS will be extracted from the MRI images using tools available on the MRI workstation. A correction factor for the T1 value will be applied based on the T2* value using a patented algorithm developed by Perspectum Diagnostics. The MURAL subset will have T1, T2* and MRS values measured from multiple regions in the liver.

The MRCP taken in the LAMP sub set will be reported by expert radiologists and will undergo image analysis.

During the MRI the participant will be lying on their back in a comfortable position. There is a choice of music for the participant to listen to during the scan.

Patients are required to fast for 6 hours prior to blood tests.

Liver biopsy

The liver biopsy included in this study is part of the patient's routine care and so consent for the procedure itself will be taken outside of this study. No biopsy is required for the LAMP or MURAL study groups or for volunteers.

The liver biopsy and the explanted liver will be processed in the local hospital histology laboratory in the routine manner and assessed by expert pathologists. Semi-quantitative assessments of siderosis, steatosis and fibrosis will be made using the following techniques:

Fat content method by Brunt et al 1999 (14)

Iron content method by Scheuer et al 1962 (15)

Stage of fibrosis method by Ishak et al 1995 (16)

Further detail of these methods is contained in appendix 1.

Alongside expert histological assessment high quality digital photographs will be taken of stained slides and image analysis software used to determine the collage proportionate area. (17, 18)

The size of the biopsy (length and width) and the number of portal tracts in each biopsy will be documented to determine the quality of the biopsy sample.

Breath sampling

CALM study participants in Edinburgh may be asked to submit up to three breath samples by breathing into a clear plastic mask, attached to the E-nose device. We would also like to collect samples of their breath for storage and further analysis by mass spectrometry. Their metabolic profile will be analysed and compared to liver biopsy results.

Analysis

The data from LiverMultiscan^{TM}, blood tests, Fibroscan, metabolic profile and breath sampling will be compared to the gold standard of liver histology. The performance of LiverMultiscan^{TM} will also be compared to the other non-invasive methods. The histology data will be assessed for agreement using weighted kappa statistics.

Power Calculation

Based on data from a previous study, the distribution of patients across the 4 groups (ISHAK 0, 1-2, 3-4 and 5-6) was 9%: 52%: 17%: 22%. The pooled value for the difference between sequential groups in this data was found to be approximately 90. Due to the large differences in the standard deviations across the groups, the data was powered on the "worst case" pairwise comparison, based on the combination of the observed standard deviation and the proportional sample size. This was between ISHAK 3,4 (SD=57, 17% of patients) and ISHAK 5,6 (SD=90, 22% of patients).

For a comparison between these groups using an alpha level of 0.8% (i.e. 5% after adjustment for 6 comparisons), sample sizes of 12 and 22 for ISHAK stages 3,4 and 5,6 respectively would be sufficient to detect a difference of 90ms in T1 at 80% power. Assuming that that the distribution of cases is similar to the previous study, this means that a sample size is 100 patients (9, 52, 17 and 22 in the four groups) would be sufficient to detect a difference between groups of 90ms at 80% power and with 5% alpha. However, approximately ten percent of biopsies yield inadequate samples for analysis, and some patients may miss their appointment, so we envisage a total recruitment of 150 participants.

Data Analysis

Initially, the data will be analysed using ANOVA, to test whether T1 varies significantly by ISHAK stage. As a secondary analysis, this model will be broadened to include the type of disease, to test whether the relationship between T1 and ISHAK stage differs by diagnosis.

In order to define T1 cutoffs to differentiate between ISHAK stages, ROC curves will be produced comparing the T1 values for patients at one stage to those at subsequent stages. Based on the resulting values of sensitivity and specificity, the optimal cutoffs will be selected.

Safety

MRI and Fibroscan are safe, painless and do not involve ionising radiation. Those with contraindications to either MRI of Fibroscan will be carefully excluded. Blood tests can cause brief discomfort but form part of the routine care of patients undergoing liver biopsy. There are no anticipated serious adverse events with this study.

Study scans will be reported to check for unexpected clinically relevant findings. A clinically trained member of the research team will counsel the patient and, with their permission inform their clinical consultant to provide appropriate ongoing care.

Expenses

Patients will be able to claim expenses for their travel to and from the hospital on the day of their MRI scan.

Patient confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified by only a participants ID number on the Case Record Form (CRF) and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. Any electronic records will be encrypted. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. Any data transferred between study sites will be anonymised.

Ethics

This trial will be conducted in a manner consistent with the declaration of Helsinki and in accordance with GCP guidelines. Ethical approval has been sought from the research ethics committee through the IRAS system (reference: 140543). This study has also received institutional approval from the University of Birmingham, who will act as sponsor for the study. Favourable opinion granted 9 January 2014 ref: 14/WM/0010.

Amendment to include liver transplant waiters submitted 29 January 2014. This amendment asks for permission for transplant waiters to undergo MRI, Fibroscan and blood tests. The histological assessment of the explanted liver is covered by an existing ethics committee favourable opinion (reference: 98/CA/5192).

