BARRIERS AND FACILITATORS FOR COLORECTAL CANCER TREATMENT DELIVERY IN INDIA

By

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A thesis submitted to the University of Birmingham

for the degree of Doctor of Philosophy

Institute of Cancer and Genomic Sciences

NIHR Research Unit on Global Surgery

College of Medical and Dental Sciences

University of Birmingham

July 2022

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Abstract

Introduction: Cancer is a leading cause of mortality worldwide, accounting for nearly 10 million deaths in 2020. Surgery is usually needed to achieve cure and control the disease. The financial burden of cancer surgery for patients and their households at a global level has not been studied before. This thesis aimed to (i) assess out-of-pocket payments (OOPP) for cancer surgery across country income settings; (ii) explore catastrophic expenditure and treatment attrition rates in a cohort of patients with a new treatment decision for colorectal cancer in tertiary care hospitals in India; and (iii) explore barriers and facilitators for colorectal cancer adherence in India.

Methods: An international prospective cohort study compared the proportion of surgeries where out-of-pocket payments were used to pay for the majority of the cost of cancer surgery across country income groups and identified factors associated with OOPP in low- and middle- income countries. A prospective multicentre cohort study of patients with a new treatment decision for colorectal cancer in five tertiary care hospitals in India, reported costs of treatment, catastrophic expenditure and treatment attrition. Catastrophic expenditure was defined as treatment cost being higher than 25% of annual household income. A qualitative study explored the views and perspectives of colorectal cancer professionals on barriers and facilitators for treatment adherence in India.

Results: OOPP for the majority of the cost of cancer surgery were more common in lower country income groups: 0.5% in high income, 5.7% in upper-middle income, 38.6% in lower-middle income, 48.1% in low-income countries. OOPP in low- and middle- income countries were independently associated with male sex, elective surgery and income group. The average OOPP for colorectal cancer care in India was 365,768 Indian Rupees (4667 USD), with surgical costs being among the highest. The catastrophic expenditure rate was 90.1% (182/202) and the treatment attrition rate was 9.4% (19/202). Catastrophic expenditure was independently associated with male sex, primary or no education, private treatment, advanced cancer stage, rectal cancer, and surgical resection. Barriers and facilitators for colorectal cancer adherence in India were identified from fourteen cancer care professionals, summarised into (1) social background and support, (2) patient awareness, education, and beliefs, (3) healthcare system capacity and organisation, (4) clinical events and (5) financial and job protection.

Discussion: There was global inequality in financial protection among patients accessing cancer surgery. Among households seeking tertiary care for colorectal cancer in India, a large proportion suffered catastrophic expenditure. Better financial protection policies are needed to prevent the detrimental effects of OOPP. Treatment adherence is influenced by social, education and financial factors that can be targeted with community and policy interventions. Increasing healthcare system capacity and improving communication with patients can improve the understanding of the available treatment pathways, contributing to better cancer outcomes.

Research outputs from this thesis

Publication: Catastrophic expenditure rates and barriers for treatment adherence in patients with colorectal cancer in India: The CROCODILE study protocol, *Colorectal Disease*, April 2021, DOI: 10.1111/codi.15674.

Accepted for publication: Catastrophic expenditure and treatment attrition in patients seeking comprehensive colorectal cancer treatment in India: a prospective multicentre study, with *Lancet Regional Health - Southeast Asia*.

Paper currently under review: Feasibility of the International Wealth Index and the Gapminder tool as instruments to assess household income, with *PLOS One*.

Conferences:

Lancet summit on Cancer Care in Asia and Latin America, July 2022: abstract accepted for the conference and for publication in *The Lancet Oncology*.

Bethune Round Table, June 2022: presentation of results, awarded the prize for best oral communication.

Bethune Round Table, May 2021: presentation of study protocol.

Other research meetings: NIHR Health Economics Network for Global Health, March 2021; West Midlands Research Collaborative, October 2021.

Publications 2019-2022 (as first or corresponding author)

Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. COVIDSurg Collaborative. *The Lancet*, 2020, 396.10243:27-38. (joint first author)

Elective Cancer Surgery in COVID-19-Free Surgical Pathways During the SARS-CoV-2 Pandemic: An International, Multicenter, Comparative Cohort Study. COVIDSurg Collaborative. *Journal of Clinical Oncology*, 2021, 39(1):66-78. (joint first author)

Effects of pre-operative isolation on postoperative pulmonary complications after elective surgery: an international prospective cohort study. GlobalSurg and COVIDSurg Collaboratives. *Anaesthesia*, 2021, 76.11:1454-1464. (joint first author, corresponding author)

Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. GlobalSurg and COVIDSurg Collaboratives. *Anaesthesia*, 2021, 76.6. (joint first author)

Predictors of low quality of life after open inguinal hernia repair using the EuraHS-QoL score: prospective multicentric cohort study across 33 hospitals. PTSurg Collaborative. *Hernia*, 2021, 26(1):225-232. (first author, collaborative chair)

The impact of surgical delay on resectability of colorectal cancer: An international prospective cohort study. COVIDSurg Collaborative. *Colorectal Disease*, 2022, 24:708–726. (joint first author, corresponding author)

Dedication

I dedicate my thesis to my grandmother Irene,

For teaching me the simplicity of life, the comfort of unconditional love and the joy of a loud laugh.

Com a tua mão generosa,

Ensinaste-nos aquilo que é certo.

É encantadoramente simples a tua prosa,

Está nos nossos genes o teu sorriso aberto.

Acknowledgements

I would like to thank my supervisors. To Mr Bhangu, for teaching me how to navigate leadership. To Professor Morton, for teaching me when to take risks and when to take responsibility. To Professor Jolly and Dr Joanne Clarke, for teaching me that rigour and kindness can go alongside. To Dr Raymond Oppong, for showing me that science fields are most productive when combined.

A special thank you goes to all the research partners in India who helped me designing and delivering the CROCODILE study, with an amazing collaborative mindset and insightful contributions at all stages of this work.

I would like to acknowledge the India Institute of the University of Birmingham for a three-year fellowship that funded most of the field work in India, as well as the Strategic Global Engagement Programme of the Institute of Cancer and Genomic Sciences for funding my PhD post.

Thank you António, for introducing me to collaborative research and for always asking the much-needed inconvenient questions. Thank you to my fellow Bhanguists and boiler room members - Dmitri, James, and Lizzy - for the inspirational companionship and leadership, only the beginning of a lifetime relationship. Thank you Maria, for taking challenges, for making me proud and for bringing home to me when I most needed.

Finally, a warm thank you to my parents, David and Noémia, who supported me with immense love, who let me grow in my own direction with acceptance and pride. To my little brother for existing and being a huge Man. A vibrant thank you to Inês, João, Sofia, Sandra, Kika, Ana, Bárbara and Vasco for keeping me in their lives and their hearts, for being soulmates at distance. Last but not least, to Niels, for bringing the most exciting and warm texture to my life.

I am not just me when I am alive.

I need more than just me for the whole thing to thrive.

I dream of a world within our big world,

Where authentic are children and so are the elder.

I dream of a world where an arm is a bridge,

A heart is a sponge, and a shadow is shelter.

I am not just me when I am alive.

If I'm only me,

And I can't help you see,

Proceed without me,

Alive I won't be.

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Abbreviations

AIDS - Acquired immune deficiency syndrome

AJCC - American Joint Committee for Cancer

ASA - American Society of Anaesthesiology

ASHA - Accredited social health activist

AYUSH - yoga, unani, siddha, and homoeopathy

BPL - Below the poverty line

CEA - Carcinoembryonic antigen

CI - Confidence Interval

CTRI - Central Trials Registry of India

CT scan - Computed tomography scan

DALYs - Disability-adjusted life years

DRE - Digital rectal examination

FOBT - Faecal occult blood test

GBD - Global burden of disease

GDP - Gross domestic product

GLOBOCAN - Global cancer observatory

HIC - High income countries

HIV - Human immunodeficiency virus

INR - Indian rupees

ITU - Intensive treatment unit

IWI - International wealth index

LIC - Low income countries

LMIC - Lower middle income countries

L&MIC - Low and middle income countries

MIC - Middle income countries

MRI - Magnetic resonance imaging

NCD - Non-communicable diseases

NGOs - Non-governmental organisations

NIHR - National Institute for Health Research

OOPP - Out-of-pocket payments

OR - Odds Ratio

PM-JAY - Pradhan Mantri Jan Arogya Yojana

PPP - Purchasing power parities

RCRI - Revised cardiac risk index

SD - standard deviation

SDI - Sociodemographic Index

SEM - Socio-ecological model

STROBE - Strengthening the reporting of observational studies in epidemiology

TNM - Tumour Node Metastasis

UHC - Universal Health Coverage

UMIC - Upper middle income countries

UNICEF - United Nations International Children's Emergency Fund

USA - United States of America

USD - United States Dollars

WHO - World Health Organisation

1 Introduction

1.1 Summary

This introductory chapter will provide background information on the epidemiology of cancer worldwide, the challenges for global cancer control and the financing of cancer care. A middle section will provide details on the diagnosis and management of colorectal cancer. The chapter finishes with a description of the Indian health and cancer care context. At the beginning of each section, key points are highlighted in a box.

1.2 Global cancer care

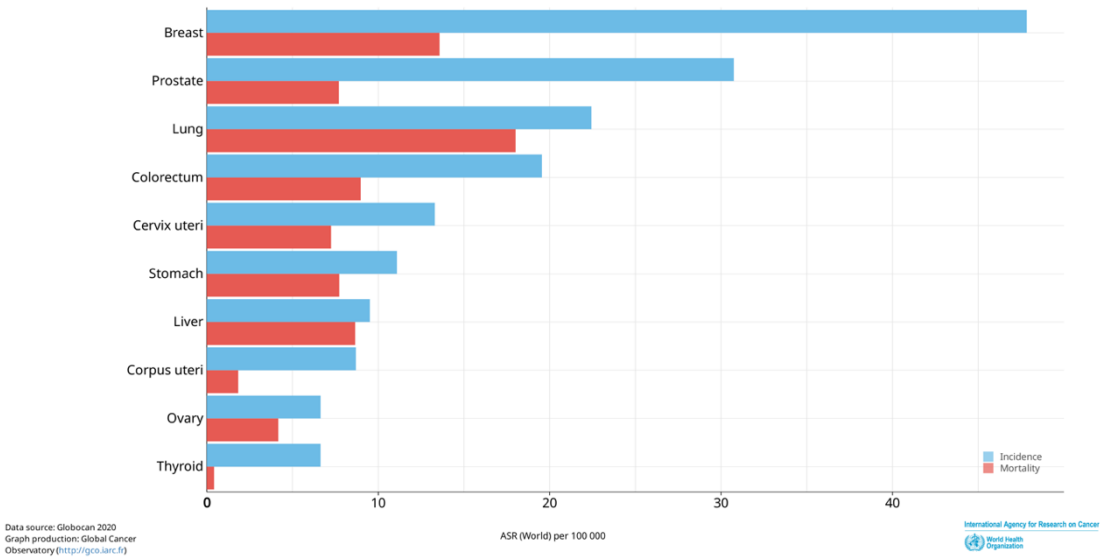
1.2.1 Global burden of cancer

Cancer is the second cause of death globally and is responsible for a high burden of disability life years worldwide.