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APPENDIX 1: Histological Assessment

Steatosis

Brunt et al 1999 (14)

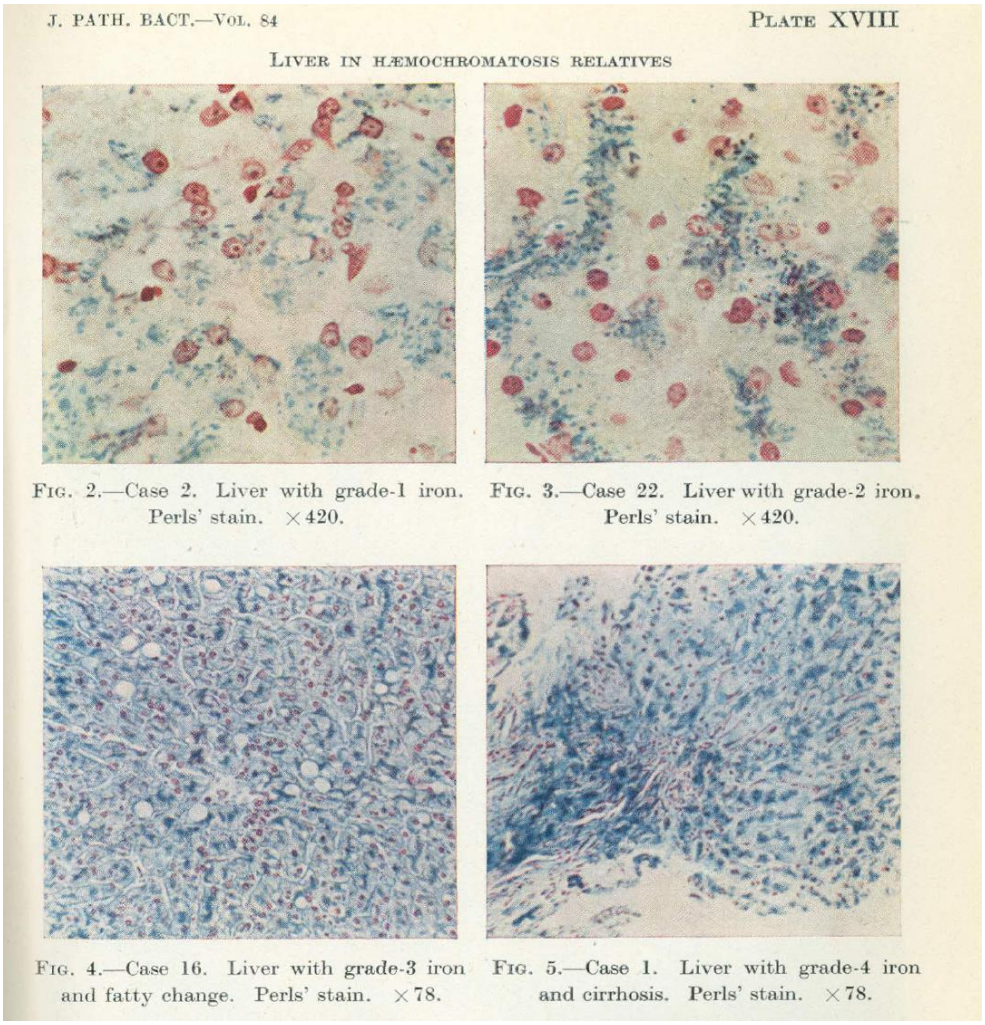
Graded 0–3 based on the percentage of hepatocytes in the biopsy containing a fat globule.

Grade	Definition
0	None
1	< 33%
2	33 – 66%
3	> 66%

Iron content

Scheuer et al 1962 (15)

Graded 0–4 based on the amount of iron visible


J. PATH. BACT.—VOL. 84 PLATE XVIII

LIVER IN HÆMOCHROMATOSIS RELATIVES

FIG. 2.—Case 2. Liver with grade-1 iron. Perls' stain. ×420.

FIG. 3.—Case 22. Liver with grade-2 iron. Perls' stain. ×420.

FIG. 4.—Case 16. Liver with grade-3 iron and fatty change. Perls' stain. ×78.

FIG. 5.—Case 1. Liver with grade-4 iron and cirrhosis. Perls' stain. ×78.

Fibrosis

Ishak et al 1995 (16)

Descriptive assessment of fibrosis.

Stage	Definition
0	No fibrosis
1	Fibrous expansion of some portal areas, with or without short fibrous septa
2	Fibrous expansion of most portal areas, with or without short fibrous septa
3	Fibrous expansion of most portal areas, with occasional portal to portal bridging
4	Fibrous expansion of portal areas with marked bridging
5	Marked bridging with occasional nodules (incomplete cirrhosis)
6	Cirrhosis, probable or definite

APPENDIX 2: LAMP extension

Cohort:

A total of 180 patients will be recruited from clinic cohorts, including 60 each with AIH, PBC, PSC.