Cancer is the second lead cause of mortality, after cardiovascular diseases, responsible for 7.6 million deaths, corresponding to 21% of the 36 million deaths due to non-communicable diseases every year(1). At a global level, 250 million disability-adjusted life years (DALYs) are estimated to be due to cancer, which represents an increase of 16% from 2010 to 2019(2). Projections estimate that by 2040 there will be 30.2 million new cancer cases and 16.3 million cancer-related deaths.

The most common cancers worldwide are breast, prostate, lung, colorectum and cervical malignancies. The leading causes of cancer-related deaths and DALYs are lung, colorectal, gastric, breast and liver cancers(2). Figure 1 shows GLOBOCAN estimated age-standardised incidence and mortality rates.

Figure 1: Estimated age-standardised incidence and mortality rates in 2020 worldwide.

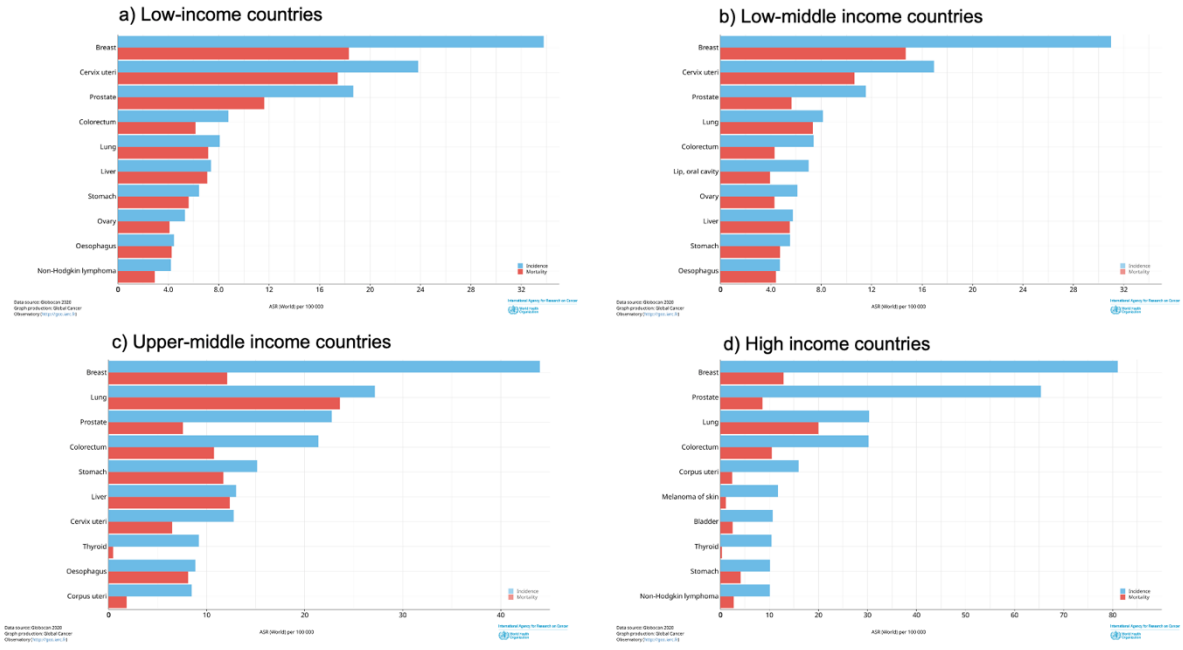


(From GLOBOCAN, 2020) (3)

Chart shows incidence and mortality rates for both sexes, all ages excluding non-melanoma skin cancer.

The burden of the various cancer types varies across country income levels, with the three most incident cancers being breast, cervix and prostate in low and low-middle income countries and breast, lung and prostate cancers in upper-middle and high income countries (Figure 2)(3). Prevalent diseases and risk factors can have an influence on cancer types and might explain the geographic differences. A trend shift has been seen in L&MIC but a reduction in infection-related cancers is expected to be offset by an increase in cancers related to reproductive, dietary and hormonal factors(4).

Figure 2: Estimated age-standardised incidence and mortality rates in 2020 worldwide, by country income group.



(From GLOBOCAN, 2020) (3)

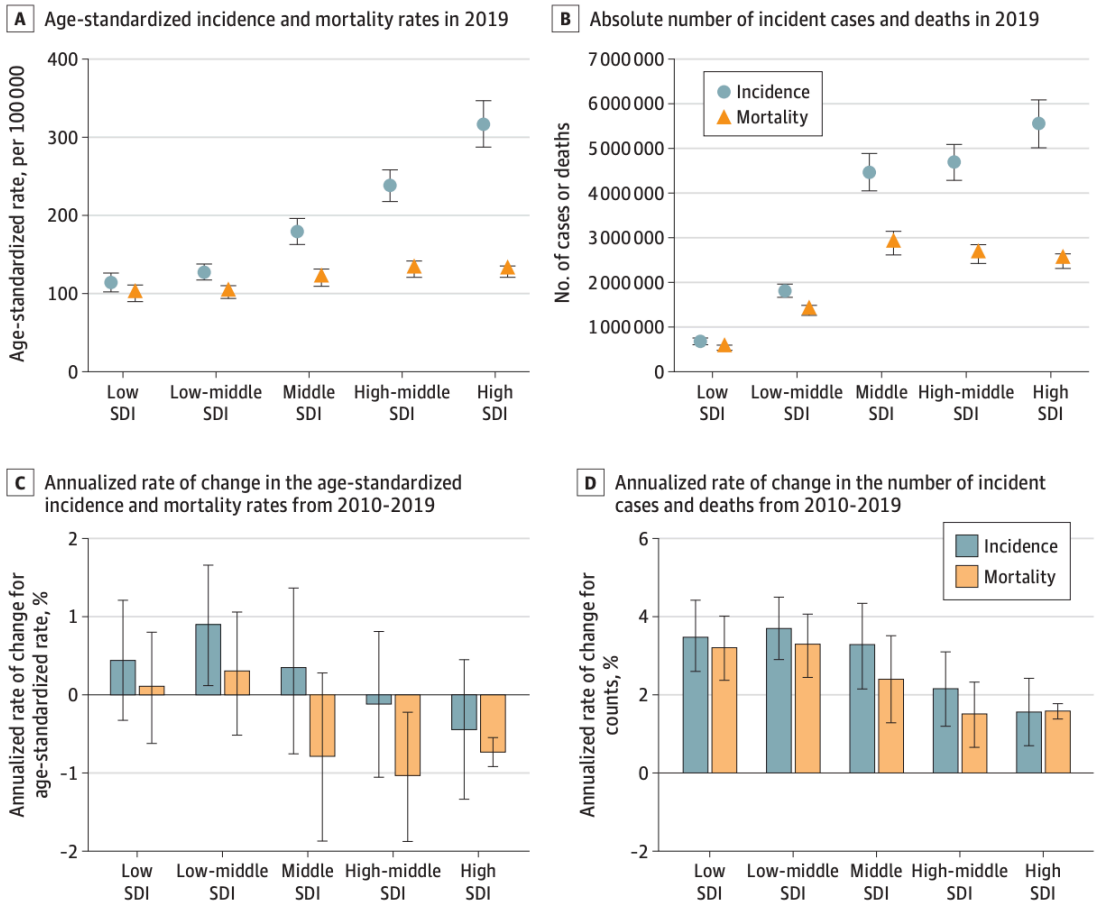
Chart shows incidence and mortality rates for both sexes, all ages excluding non-melanoma skin cancer.

1.2.2 Global challenges in cancer care

Cancer incidence is higher in high sociodemographic index (SDI) countries but the burden of mortality is higher in low SDI countries.

In 2008, 80% of all deaths (29 million) from noncommunicable diseases occurred in low- and middle-income countries, and a higher proportion (48%) of the deaths in the latter countries are premature (under the age of 70) compared to high income countries (26%)(1). Whereas half of the global cancer cases occur in High Income Countries (HIC), 75% of cancer-related deaths happen in low and middle-income countries (L&MIC). Figure 3 demonstrates the trends of cancer incidence and mortality across sociodemographic index quintiles (a country level metric that summarises income per capita, average educational attainment and fertility rates). This figure highlights that the lowest SDI quintiles have been observing an increase in incidence and mortality, whereas high SDI quintiles experienced a decrease in both(2). These trends raise concerns about access to curative treatment in L&MIC and highlight the relevance of developing global strategies to prevent death and disability from cancer across all income settings(2).

Figure 3: Total cancer incidence and mortality age-standardised rates from 2010 to 2019 by socioeconomic index quintile.



(From Global Burden of Disease 2019 Cancer Collaboration, 2022, p.429) (2).

Panels provide global estimates for total cancers, except non-melanoma skin cancer. Annualised rate of change from 2010 to 2019 represents the mean percentage change per year during this period. Black bars represent 95% uncertainty intervals.

The increase of cancer incidence and mortality in L&MIC has been interpreted as a result of an increase in life expectancy, rising rates of diagnosis and the so-called westernization of lifestyle(5, 6). Russia, India and China are the home of 40% of the world's population, experience 46% of all new cancers worldwide, and account for 52% of cancer deaths globally(7). Given that cancer is a complex disease requiring complex health pathways from prevention to palliative care, its control can provide benchmarking for understanding and responding to wider health-system challenges(8). Between 30% and 50% of cancers can be prevented by avoiding risk factors and implementing evidence-based prevention strategies. The lack of prevention policies to act on modifiable risk factors and promote early diagnosis results in loss of productivity and escalation of healthcare costs(1). A healthy population is a productive one, and a productive population creates national wealth and social wellbeing(7). Cancer control policies should be data driven and my thesis is contributing to knowledge on out-of-pocket payments for cancer care, as well as patients' attitudes towards their treatment course, to inform decision making with whole societal benefits.

Although cancer outcomes and financing are a challenge in L&MIC, cancer care in HIC does not come without challenges, which might be future challenges for L&MIC if government health spending is to increase. Drug over-use, short life-cycle of cancer technologies, lack of suitable clinical research, appropriate economic evaluations, defensive medical practice, and lack of an evidence-based socio-political debate contribute to an increase in cancer care expenditure that is disproportionate to the cancer care burden in HIC(9).

1.2.3 Components of cancer care

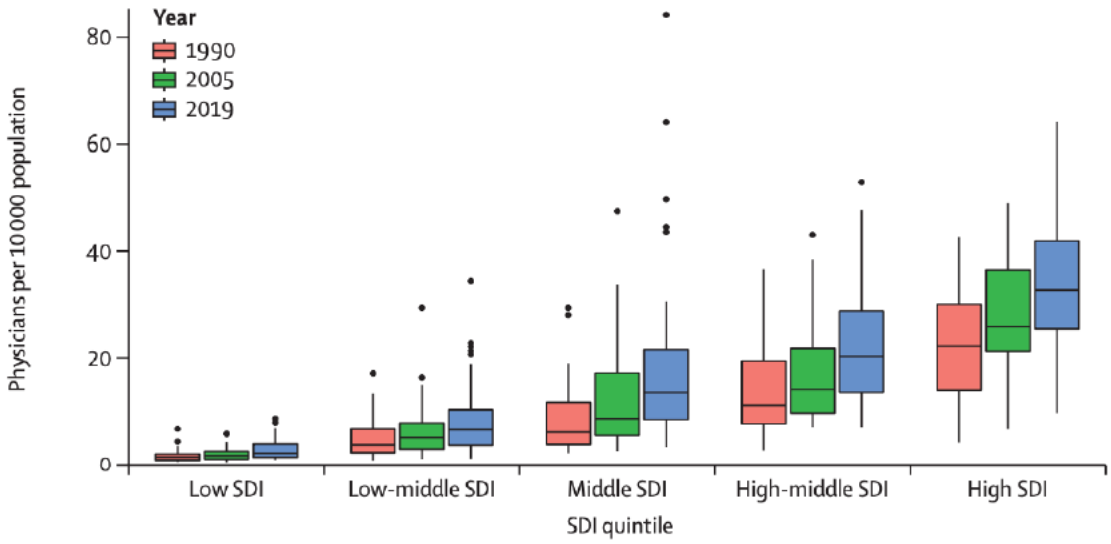
a) There is a global shortage of healthcare workers, essential medicines and radiotherapy services that is more concerning in low and middle-income countries (L&MIC).

b) Surgery is needed in about 80% of cancer cases (curative and palliative). In 2010, there was a shortfall of 9 million cancer operations worldwide. The global need is likely to increase to 45 million in 2030 and cancer care expansion is needed.

1.2.3.1 Cancer workforce

With cancer care needing to expand, workforce shortage is a growing problem particularly in countries with high SDI (Figure 4). It was estimated that, to achieve a UHC effective coverage of 80 out of 100 at a global level, the minimum required number of physicians per 10,000 population would be 20.7, which is much higher than the 16.7 physicians per 10,000 population existing in 2019 (10). The lack of trained professionals is one of the factors limiting the access to cancer care, that requires either the employment of additional workers or some form of task-shifting to increase whole system capacity.

Figure 4: Physician densities by SDI quintile in 1990, 2005 and 2019.



(From GBD 2019 Human Resources for Health Collaborators, 2022, p.2143) (10)

Boxplots show medians and IQRs. SDI=Socio-demographic Index.

1.2.3.2 Cancer treatments

Cancer medicines defined as essential by the WHO are not always included in national priorities, especially in L&MIC(11). A survey of 948 eligible oncologists from 82 countries showed that the availability of each top 20 cancer drugs from the WHO Essential Medicine List was lower in low and middle income countries (L&MIC) (9-54%) than in upper middle-income countries (UMIC) 13-90% and high-income countries (HIC) (68-94%), with the risk of catastrophic expenditure being higher in the former (13-68% in L&MIC, 2-41% UMIC, 0-9% in HIC)(12). The scarcer availability and likely unaffordable costs of cancer drugs can represent a challenge in cancer control in L&MIC.

Radiotherapy is an important component of oncological treatments and around half of the cancer patients would be eligible to receive it, either for local control or palliation(13). However, radiotherapy availability is heterogeneous and it is estimated that more than 90% of the patients requiring it in low-income countries does not have access to it(14). The density of radiotherapy machines per million population in HICs ranges from 0.4 to 11.6 but only from 0 to 0.4 in L&MIC, resulting in low availability and high cost(15). Although upscaling of radiotherapy services could save 26.9 million life-years in L&MIC and bring a net economic benefit of 278.1 million dollars, several barriers exist(16). Implementation of radiotherapy services requires a supportive technology eco system, high costs of initial construction, regular maintenance and staff upskilling(17). Cultural factors can also be a challenge, namely stigma and patients' fear of radiotherapy treatment(18).

Surgery is required in about 80% of cancer treatment courses, representing a necessary step towards cure for many patients. Almost half of cancer admissions require surgery in HIC, like Sweden. Although patients in L&MIC are expected to present at a later stage, palliative surgery is still needed in many cases (e.g., obstruction and bleeding control)(19). Expanding gaps exist in cancer care in low-income countries, as few efforts have been made to improve access to surgery, or upskill or expand professionals in surgical oncology(19). Data from 2010 Global Burden of Disease (GBD) data found that 321 million operations would be needed to treat all surgical conditions worldwide, of which more than 9 million were only for malignancies(20). The Lancet Commission on Global Surgery published that three-quarters of cancer patients would not receive safe, affordable, or timely surgery. Forward looking estimations suggest that the need for cancer surgery globally will increase to 45 million procedures by 2030 and that the lack of investment in surgical training can result in a 6.2 trillion USD loss of cumulative gross domestic product globally(21).

1.2.3.3 Primary and palliative care

Primary care can play a role in global cancer control, given its continuous, coordinated and comprehensive nature. This is applicable to all settings in different ways. Whereas in HIC it is desirable that primary care enhances mainly prevention and end-of-life care, in L&MIC a boost in early diagnosis and screening are still needed to improve outcomes(22). End-of-life suffering is also a

larger problem in L&MIC. The 2018 Lancet Commission report on palliative care reported that about 25.5 million of the people who died in 2015 experienced serious health-related suffering, and another 35.5 million experienced serious health-related suffering due to life-threatening and life-limiting conditions. More than 80% of these 61 million individuals lived in L&MIC. A recommendation was made for an essential package of palliative care to be available widely at a cost of 3 dollars per capita, potentially reducing health suffering for patients with palliative conditions, of which HIV and cancer are the most burdensome(23). Establishing wide networks with an outpatient component and community involvement is beneficial for both patients and families. It requires less in-hospital admissions, enabling less disruption of household daily activities days and cost savings(24).

Primary health care is a pilar of UHC expansion, that should encompass three components: comprehensive integrated health services, multi-sectorial policies to address the determinants of health and empowering individuals and communities to be active citizens and enhance their self-care and self-reliance for health maintenance. Public health is another key area that demands public investment and needs evidence-based policies, risk communication to individuals and families allowing them to better manage their own health, information systems, data analysis and surveillance, regulation of health products and subsidies to public health programmes(25).

1.2.4 Financing cancer care

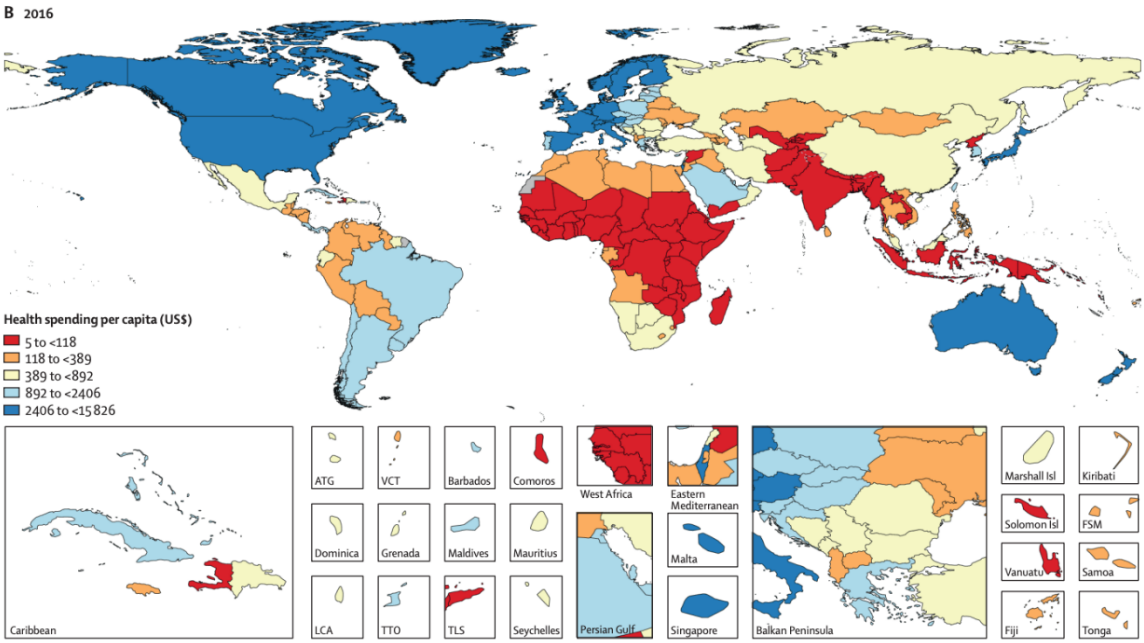
a) L&MIC generally have lower public spending in healthcare and higher rates of out-of-pocket payments (OOPP) for healthcare.

b) Healthcare related OOPP have a detrimental effect on individuals and their households (microeconomic) but also on the whole society (macroeconomic).

c) Universal Health Coverage (UHC) includes access to essential health services without suffering catastrophic health expenditure.

There is variation in healthcare spending across the world (Figure 5). Global health spending reached US$ 8.5 trillion in 2019, representing 9.8% of global GDP. Although this spending more than doubled over the past two decades, it was unequally distributed, with high income countries accounting for approximately 80%(26). Other estimates from 2016, showed that the per capita spending was $5252 in HIC, $491 in UMIC, $81 in LMIC and $40 in LIC. Lower government spending in health care is usually associated with higher OOPP expenses made by patients. The global rate of out-of-pocket payments for healthcare in 2016 was 18.6%, rising from 13.8% in HIC, to 35.9% in UMIC, to 56.1% in LMIC and 42.4% in LIC(27).