Within each of the above three groups; 30 patients will be recruited with high risk features, and 30 patients with low risk features (see section 16.2).

Patients with the diagnosis of an overlap syndrome will be allocated to a group according to their predominant mechanism of injury.

These patients may or may not already be recruited to UK-AIH/PSC/PBC.

Inclusions:

18 years of age or over

Confirmed diagnosis of an auto-immune liver disease:

AIH (defined by UK-AIH criteria):

High risk – 30 patients recruited to UK-AIH Group 2b (representing incomplete response to treatment) or otherwise agreed to be high risk by the lead investigator.

Low risk – 30 patients recruited to UK-AIH Group 2a criteria (representing complete response to treatment and without progressive cirrhosis) or otherwise agreed to be low risk by the lead investigator.

PSC (>6 months of cholestasis AND a consistent MRI and/or biopsy):

High risk – 30 patients with ALP >2 x ULN at time of recruitment (BUTEO criteria).

Low risk – 30 patients with normal liver tests (excluding gGT) at time of recruitment (if we experience difficulties in recruitment we will then consider patients with ALP ≥1.5xULN) AND without established cirrhosis or portal hypertension on imaging/endoscopy.

PBC (defined by AASLD criteria):

High risk – 30 patients with non-response (or intolerance) to UDCA after 12 months of therapy and at time of recruitment (POISE criteria: ALP ≥ 1.67x ULN or bilirubin >ULN but less than X2ULN OR COBALT criteria: Bilirubin > ULN but ≤ 3x ULN AND/OR ALP > 5x ULN).

Low risk – 30 patients with normal liver tests (excluding gGT) 12 months after introduction of UDCA and at time of recruitment (if we experience difficulties in recruitment we will then consider patients with ALP <1.67xULN with normal bilirubin), AND without established cirrhosis or portal hypertension on imaging/endoscopy.

Patients on the liver transplant waiting list and those enrolled in other studies can be included.

Exclusions:-

Unable or unwilling to consent.

Contraindication to MRI.

Including but not limited to 1st or 2nd trimester of pregnancy, cardiac pacemaker or other implanted device and severe claustrophobia

Presence of external biliary drains/stents (risk of causing MRI artefact)

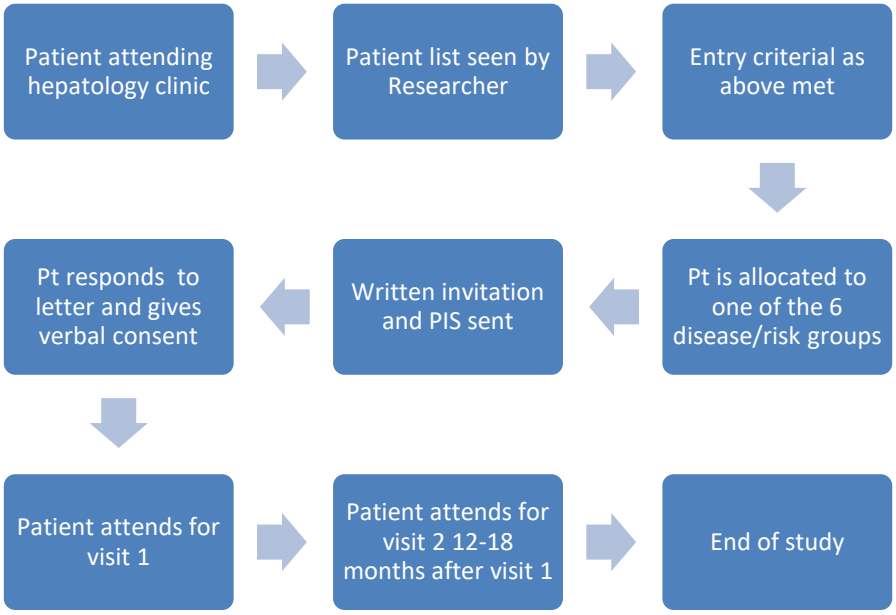
Previous orthoptic liver transplant

Any current evidence of overt hepatic decompensation, such as gross ascites or recurrent episodes of hepatic encephalopathy.

Presence of alternative causes of liver disease, that are considered by the Investigator to be the predominant active liver injury at the time of screening, including viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis.

For PSC only, the presence of documented secondary sclerosing cholangitis on prior clinical investigations.

Flowchart for the LAMP extension



PATIENT INFORMATION LEAFLET – VERSION 4.0

LiverMultiscan^{TM} – Replacing liver biopsy

Longitudinal Assessment with MRI in auto-Immune Liver Disease (LAMILD)

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish.

Ask us if there is anything that is not clear or if you would like more information.

Thank you for taking the time to read this and consider our study.

What is the purpose of the study?