Figure 5: Health spending per capita in 2016, by country.



(From Global Burden of Disease Health Financing Collaborator Network, 2019) (27)

Health spending per capita is reported in inflation. ATG=Antigua and Barbuda. VCT=Saint Vincent and the Grenadines. LCA=Saint Lucia. TTO=Trinidad and Tobago. Isl=Islands. FSM=Federated States of Micronesia. TLS=Timor-Leste.

Cancer is one of the most expensive health challenges in the current and future health systems. Although, as shown before, L&MIC have the highest burden in terms of cancer-related mortality in the world, only about 5% of the global spending on cancer occurs in L&MIC(19). There are three major funding sources for cancer care in L&MIC: the public or governmental sector (general revenues or social insurance contributions), the private sector (out-of-pocket payments and private insurance), and external sources (eg, grants from international funding agencies or concessional loans from development banks)(19). Health spending in low income countries is primarily financed by out-of-pocket spending (44%) and external aid (29%), while government spending dominates in high income countries (70%)(26).

The low governmental spending on healthcare in L&MIC, which often leads to biased allocation of resources and to underinvestment in equipment and resources, results in fragmented health systems and inequities in cancer care(28). The Union of International Cancer Control reported financial concerns from 172 countries regarding cancer care delivery during the COVID-19 pandemic, including a reduction in fundraising (63% organisations), lower philanthropic giving (48%), weak cash-flow (30%), no government funding (22%), and delayed or non-payment of service fees (16%)(29).

1.2.4.1 Universal Health Coverage

Universal Health Coverage (UHC) is achieved when all individuals and communities receive health services they need without suffering financial hardship. Understanding the ability of households to afford the necessary healthcare for their members is crucial to identify future areas for investment. Investing in affordable and appropriate health coverage for all is a way of protecting new generations, allowing them to develop humankind. The WHO has established UHC as a Sustainable Development Goal, that involves service coverage and financial risk protection(25):

SDG 3.8.1: Service coverage is monitored through the proportion of a population that can access essential health services, including four health domains: (1) reproductive, maternal, newborn and child health, (2) infectious disease, (3) noncommunicable diseases and (4) service capacity and access(30).

SDG 3.8.2: Financial risk protection is achieved when direct payments made to obtain health services do not expose people to financial hardship and do not threaten their living standards(31). This is monitored through the proportion of a population that suffers catastrophic and impoverishing expenditure(32). Catastrophic expenditure happens when out-of-pocket payments for healthcare are higher than a percentage of the annual household income (10 or 25%). Households face impoverishing expenditure when the per adult equivalent consumption is above the poverty line before spending out-of-pocket for healthcare, and below the poverty line after that(33). Households that were

initially below the poverty line can also suffer what is called further impoverishment if their per capita consumption falls even further.

Achieving UHC involves multiple approaches and requires robust financing strategies. As countries develop, they tend to transition towards indirect financing mechanisms that pool risks, thereby protecting against unexpected financial shocks from people accessing health care. Therefore, in MIC, a mix of direct and indirect financing for surgical cancer care exists, often within the same country. Unless financing mechanisms in L&MIC explicitly address equity or adopt a pro-poor approach—either by targeting the poor or by targeting the types of diseases the poor are most likely to experience—the wealthier tend to have greater access to coverage, whereas the economically and socially disadvantaged are at highest risk of being uninsured or underinsured(19).

1.2.4.2 Out-of-pocket payments

Out-of-pocket payments are expenses that patients have to pay for at the time of healthcare service use, as opposed to those expenses being pre-paid for. Pre-paid mechanisms can be publicly provided (through free healthcare systems or governmental health funds allocated to patients) or privately bought in advance (in the form of individual or employer provided insurance). Less frequent pre-paid healthcare is funded by charities, non-governmental organisations or other bodies of human development aid.

Families and households who need to make OOPP for healthcare are often plunged into a vulnerable situation where these expenses are high and difficult to support. The use of savings, purchase of loans, property sale, and other financing distress strategies threaten the living standards of these households and can compromise their social stability. OOPP can plunge households into a downgrade of their socio-economic status, meaning that some will be pushed into poverty. Poverty and poor health status are a cause and a consequence of each other. Poverty leads to poor health due to difficulties paying for appropriate care, with a negative effect on clinical outcomes. Poor health status leads to poverty due to disability and the extra-costs of medical complications(34).

OOPP for healthcare have both a microeconomic effect (on individual and household finances) and a macroeconomic effect (national, regional and global productivity and human development)(19). It is estimated that between 2015 and 2030 cancer surgery will cause a cumulative GDP loss of 12 trillion USD at global level, representing a drop of 0.5 to 1.5% national GDP in high income countries and low income countries, respectively(19). Among the non-communicable diseases that are treatable with surgery, cancer is one of the highest contributers to GDP loss, together with trauma injury(19). OOPP causing catastrophic and impoverishing expenditure have a negative impact on per capita earning and expenditure, reducing the purchasing power of the population and contributing to economic stagnation(35). Additionally, is has been proved that reducing user charges at the point of service use is associated with improved health outcomes,

which enables societies to preserve healthy and active citizens, that contribute to economic growth overall(36).

1.2.4.3 Catastrophic expenditure

Catastrophic expenditure is a measurable indicator of the level of health-related financial protection in a particular population. Healthcare related catastrophic expenditure was estimated to affect 808 million people worldwide in 2010(37). The rates of healthcare catastrophic expenditure are particularly high in Latin America, Africa and Asia – where most L&MIC are located(38).

Although pre-paid financing strategies, namely through public taxes, seem to be the most efficient way to achieve UHC, catastrophic expenditure can happen in countries with and without good levels of UHC(37, 39). This demonstrates that patients might need to make out-of-pocket payments for healthcare, regardless of how easy it is to access healthcare in their country. Additionally, underinvestment in the public healthcare sector can lead to overwhelmed hospitals and professionals. This usually causes the perception that the public healthcare is low quality. It also gives the opportunity for private hospitals to provide services at a high cost, which become unreachable or financially toxic for many patients(40)

There is no consensus definition of catastrophic expenditure and different definitions have been used across studies and reports(32, 41). Catastrophic

expenditure encloses the concept of out-of-pocket health expenses being too high for a particular household to support them and not downgrade their socioeconomic status. This is usually measured as out-of-pocket expenses being higher than a particular proportion of the household's income, which would expose them to financial stress.

The threshold at which financial stress would be introduced into households is not clear and can be different across settings. Previous protocols of the WHO used the threshold of 40% in studies, for example, on the financial burden of tuberculosis(42). More recently, the WHO has been using the thresholds of 10% and 25%(43, 44). Other single and multi-country studies used diverse definitions that make rates of catastrophic expenditure difficult to compare across projects(41).

The other debatable topic on the definition of catastrophic expenditure has been which denominator to use, aiming to best reflect the ability of a household to pay for the healthcare costs. Some authors defend that non-subsistence household income might be better than total household income, as it would better reflect the actual capacity to pay, defined as the amount of money that is left after subsistence needs are met (food and housing)(42). Other authors advocate for the use of household expenditure, as this would better reflect the purchasing power of that household, provided that income is not the only source of wealth(45) (46).

The numerator of catastrophic expenditure is OOPP for healthcare, in which studies inconsistently include the sources of cost. I aimed for my study to be comprehensive and include all the possible sources of out-of-pocket spending for the patient, namely direct medical expenses (to pay for treatment), direct non-medical expenses (food, accommodation and transport to receive treatment) and indirect expenses (income loss).

My decision to use one of the definitions provided by the WHO (25% of total household income) was to make this work as comparable to others as possible, as well as benchmarkable to published global health indicators. Additionally, reporting actual costs and not only catastrophic expenditure rates seemed important to me, so the absolute costs incurred by patients could be known in detail and the findings could be interpreted into the context of previous literature more easily.

Cancer financing is complex not only because of the range of treatments involved that require distinct levels of funding, but also because every type of cancer is different in its natural history and treatment course. This means that it is important to study the costs and financial implications of several types of cancer to raise awareness of this range and inform cancer policies. The costs of colorectal cancer have been scarcely studied, with specific catastrophic expenditure rates

described only from Thailand. As its incidence expands, it is important to draw attention to this type of cancer to financially protect future patients.

Rates of catastrophic expenditure in NCDs in L&MICs were reported in a systematic review, with cardiovascular disease and cancer being the ones associated with highest rates, of above 60% of the patients(41). Another systematic review of cancer patients in India described financial toxicity rates of 40% to 84% in the included studies(47). The heterogeneity in methods and definitions prevents an easy comparison across studies.

1.3 Colorectal cancer

1.3.1 Epidemiology and risk factors

Colorectal cancer burden is increasing globally, with highest recent increase of incidence and mortality in L&MIC.

Colorectal cancer is the fourth most incident cancer in the world with 2.17 million new cases in 2019, meaning that the incidence more than doubled in the last two decades (3, 48). Colon and rectum malignancies are the third leading cause of cancer deaths worldwide (1.9 million in 2019) and the second most frequent cause of cancer DALYs (Disease Adjusted Life Years) (2, 48). Age standardised rates are higher in regions with HIC like Australasia and Central Europe but the burden is growing rapidly in L&MIC.

About 75% of colorectal cancers are sporadic and associated with modifiable risk factors, with the remaining being affected by genetic conditions (personal or family history of colorectal cancer)(48). Common environmental risk factors associated with colorectal cancer are alcohol consumption, smoking, high body mass index, sedentary habits and unbalanced diet(48). The increase seen in colorectal cancer incidence seems to be related to increasing exposure to these risk factors worldwide, as well as the growing availability of screening. In countries with high SDI, the incidence and mortality of colorectal cancer has remained stable, whereas in low and middle SDI quintiles they have increased (27). This can be explained, at least partly, by the fact that the populations with

low and middle SDI are experiencing a lifestyle shift where risk factors for colorectal cancer are more frequent, together with increased availability diagnostic tests, explaining the increase in countries with previous low incidence rates.

An increasing incidence in young adults in high SDI quintiles has also been observed in GBD 2019 data(2). There are some reports from L&MIC describing a younger age at presentation of colorectal cancer patients in these settings(49), with some series reporting a mean age at presentation under 50 years old, when the average at a global level is over 60 years old. However, there is a global trend in a decreasing age at colorectal cancer presentation in high and low income settings (2). The fact that young patients are being more and more affected needs to be tackled with research and cancer policy, as this can bring even more negative effects on the structure of these societies where men are commonly “breadwinners”.

The most common hereditary conditions increasing the risk of colorectal cancer are familiar adenomatous polyposis and hereditary nonpolyposis colorectal cancer (Lynch syndrome). There is no strong evidence that genetic features of colorectal cancer would be different across world regions.

1.3.2 Screening, diagnosis and staging

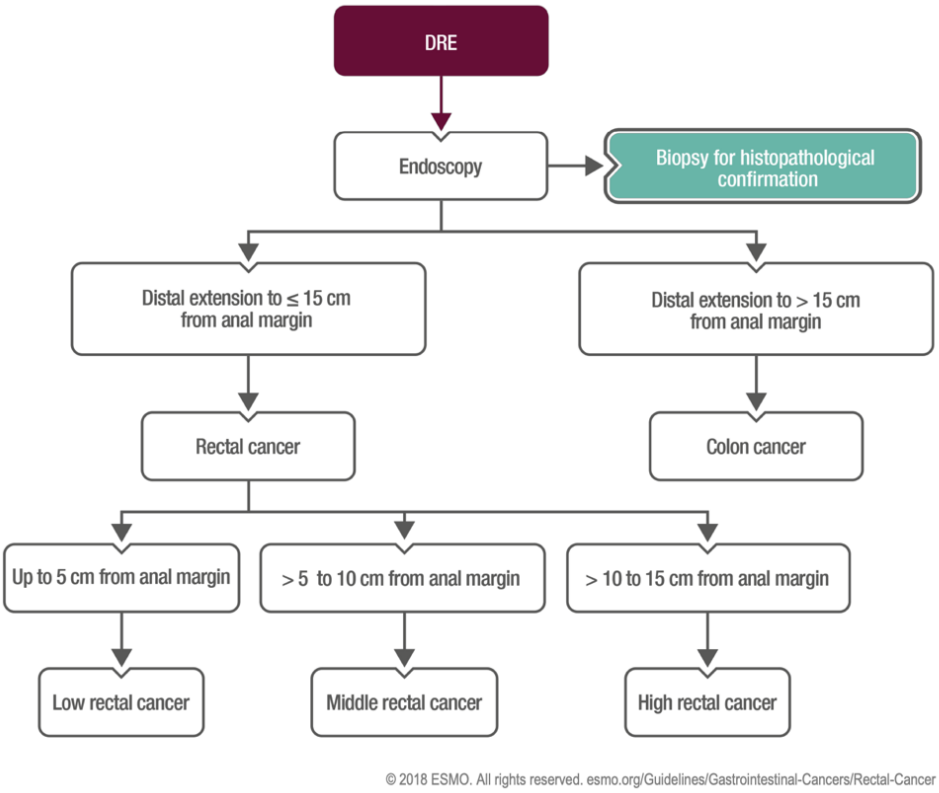
Screening of colorectal is not routinely performed in most L&MIC. The availability of diagnostic colonoscopy and staging CT scan is also constrained.

Colorectal cancer screening programmes often include annual or biennial faecal occult blood test (FOBT) or colonoscopy for early detection of malignant and pre-malignant lesions. Screening programmes are commonly available in HIC but not in L&MIC, as other cancers have been considered to represent a higher burden(50). With the increasing incidence of colorectal cancer in L&MIC, this decision might need to be revisited(51).

The diagnosis of colorectal cancer is usually made through colonoscopy, confirmed by biopsy (see Figure 6). In the cases where the presentation is an emergent admission for occlusion or bleeding, this confirmation might not be possible ahead of a therapeutic intervention. Staging examinations include thorax, abdomen and pelvis computed tomography scan (CT scan), with rectal cancers requiring endoanal ultrasound or pelvic MRI for loco-regional staging as well. In L&MIC these tests are not widely available and sometimes abdominal ultrasound and a chest x-ray are used to assess staging in resource constrained environments(9). A screening test needs to be accessible, acceptable, economically efficient for the population and requires sufficient system capacity to follow-up on its results. Is it arguable that in the absence of these assumptions,

resources are better allocated to health literacy programmes and reduction of risk factors(52).

Figure 6: Anatomical definitions of colon and rectal cancer based on diagnostic colonoscopy.



(From ESMO Clinical Guidance Practice, 2018) (53)

The flowchart describes the diagnosis of colorectal cancer location based on colonoscopy findings, which will then drive the way the tumour is staged and treated. DRE = Digital Rectal Examination.

The staging of colorectal cancer usually follows the American Joint Commission for Cancer guidelines and is the basis of the treatment approach. Figure 7 shows the colorectal cancer stages, indicating the local (T - tumour), regional (N - nodes) and distant (M – metastasis) involvement in each stage.

Figure 7: AJCC 8th edition TNM staging of colon and rectal cancer.

(A) Definition of T (tumour), N (node) and M (metastasis) stages.

TNM Clinical Classification	
T—Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*: invasion of lamina propria[a]
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures[b,c,d] and/or perforates visceral peritoneum
T4a	Tumour perforates visceral peritoneum
T4b	Tumour directly invades other organs or structures
N—Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumour deposit(s), i.e. satellites,[e] in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue *without* regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M—Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s)) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement

(B) Definition of colorectal cancer stage based on TNM status.

TNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Stage			
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0
Stage IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
Stage IIIC	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

TNM, tumour, node, metastasis.

Reprinted from [16], with permission from John Wiley & Sons, Inc.

(From ESMO Clinical Guidance Practice, 2018) (53)

1.3.3 Treatment

The treatment of colorectal cancer is planned according to the AJCC staging system, usually involving surgery with or without chemo or radio therapy for curative cases. Palliative patients are mostly eligible for chemotherapy and supportive care.

The treatment of colorectal cancer is based on the stage and tumour location(53). Treatment for colon cancer without distant involvement generally includes upfront resection surgery, whose extension is determined by tumour location and should include total mesocolon excision to achieve an adequate lymphadenectomy. Adjuvant chemotherapy is only recommended for Stage III cancer and Stage II if there are intermediate risk (stable microsatellites with any of: lymphatic, perineural or vascular invasion, histological grade 3, tumour obstruction, preoperative CEA (carcinoembryonic antigen) >5 ng/mL) or high-risk features (pT4 or multiple intermediate risk factors)(53).

High rectal cancers are treated in a similar manner as their biological behaviour is expected to be comparable to colon cancers, except for the fact that very early rectal cancers (for cT1 N0 with favourable histopathology) are eligible for local excision through a transanal endoscopic approach without mesorectal excision. The remaining high and middle rectal cancers up to cT3 N0 are eligible for rectal resection surgery alone, with total mesorectal excision to ensure complete lymphadenectomy. In cT4 cancers, cT3 with muscularis propria invasion of more

than 5mm, threatened sphincters and nodes are affected, pre-operative neoadjuvant therapy should be considered(53).

Colorectal cancer patients with metastatic involvement can receive treatment with curative intent if they have resectable liver of lung metastases. Palliative treatment is recommended for patients with non-resectable metastases and various treatment modalities might be required for symptom control. Bowel obstruction is usually handled with the formation of a diverting stoma or the use of an endoscopic stent to maintain the continuity of the bowel lumen. Tumour bleeding in need for treatment is more common in left sided colon cancers and rectal cancers, for which haemostatic radiotherapy or surgery might be needed. Palliative chemotherapy is commonly suggested for palliative cases, to slow down progression and control symptoms(53).

From the recommended treatment pathways, one can conclude that surgery is needed for most patients regardless the disease stage, hence the need to better understand the impact of surgical costs in patient's finances. At a global level, it was estimated that surgery could have prevented death in 357 of each 1000 with cancer, reinforcing that the research is important across various types of cancer(9).

1.3.4 Surveillance

Colorectal cancer surveillance requires clinical, radiological and endoscopic follow-up.

Surveillance after treatment for colorectal cancer is recommended for five years and includes periodic measurement of CEA, CT scan assessment and colonoscopy, together with routine clinical assessment. Overall, 30-50% of patients with colon cancer will experience recurrence and might die as a consequence(53). Patients with rectal cancer have higher chances of recurrence and therefore have the highest benefits of clinical follow-up, particularly if the disease stage was advanced at presentation. About 10% of patients can still be salvaged from recurrence(53). Periodic clinical assessment in L&MIC can be a challenge, given the compromised whole system capacity.

1.4 Cancer care in India

1.4.1 Burden and epidemiology of cancer in India

Colorectal cancer is increasing in India and there is a lack of early diagnosis, hence the need for evidence-based strategies for its control and financing.