This study is to look at whether a combination of two special types of MRI scan (called a LiverMultiscan^{TM} and an MRCP) can be used to monitor autoimmune liver disease. We hope it will also be able to tell your doctor the stage of scarring in autoimmune liver disease. Grading the scarring in autoimmune liver disease is currently very difficult as there are no tests that tell the full story. Current scans do not tell us everything about scarring in the liver and a liver biopsy can miss-diagnose the stage of autoimmune liver disease as the changes in the liver are patchy. LiverMultiscan^{TM} and MRCP together have the potential to look at the whole liver and tell your doctor all they need to know about your autoimmune liver disease. The two scans will be done together. It is quick and does not involve any needles or radiation. People who would like to take part in this study will have a LiverMultiscan^{TM} and a MRCP together on the same day. You will be called back to have the same scan done again in 12-18 **months' time.** Nothing else will change about your care. Everything else will be the same whether you do or do not take part.

Why have I been chosen?

You have been invited to take part because you have either Primary Sclerosing Cholangitis (PSC), Autoimmune hepatitis (AIH) or Primary Biliary Cholangitis (PBC) and you are under the care of the Queen Elizabeth Hospital, Birmingham.

Do I have to take part?

No! It is entirely up to you whether to take part or not. Taking part in this study will not change anything about the care you receive.

Can I change my mind?

Yes, you are free to withdraw from this study at any time. You don't need to give a reason. A decision to withdraw at any time or a decision not to take part will not affect the care you receive.

What will happen to me if I take part?

If, after reading this leaflet, you decide that you want to take part you will be asked to sign a consent form. This is a form that says you understand what we are doing and confirms you are happy to take part.

You will then come to the hospital for your MRI scan. We will do our very best to choose a time that suits you. You will need to have nothing to eat for **4 hours** prior to your MRI scan. At this appointment you will fill in an MRI safety questionnaire and have the scan. The scan usually takes about **45 minutes**. It does not involve any injections or other contrast. We would like you also to have some blood tests and a quick, painless ultrasound test on the day of your MRI. We will pay your travel expenses for this trip to the hospital.

We will contact you again in 12-18 months to come for a second scan that will follow the same pattern as the first.

What is the blood being tested for?

We will test your blood for several common markers of liver disease. We will also test your kidney function, blood count and how well your blood clots. Most of these tests are part of your routine care. If you give us permission we will store some of your blood to do ethically approved research in the future. No genetic tests will ever be done on your blood sample either now or in the future.

What are the advantages of taking part in the study?

The study may not be of immediate personal benefit to you. In the future we hope that these scans will improve the monitoring of autoimmune liver disease and this may be of benefit to you or to others in the future. You will not stand to gain financially if the findings from this work lead to commercial development of the technique.

What are the disadvantages?

Blood tests can be briefly uncomfortable and may bruise. There is also some time spent coming to the hospital. We will make sure we cover the cost of you coming to the hospital for your scan. Other than that there should be no disadvantages to taking part. The MRI scan is safe, painless and does not involve any radiation.

Are there any risks?

The study does not pose any serious risk to your health at all. Blood tests for this trial carry the same minimal risk as any other blood test.

What happens if you find something unexpected on the scan?

If we were to find something on the scan that is relevant to your health a liver specialist from the study team would let you know. If you gave us permission we would also tell the doctors looking after you so that they can arrange any further tests or scans that are necessary. It should be understood that this test is not designed to do this and you should not see it as a substitute for other liver scans that your doctor may have planned.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens one of the research team will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study then your doctor will continue your care for you. If you decide to continue in the study you will be asked to sign an updated consent form. Occasionally on receiving new information your doctor may consider it in your best interests for you to withdraw from the study. He/she would explain the reasons and arrange for your care to continue.

What if something goes wrong?

We don't expect anything to go wrong in this study as the MRI scan is very safe. If you feel anything is wrong then please tell us.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study then please contact the study team. If you do not wish to do this or you feel we have not satisfactorily dealt with any complaint or concern then complaints can be made by contacting the Queen Elizabeth Hospital Birmingham Patient Advice and Liaison Service (PALS) on 0121 371 3280.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be anonymised and kept in strict confidence. Your data will be kept in accordance with the data protection act. This is a collaborative work between Trusts, Academic partners (University of Birmingham and University of Edinburgh) and commercial groups to develop this technique. As such your tissue/anonymous data would be shared between the parties to maximise the use and benefit your involvement can provide. No personal information will be passed on to anyone outside the study. Paper records will be kept securely and electronic records will be encrypted.

What will happen to the results of the research study?

The results of the trial will be submitted for publication in a scientific or medical journal and may be presented in meetings. You will not be identified within the trial report. You can request a copy of any published article by contacting the study team.

Who is funding the research?

The research is funded by the National Institute for Health Research - Rare Diseases Translational Research Collaboration.

Who is running the study?