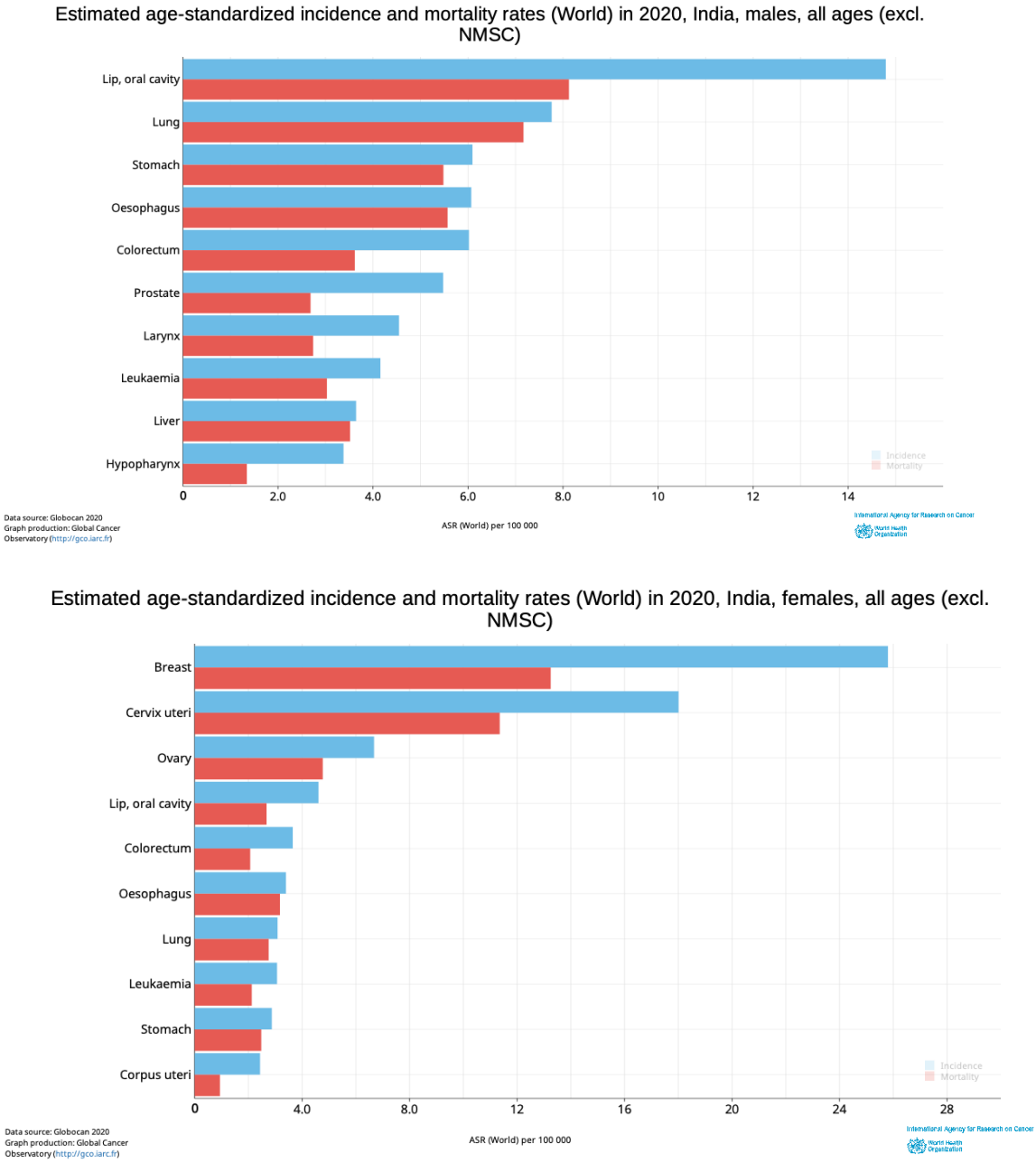
In terms of populations, India is the largest country in the world after China, whose inhabitants account for 17.7% of the global population being divided into 35 states and union territories(28). Although the population has gradually been

moving to cities, the census in 2011 revealed that 70% of the people still live in rural areas(9, 28). The age structure in India is expansive (large young population), with a median age of 26.5 years and life expectancy is around 64 and 68 years of age, for men and women respectively(28). The national expenditure on health is low (around 1% of the GDP) and the density of physicians is insufficient (0.6 physicians per 1000 population) (28, 54). Although infectious diseases are still a cause of concern in India, non-communicable diseases are responsible for 50% of the deaths in the country(28). The burden of cancer is expected to double in the next two decades, with a predicted cancer incidence of 1.7 million in 2035(55).

The most common cancers in India are shown in Figure 8, being oral cavity, lung and stomach cancer in males, and breast, cervical and ovary in women. Colorectal cancer is the 7th most incident cancer in India, with an age-sex adjusted incidence rate of 4.8 (3). Cancer mortality rates are proportionately high in India, as in other L&MIC, being at 68% (55). Cancer accounts for 6 to 10% of all the deaths in the country every year (low percentage but concerning due to high absolute numbers) and 71% of the cancer deaths happen during a person's productive years (30 to 69 years) (28, 55). Data from the National Cancer Registry Programme, Global Burden of Disease and the Million Death Study show that cancer incidence and mortality vary across the states in India, with incidence being higher in more affluent states (probably related to life-style risk factors) and predominantly rural states and less educated people having higher

mortality rates (probably related to barriers accessing treatment) (Figure 9) (56, 57).

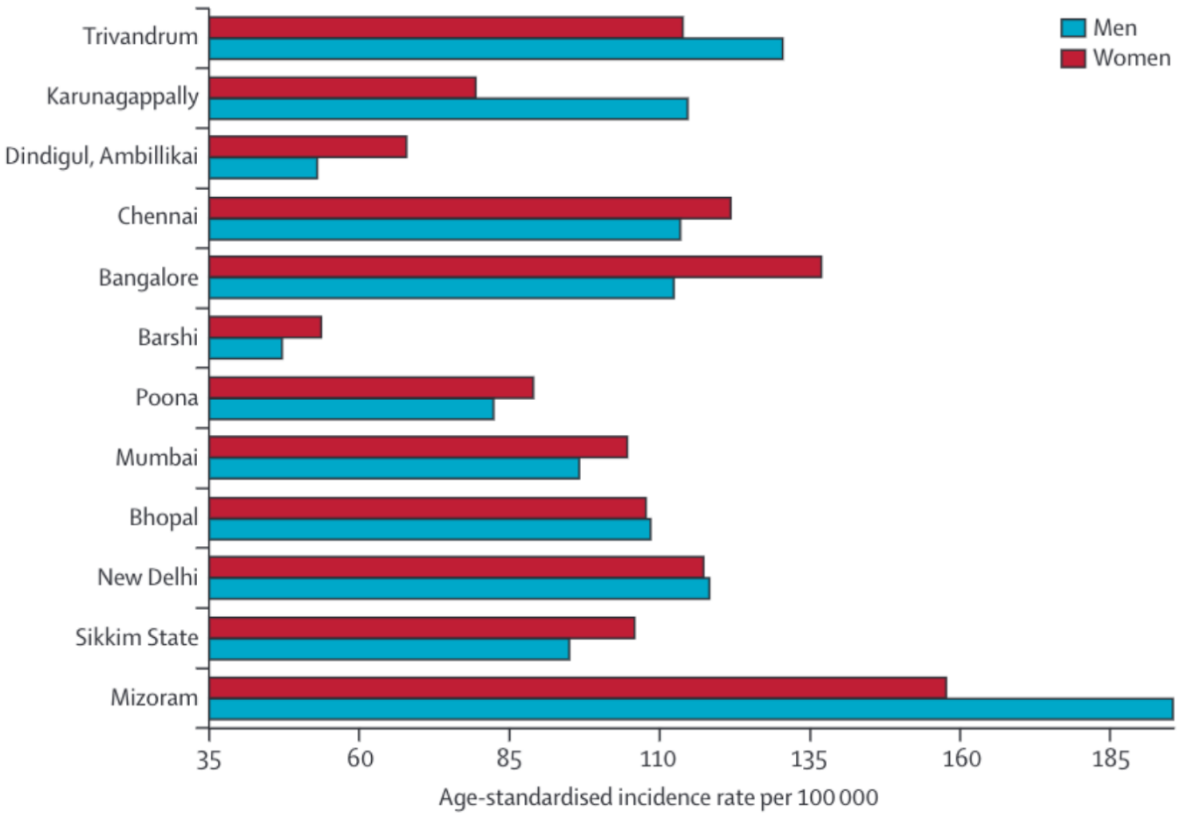
Figure 8: Cancer incidence and mortality in India by cancer type.



(From GLOBOCAN, 2020) (3)

Charts shows incidence and mortality rates for males and females, respectively, all ages excluding non-melanoma skin cancer.

Figure 9: Cancer incidence and mortality varies across states in India.



(From Million Death Study, 2015, p. e208) (55)

Chart shows regional variations in the age-adjusted incidence rates of cancer in men and women in different regions of India.

1.4.2 Structure of cancer care in India

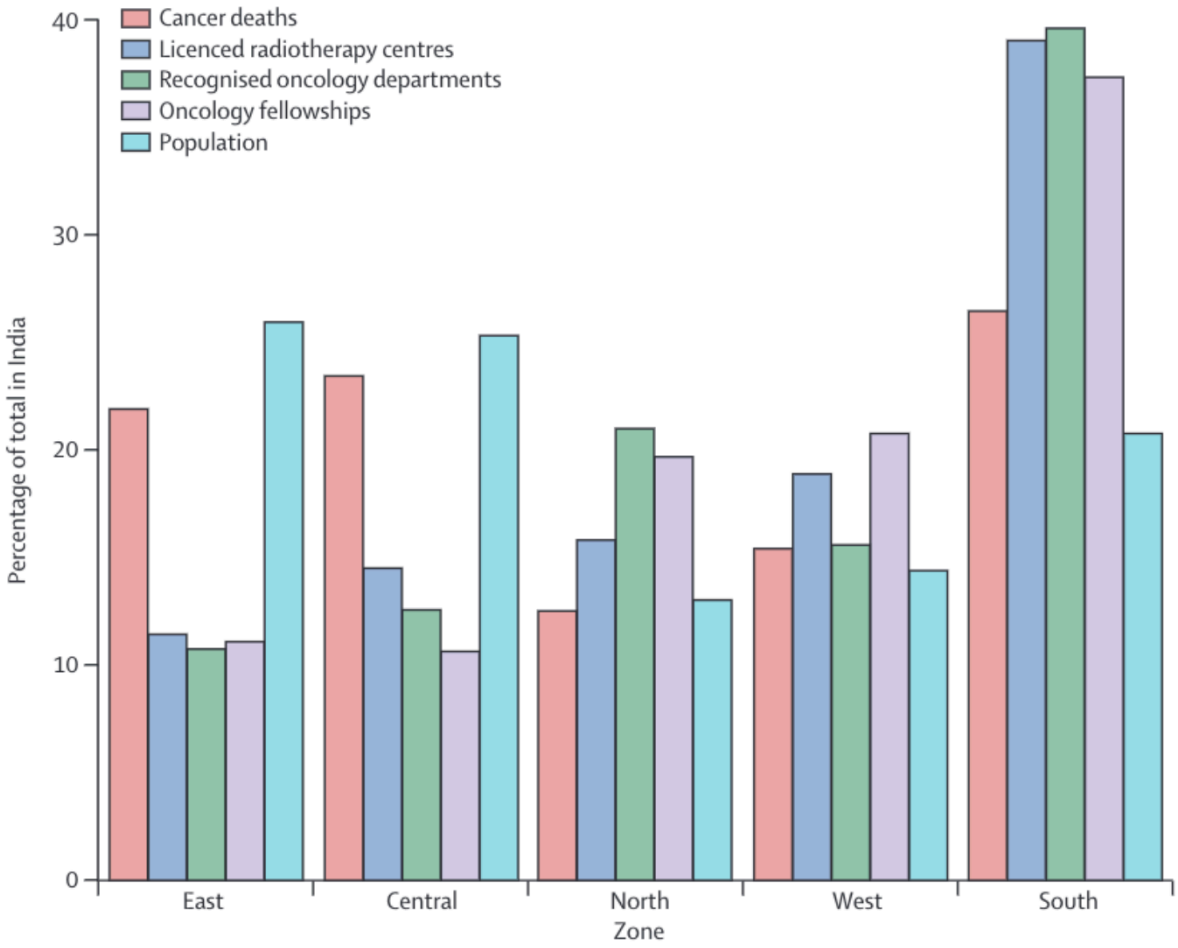
Health and cancer care in India is largely provided by private or charity funded facilities with only 37% of hospitals being public. There are asymmetries and shortages in cancer treatment availability across India.