Professor Gideon Hirschfield (Professor of Hepatology and consultant hepatologist) is in charge of the study. The day to day running of the study will be done by Dr Katie Arndtz (Clinical research fellow and specialist registrar in hepatology).

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the committee. It has also been approved by the university and hospital ethics committees.

Contacts for further information:

Chief Investigator:	Professor Gideon Hirschfield	Professor of Hepatology and Consultant Hepatologist, Centre for Liver Research, University of Birmingham
Investigator: (first point of contact)	Dr Katie Arndtz	Clinical Research Fellow, Centre for Liver Research, University of Birmingham

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09 October 2022

Dear

Longitudinal Assessment using MRI in auto-Immune Liver Disease (LAMILD)

We are undertaking a research study at the Queen Elizabeth Hospital Birmingham looking at how best to assess and monitor Primary Sclerosing Cholangitis (PSC), Primary Biliary Cholangitis (PBC) and Autoimmune Hepatitis (AIH) with Magnetic Resonance Imaging (MRI) scans.

I am inviting you to take part in this study. We are contacting patients with the above liver conditions who attend specialist auto-immune liver clinics at our hospital. I enclose an information sheet which explains this study.

You are under no obligation to take part. Whether you take part in this study or not will have no effect on your care at the hospital.

Many thanks for thinking about this. If you have any questions or would like to take part, please contact me as above.

Yours faithfully

Dr Katie Arndtz

Clinical Research Fellow

Dr Gideon Hirschfield

Consultant Hepatologist

LiverMultiscanTM – Replacing liver biopsy

Longitudinal Assessment with MRI in Auto-immune Liver Disease

Patient Consent Form

Patient trial number: Patient initials:

Please initial box

I confirm I have read and understand the information sheet dated 28th October 2016 (version 4) for the above study and have had the opportunity to ask questions	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving reason and without my medical care or legal rights being affected	
I understand that sections of my medical notes may be looked at by responsible individuals involved in the study and by regulatory authorities where it is relevant to me taking part in this research. I give permission for these individuals to have access to my records	
I understand that anonymised data, including tissue samples, will be shared between research partners during the study.	

I give permission for MRI scan results, liver biopsy results and any samples of blood left over from the study to be used for ethically approved research that may be conducted in the future

I agree to take part in the above study

Name of patient (PRINT)	Date	Signature
.....	.....	.....
Name of Researcher (PRINT)	Date	Signature
.....	.....	.....

Longitudinal Assessment using MRI in PSC (LAMP)

CASE REPORT FORM

ID number	LAMP-	Patient initials	
Date of consent		Gender	M F
Consent for serum storage?	Yes No	DoB	
Race (see guide)			
Height (m)			
Weight (Kg)			
Pregnant	Yes (exclusion criteria)	No (continue)	Unsure (pregnancy test required)

Diagnosis				
PSC	**PBC**	**AIH**	**Overlap**	**Other**
			Specify	Specify
IBD Y/N UC/Crohn's Last flare: On Rx: Y/No 5-ASA Pred Aza	Urso Yes No Dose: Started:	Pred Aza MMF Other		

Decompensation		Never	Current	Past, Date:
Varices		Ascites	Encephalopathy	SBP
I	II III	Mild Severe	I / II	III / IV

Meds	PMH	
	Smoking	Current Past Never
	Pack years	
Alcohol intake (units/week)	Diabetes	Yes No
	Type	I II
Coffee intake (cups/day)	Insulin	Yes No
	Dialysis	Yes No

Blood

DATE				FASTED	Yes No
Hb		Sodium		Bilirubin	
Platelets		Urea		AST	
PT		Creatinine		ALT	
APTT		eGFR		ALP	
INR		Ferritin		gGT	
Igs		TF Sats		Albumin	
		Trigs			
ELF		Cholesterol			

Storage

Booking in number:	LL

Plasma:				
	Number:		Volume	
	Location:	Box	Tubes	

Serum:				
	Number:		Volume	
	Location:	Box	Tubes	

MRI

DATE		FASTED	Yes No
T1 (ms)		Fat fraction (%)	
cT1 (ms)		Scan time (min)	
T2* (ms)			
Report			

Fibroscan

DATE		FASTED	Yes No
Probe	M XL	Successful attempts	
Stiffness (kPa)		IQR	
		IQR:mean	
CAP (dB/m)		CAP IQR	

24 Appendix M. Visit 2 Correlations between MRI metrics with markers of liver disease

	PSC (n=61)			AIH (n=62)			PBC (n=61)		
	cT1 mean	*cT1 mode*	*cT1 IQR*	*cT1 mean*	*cT1 mode*	*cT1 IQR*	*cT1 mean*	*cT1 mode*	*cT1 IQR*
Correlation with Serum Liver and Serum Liver tests									
Platelets	0.135 p=0.355	**0.346** p=**0.015**	**0.360** **0.011**	-0.069 p=0.625	0.049 p=0.727	**-0.414** **p=0.002**	**-0.327** **p=0.014**	**-0.289** **p=0.031**	**-0.443** **p<0.001**
ALT	-0.192 p=0.186	**-0.329** **p=0.021**	0.243 p=0.092	**0.482** **p<0.001**	**0.468** **p<0.001**	0.074 p=0.596	0.018 p=0.897	-0.012 p=0.927	0.090 p=0.511
AST	-0.132 p=0.364	-0.374 p=0.008	**0.462** **p=0.001**	**0.451** **p=0.001**	**0.413** **p=0.002**	0.224 p=0.104	0.161 p=0.236	0.165 p=0.223	0.205 p=0.129
Bilirubin	0.106 p=0.469	-0.075 p=0.610	**0.485** **p<0.001**	0.038 p=0.786	-0.074 p=0.597	0.226 p=0.101	0.191 p=0.158	0.195 p=0.151	**0.392** **p=0.003**
ALP	0.003 p=0.984	-0.210 p=0.148	**0.419** **p=0.003**	0.111 p=0.425	0.153 p=0.270	-0.093 p=0.504	0.247 p=0.067	0.221 p=0.102	0.162 p=0.234
IgG	**0.383** **p=0.007**	0.231 p=0.110	**0.309** **p=0.031**	0.205 p=0.137	0.219 p=0.112	0.177 p=0.200	**0.398** **p=0.002**	**0.398** **p=0.002**	0.183 p=0.177
Correlation with Surrogate Disease severity markers									
Liver Stiffness	**0.286** **p=0.046**	0.019 p=0.899	**0.571** **p<0.001**	**0.517** **p<0.001**	**0.414** **p=0.002**	**0.330** **p=0.016**	**0.413** **p=0.002**	**0.443** **p=0.001**	**0.330** **p=0.14**
APRI	0.194 p=0.181	**-0.461** **p<0.001**	**0.524** **p<0.001**	**0.297** **p=0.031**	0.206 p=0.140	**0.353** **p=0.009**	**0.268** **p=0.046**	0.254 p=0.058	**0.398** **p=0.002**
MELD	0.195 p=0.180	0.076 p=0.604	**0.342** **p=0.016**	**0.371** **p=0.006**	0.267 p=0.051	0.210 p=0.127	0.209 p=0.123	0.169 p=0.212	**0.405** **p=0.002**
ELF	0.222 p=0.124	0.033 p=0.823	**0.345** **p=0.015**	**0.306** **p=0.025**	0.262 p=0.056	0.147 p=0.290	**0.419** **p=0.001**	**0.55** **p=0.008**	**0.408** **p=0.002**
INR	0.247 p=0.087	0.181 p=0.214	0.172 p=0.237	**0.384** **p=0.004**	**0.323** **p=0.017**	0.125 p=0.368	**0.373** **p=0.005**	**0.331** **p=0.013**	0.257 p=0.056

Data are reported as Spearman's rho correlation coefficients and p-values. Bold values are significant at p<0.05. Due to those lost to follow up or whom declined repeat MRI, this analysis is based on n=49, n=54 and n=55 respectively. Significant associations are highlighted in bold.

25 Appendix N. Updated Scoping Review Post COVID-19

The original scoping reviews looking into telemedicine performed for this thesis were completed in 2017, prior to the Covid-19 pandemic. The resulting need for social distancing led to widespread uptake of telemedicine worldwide, in the form of both video and telephone clinics, as an attempt to continue some non-urgent management for chronic diseases. This was the case at QEHB, who were able to accelerate the virtual video clinic roll out in many cohorts, including the AILD population.

Personal experience of having a chronic disease managed virtually are therefore much more common and attitudes of patients to this form of telemedicine may have changed as a result. It is also possible that further literature may have been published in the time since the original scoping reviews were performed. A new scoping review was therefore performed, as described below, the aim of which was simply to scope for any new publications assessing the evidence for telemedicine in liver disease.

Method

This scoping review was conducted in the same manner as those described in Chapter 4. Multiple database sources were interrogated in both searches, in order to find the relevant literature. These databases were PubMed, OVID Medline, Open Grey, Cochrane Library, Embase, PsychInfo, Scopus, Web of Science and CINAHL. These databases were searched for articles written in the English Language and published between 01/11/2016 (when the original scoping reviews completed their data trawl) and 01/08/2021. Reference lists were also searched and duplicates were removed.

All articles were considered for inclusion, if they were in the English language and included some evidence of a remote video consultation occurring with the patient present live at one

end. The abstracts of all potentially relevant articles were reviewed and articles were excluded as per the above criteria. For potentially relevant articles, the full article was reviewed in detail, where this was available. Relevant articles were interrogated to appropriately collate and summarise the data from each article. These charts were created to include the authors, year of publication, geographical population studied, the number of subjects involved (where applicable), the methodology used and the main focus of the study. Themes were then identified for discussion.