Similarly to the geographic variation in incidence and mortality, there is variation in treatment availability across India. As the costs of cancer drugs are very visible to the population, policies have been focusing on them. Radiotherapy and surgical services, equally crucial to the success of cancer treatment, are lacking, particularly in the east and central regions of India (Figure 10), creating asymmetries in access to care and forcing patients to travel long distances to get treated (55). The public health expenditure per person varies, being 93 Indian Rupees (INR) in Bihar and 630 INR in Himachal Pradesh in 2005. The public health expenditure per capita in India has been increasing on the last few decades, but regional and state asymmetries are still evident(58). This generates and imbalanced resource allocation and creates inequality in access to good quality services(59).

The concept of healthcare worker in India includes a diverse group of providers, namely trained doctors, Ayurveda practitioners, AYUSH (yoga, unani, siddha, and homoeopathy), nurses, dentists, midwives, pharmacists, technicians, community health workers, accredited activists for social health, registered medical practitioners without formal medical training, traditional medicine practitioners and

faith healers. It is therefore difficult to have an accurate idea of the density of healthcare workers but estimations point to 20 healthcare workers per 10,000 population, of which only 3.8/10,000 population are qualified physicians(28).

Figure 10: Population, cancer deaths, radiotherapy centres, oncology departments and fellowships available across regions of India.



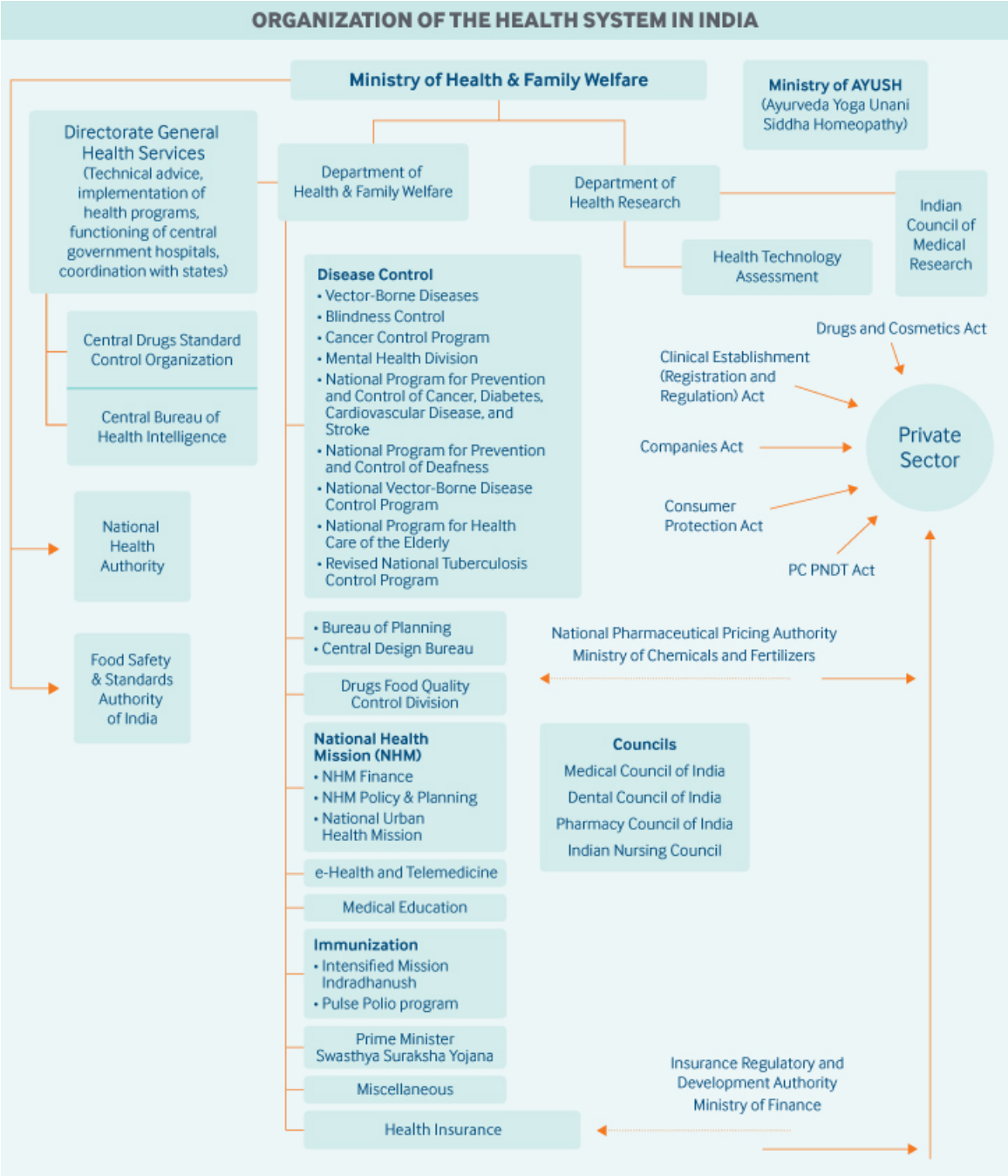
(From Million Death Study, 2015, p. e208) (55)

Chart shows the distribution of the population (in 2011), cancer deaths (in 2010), oncology training positions, oncology departments and radiotherapy centres in five regions of India.

In 1975 the Central Government of India launched the National Cancer Control Programme that aimed to support primary and secondary prevention of cancer, advance care delivery in the existing facilities and improve palliative care(28).. Figure 11 shows how the Cancer Control Programme fits into the structure of the healthcare system in India. This programme included a national registry that identified the need to create cancer centres to improve cancer outcomes, resulting in the formation of 27 cancer centres in India, additional funding for cancer services in other 80 public hospitals and at local health practices(28).

Furthermore, Onconet was created to provide telemedicine services to peripheral hospitals from professionals based at cancer centres. Although these are steps towards cancer control in India, the existing cancer centres appear to be insufficient to cover current needs. There is only one licensed CT scanner per 500 000 population in India, the ratio of oncologists to cancer patients in India is 1:16,000, as opposed to a ratio of 1:100 in western countries like the USA (60) and there is a major shortage in radiotherapy services with only 545 machines existing in the country(19). General surgeons in district hospitals undertake up to 80% of the cancer surgery in India, where new technologies, techniques and infrastructure are usually not available, leading to suboptimal outcomes. The lack of an organised system of referrals and centralisation for complex cancer surgeries results in fragmentation of care(19).

Figure 11: Organisation of the Healthcare System in India.



(From International Health Care System Profiles: India, Commonwealth Fund, 2020) (61)

There are three main types of cancer care providers in India, government hospitals, charity hospitals and private hospitals. The Centre for Disease Dynamics, Economics and Policy reported that in 2021 there were 69,265 hospitals in India, of which 62.8% were private and 37.2% were public, with obvious consequences for system and individual costs(62). In government funded hospitals, treatment tends to be free or at least much cheaper but the capacity is limited and waiting lists are often long. The charity sector applies charges but usually favours poorer patients, charging lower fees, providing discounts, or facilitating access to government funding schemes. The private sector fully charges patients for their care, although patients might have insurance or access government schemes to pay for the treatment or at least part of it. The fees applied to patients in charity and private hospitals are grouped into two categories, a general category and premium category (more expensive but higher quality care)(61). The chronic underfunding of the governmental health sector, along with general perceptions that public hospitals provide lower quality care, has led to the emergence of an expensive private sector where charges are unregulated, escalating inequity in cancer care access(19).

A systematic review of quantitative and qualitative studies identified the barriers for cancer care access in L&MIC. The main obstacles found were (1) health literacy (knowledge about symptoms, risk factors and healthcare services navigation), (2) cancer stigma (fear or shame of a cancer diagnosis), (3) financial issues (inability to afford diagnostic tests or treatment) and (4) sociocultural (obstructive behaviour from family members)(63). However, little data exists in

the barriers for patients who already have a cancer diagnosis to complete their optimal treatment plan. Financial and non-financial barriers need to be explored, as money concerns are apparently not the only factor contributing to impaired optimal cancer care.

1.4.3 Out-of-pocket payments for cancer care in India

a) Cancer care in India can be funded through public funds, private and employer-provided insurance, personal out-of-pocket payments, with small amounts being raised from non-profit organisations or other external sources.

b) The unregulated private sector charges high fees and around 60% of the population is not covered by any type of pre-paid mechanism, being forced to pay out-of-pocket for cancer care.

Several central and state government funding schemes have been implemented in India aiming to protect populations from financial toxicity. However, the eligibility criteria are sometimes quite specific, the type of treatments covered varies across schemes, budgets are heterogenous and sometimes only particular diseases are included. As examples:

a) The Vajpayee Arogyashee Scheme was implemented in Karnataka state, funding up to 150,000 Indian Rupees per family of five to pay for malignant conditions in a number of selected hospitals(64).

b) The Chief Minister's Comprehensive Health Insurance scheme, initiated in Tamil Nadu, provides financial help and free transport to families living below the poverty line who need life-saving procedures, namely for cancer, with a maximum budget of 400,000 rupees within 4 years(65).