The search and exclusion criteria can be seen in Box 3.

BOX 3. Updated scoping review stage 2 search strategy & exclusion criteria

A) SEARCH STRATEGY

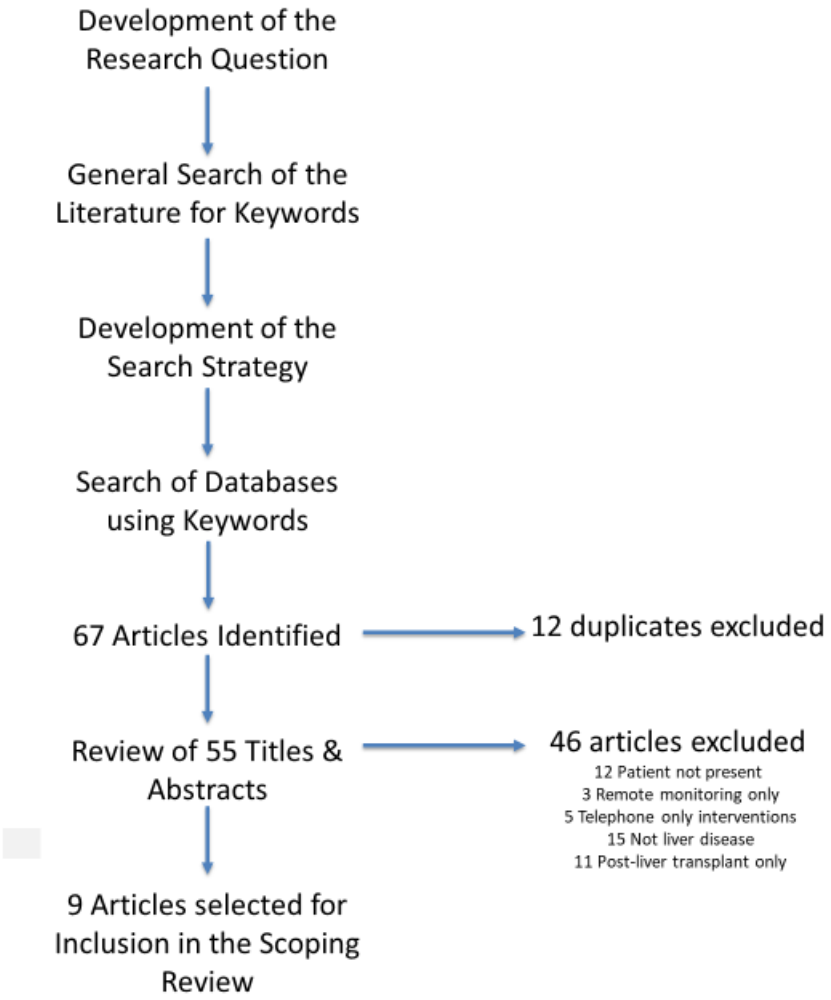
Search ((telehealth OR telemedicine OR telenursing OR teleradiology)) AND (video OR "remote consultation") AND (hepatol* OR liver)). Sort by: Relevance Filters: Publication date from 2016/11/01 to 2021/08/01. In English. In humans.

B) EXCLUSION CRITERIA (based on the Chapter 5 scoping review criteria)

1. Studies that compared different technical specifications of telecommunications technologies.
2. Studies in which the use of telecommunications technology was not linked to direct patient care.
3. Studies in which the patient was not physically present at either point of care, e.g. studies evaluating the electronic transmission of X-ray images or pathology results for routine reporting for example, 'store and forward' systems with no interaction between the patient and healthcare professional.
4. Patient monitoring systems in which the patient received only an automated voice response.
5. Interventions targeted exclusively at carers.
6. Telephone only interventions as for some conditions usual follow-up care routinely includes telephone follow-up.
7. Studies involving patients only post-liver transplantation (in line with the rest of this thesis)

Initially, “cholangitis” was added into the search criteria looking for specific data on this cohort, however no results were returned. When this criterion was removed, 67 potentially relevant articles were found during the literature search, after excluding 12 duplicates. However, all but nine of these were subsequently excluded after abstract review as falling outside the study criteria. The remaining nine included studies were subsequently analysed in full. The search strategy is depicted in Figure 22.

Figure 22. Updated scoping review search strategy flow chart



Results from the updated scoping review

The nine studies included within this updated review were all Europe, USA or Australia-based; full articles were available for all and these were reviewed in full. Four of the articles contained no de-novo data and these included one systematic review, an editorial, a brief review, and a piece of correspondence. Of the five studies with new data, only one was a randomised controlled trial; this study was of video and telephone dietary intervention consultations in a cohort of NAFLD-HIV patients and found reduced weight gain in the intervention arm compared with standard of care. The remaining studies included two retrospective audits and one prospective observational study (all describing the uptake of a new or expanded telemedicine service) and one patient feedback questionnaire on a new telehealth clinic. A full summary of the characteristics of these studies can be seen as Table 1 below.

Appendix N: Table 1. Summary of characteristics for the updated scoping review into telemedicine in liver disease

Author	Population	Aim & Intervention	Relevant Findings
Gomes et al, 2020	Portugal n=973	This study used a questionnaire to investigate patient attitudes to remote consultations in outpatient gastroenterology clinics.	Return rate of 23% (973/4228). 89% of patients were in favour of remote consultations including 87% unselected hepatology patients. 77% of those who had experienced a remote consultation were satisfied.
Perisetti & Goyal 2021	USA Systematic Review	This was a systematic review of how telemedicine can be integrated into hepatology clinical practice. No de-novo data presented	Pre-pandemic studies found were related to HCV management Intra-pandemic studies mostly represent telemedicine interactions between specialists and local doctors rather than being directly patient facing. The authors expect further expansion in telemedicine initiatives in liver disease in the future.
The Lancet Gastroenterology & Hepatology, 2019	International Editorial	This was an editorial on the use of telemedicine in gastroenterology No de-novo data presented	The authors suggest a slower update of telemedicine in digestive diseases compared to other chronic illnesses and that most articles to-date focus on HCV. They conclude that this technology has potential however must be properly evaluated in terms of cost and clinical outcomes.
Policarpo et al, 2021	Portugal Randomised control trial	This study assessed dietary telehealth intervention in a NAFLD-HIV cohort during a nationally mandated Covid-19 lockdown compared to in-person routine clinical consultations.	Patients on standard of care gained more weight with higher blood glucose levels than those in the intervention arm.
Guarino et all, 2020	Italy Prospective observational study	This study investigated the use of telemedicine in patients with chronic liver disease during a COVID-19 related lockdown	75% of outpatient care was completed via video and telephone appointments during the lockdown. Patients expressed satisfaction with this new management (no data provided).

Siegal, C, 2017	USA Brief review	This was a brief review of potential utility of telemedicine in gastroenterology. No de-novo data was presented.	The author concludes that telemedicine has potential utility in gastroenterology; by reducing face-to-face visits when patients are well, patient experiences can be improved and costs reduced. Barriers to wider implementation include re-imbursement, licensing and fear of litigation.
Macedo, G, 2020	Portugal Correspondence	This was a piece of correspondence on the use of telemedicine in gastroenterology. No de-novo data presented	The author states there is utility to telemedicine in gastroenterology however acknowledges certain disadvantages. These include not being as time efficient as previously thought, the lack of social interaction was less satisfying as a clinician and the communication between doctor and patient was different.
Keogh et al, 2016	Australia Retrospective audit	This study audited the uptake of expanding an existing HCV-related telehealth services due to Covid-19.	Virtual consultations substantially increased in number after the expansion while at the same time failure to attend rates fell. Interviews were conducted with staff members and found high satisfaction; patients were not consulted.
Serper et al, 2020	USA n=67	This study audited the expansion of a telehepatology pilot programme.	The pilot phase of a video clinic for patients with advanced chronic liver disease was described. 85% of new referrals underwent electronic consultations; two visits experienced technical issues. 26% of consultations resulted in other tests being requested and/or medication changes and 10% resulted in a liver transplant assessment referral. Patient and referrer satisfaction was high.

NAFLD-HIV = Non-alcoholic fatty liver disease with co-morbid Human Immunodeficiency Virus)

HCV = Hepatitis C Infection

Updated Scoping Review Discussion

Overall, little new evidence for the efficacy of telemedicine in chronic liver disease was found via this updated scoping review, with only one randomised control trial showing efficacy and this was in a highly selected population, with a discrete intervention over a short period of time, and during a national lockdown. No new evidence for the longer-term efficacy or safety of telemedicine in chronic liver disease was found via this updated review and therefore gaps remain in the literature in this cohort of patients.

The majority of new data instead investigated the popularity of telehealth interventions, either by describing the uptake of new virtual clinics or by exploring patient satisfaction with these new clinics; both of these factors were reported as high. These were all very recent articles and given the lack of alternatives to virtual consultations during the Covid-19 pandemic, it is unsurprising that uptake of these telehealth programmes was high. Additionally, the main questionnaire study (Gomez et al) described an unsatisfactorily low response rate of under 25%. Overall, the evidence for the longer-term popularity of telemedicine amongst patients and clinicians outside of lockdown or pandemic situations remains poor.

The review articles described ongoing high levels of interest in telemedicine in liver diseases from both patients and clinicians alike, however, most acknowledged that existing evidence for its efficacy in chronic liver disease is from the treatment of HCV. This is unchanged from the findings of the original scoping review described in Chapter 4 of this thesis. As described previously, HCV is now a highly treatable condition, a very different situation to that of PSC, and therefore is of less relevance to most of the patients described within this thesis. Further discussion is found in the main text (Chapter 6).

Reference database for updated scoping review

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