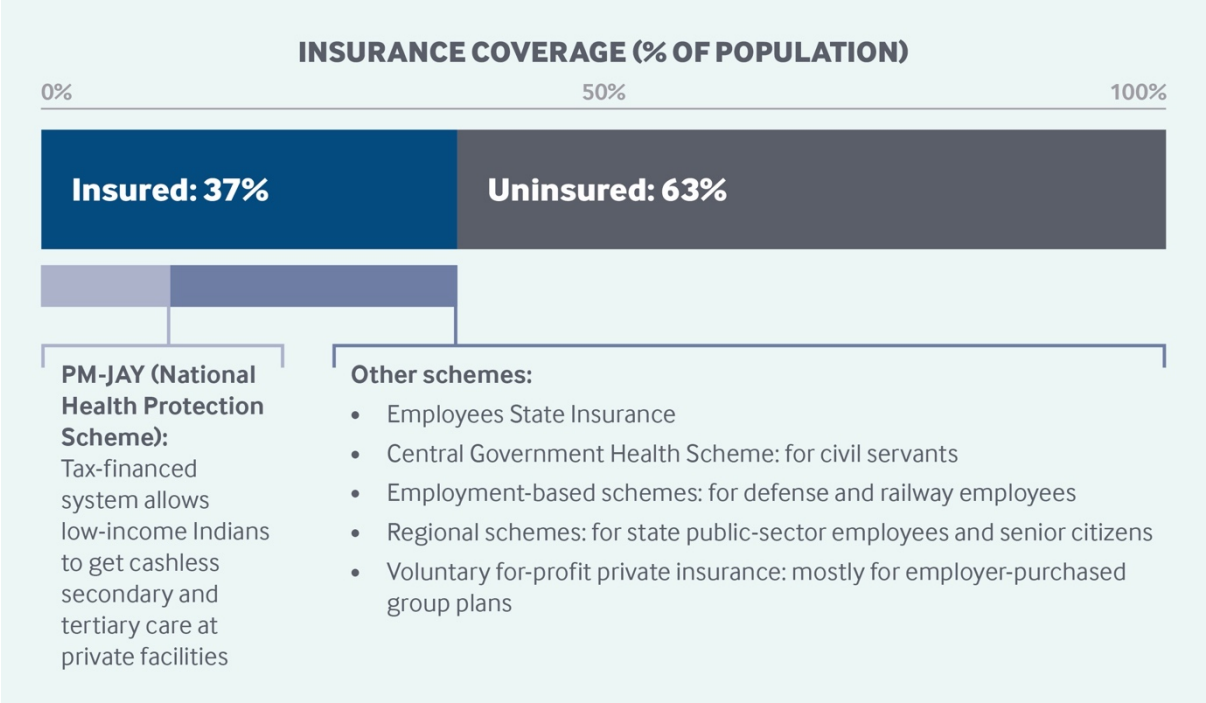
c) The Ayushman Bharat scheme (a component of the Pradhan Mantri Jan Arogya Yojana [PM-JAY] health program) is tax-funded. It covers up to 500,000 rupees per family per year for hospitalization in private and public facilities, for which families are eligible depending on their characteristics, such as age, occupation and geographical location (rural/urban). Households that hold a Below Poverty Line (BPL) card can apply for a low premium health insurance covered by this scheme(66).

There are mixed insurance schemes to which both users, their employees and the government contribute to, diluting the amount given by each part to protect patients in need for healthcare. For example, the Employees' State Insurance Scheme to which industry workers are eligible and where employees contribute with 0.75% of their wages, the employer contributes with 3.25%, with the government paying for up to 1/8 of the medical expenditures up to 1,500 rupees per capita per year(67).

There is heterogeneity in the availability of funding schemes and co-paid insurance programs that patients can benefit from. The lack of awareness and knowledge about these schemes, leaves a large proportion of the population

without any pre-paid health coverage (Figure 12), exposing these households to out-of-pocket payments that can be catastrophic.

Figure 12: Insurance coverage of the population of India.



(From International Health Care System Profiles: India, Commonwealth Fund, 2020) (61)

The overall public health expenditure in India is among the lowest in the world and more then three quarters of the health spending in India is paid privately and around 70% of the healthcare being paid through OOPP(59, 68). Most of these OOPP are directed to the private healthcare, as it is a major provider in India. In 2004, the National Sample Survey Organisation reported that 6.2% of Indian households, corresponding to 63.2 million people fell into poverty due to healthcare OOPP(68).

Overall, it is expected that only 15% of the population can pay for high quality care, 30% can co-pay for medical care and access a moderately good quality service, but 55% find it hard to subsist and meet daily expenses, let alone pay for expensive cancer treatments(28).

Although the average cost of treatment for a typical case of cancer was estimated to be around 36,812 rupees (593 USD), the real cost of cancer care is hard to unpick as it depends on several factors like socioeconomic status, geographical location, type of cancer and stage at presentation(28, 68). The average annual income is estimated to be around 1219 USD, and almost a third of the population lives with less than 0.4 USD per day, hence the difficulty of many households in supporting cancer costs(68). Households where a member is affected by cancer were proven to incur higher catastrophic health spending, when compared to a control group(69). Low-income and rural populations are generally found to be at highest risk of catastrophic expenditure when affected by cancer(70).

It seems that there is a common trait in South Asian countries for households affected by non-communicable diseases to make higher OOPP for healthcare than countries affected by communicable conditions(71). Data from a national survey delivered in 2014 showed that OOPP for hospitalization was highest in cancer patients, followed by heart diseases(72). A recent systematic review on financial toxicity in cancer care in India, looked at 22 studies reporting the costs of cancer in India and other measures of financial toxicity (e.g. coping mechanisms,

social impact, catastrophic expenditure, OOPP). Rates of catastrophic expenditure varied between 62% and 84% but none of the studies reported data on colorectal cancer(47).

1.5 Knowledge gaps and thesis aims

1.5.1 Chapter 2

There is a lack of robust studies investigating the costs and the financial burden of surgical interventions for cancer care in HIC, and almost absent data from L&MIC(19). Given that cancer is a complex disease requiring complex health pathways from prevention to palliative care, it is a prism for understanding and responding to health-system challenges(8). The proportion of cancer patients paying out-of-pocket for their treatment in unknown and surgery is expected to play a major role as it's needed in most cases. My second chapter aimed to describe out-of-pocket payments for cancer surgery across income country groups.

1.5.2 Chapter 3

Research into the cancers that are not at the top of public health priorities in India (breast, cervical and oral) is lacking(73). The complexity of cancer costing is as high as the complexity of the disease and more evidence on the societal and individual financial burden of cancers in India is needed(19). Most studies do not describe the components of the overall cost. Although colorectal cancer incidence is increasing in India, real costs have not been published and the financial burden on patients and households is unknown(28). My third chapter aimed to determine costs, catastrophic expenditure and treatment adherence rates in a cohort of patients with a treatment plan for colorectal cancer.

1.5.3 Chapter 4

A systematic review of quantitative and qualitative studies identified the barriers for cancer care access in L&MIC (63), but little data exists in the barriers for patients who already have a cancer diagnosis to complete their optimal treatment plan. Treatment adherence is crucial to optimise outcomes; a healthy population is a productive one, and a productive population creates national wealth and social wellbeing(7). Qualitative work to overcome barriers in cancer care pathways is scarce(73). Costs of colorectal cancer might influence patients' ability to complete a treatment plan but the multiple factors influencing patient's decisions and outcomes are unknown. My fourth chapter aimed to assess the views and perspectives of colorectal cancer professionals on barriers and facilitators for colorectal cancer care.

1.6 COVID-19 related considerations

My PhD was delivered during the emergence of the COVID-19 pandemic, which raised initial concerns about the continuity of elective cancer surgery across the globe and forced research to target COVID-related questions. The impact of the pandemic in my PhD work is discussed within the data chapters. I took part in the response to COVID-19, with a leading role in the COVIDSurg Collaborative. I participated in the delivery of four cohort studies between 2020 and 2022, that resulted in high impact publications and contributed to changes in clinical guidance, with an extensive media coverage. Major contributions of the Collaborative to surgical practice included: assessing the mortality rates in surgical patients with SARS-CoV-2 infection(74), the impact of preoperative testing and COVID-free operative pathways in postoperative complications (75, 76), the best timing to perform surgery after a SARS-CoV-2 infection(77), the effect of preoperative isolation in postoperative outcomes(78), the impact of the pandemic in cancer care(79, 80), the scale of surgical cancelations(81) and the relevance of preoperative vaccination for surgical patients(82).

2 Global variation in out-of-pocket payments for cancer surgery

2.1 Abstract

Introduction: Cancer is one of the most expensive global health challenges and surgery is needed in most cases. This study aimed to describe out-of-pocket payments for cancer surgery across income country groups.

Methods: International prospective cohort study of consecutive patients undergoing cancer surgery in October 2020. Out-of-pocket payments (OOPP) made to pay for the majority of cancer surgery were compared across country income groups. The use of further funding sources were described: public funds, insurance or other. A logistic regression model was used to identify variables independently associated with OOPP in low- and middle-income countries.

Results: Of the 24,498 patients included from 108 countries, 6.4% (1571/24498) made OOPP to pay for the majority of their cancer surgery. OOPP rates varied across country income groups: 0.5% (89/16680) in HIC, 5.7% (272/4784) in UMIC, 38.6% (1008/2614) in LMIC and 48.1% (202/429) in LIC. Besides country income, male sex (OR 1.16, 95%CI 1.02-1.32, p=0.024) and elective surgery (OR 1.31, 1.04-1.67, p=0.022) were associated with OOPP for cancer surgery.

Discussion: Patients accessing cancer surgery in L&MIC are lacking financial protection. Investment in pre-paid mechanisms for elective surgeries is needed. The interpretation of gender-related risks need a better understanding of the ability to pay out-of-pocket and access care.

2.2 Introduction

Achieving Universal Health Coverage for all is one of the Sustainable Development Goals established by the World Health Organisation, that implies providing the necessary healthcare to all individuals while protecting them from financial hardship(25). Monitoring global and country level UHC requires measuring out-of-pocket payments and their consequences, in the form of catastrophic expenditure (OOPP for healthcare above a threshold of household income) and impoverishing expenditure (OOPP for healthcare pushing households below the poverty line). The global rate of catastrophic health expenditure is 13.2% of the world's population, meaning that 996 million people suffer from it (31).

Cancer is one of the non-communicable diseases associated with highest rates of catastrophic health expenditure and surgery is often part of the treatment, especially when cancer is curable. Catastrophic expenditure attributable to accessing surgical care has been estimated to affect 81.2 million people and 3.7 billion people are expected to be at risk of catastrophic expenditure if they require surgical and anaesthetic care (21, 83). Although these are the available estimates, there is a lack of real-world data on OOPP for surgery, particularly cancer surgery, at global level.

The last WHO report on financial protection showed that catastrophic health expenditure rates were highest in middle income countries, while impoverishing

expenditure was highest in low-middle and low-income countries(31). The variation of OOPP for surgical care across income settings is unknown. The primary aim of this study was to describe out-of-pocket payments for cancer surgery across income country groups. Considering that OOPP rates were expected to be higher in L&MIC, the secondary aim was to identify characteristics of patients and procedures associated with higher rates of OOPP in L&MIC, to inform decision making in these settings.

2.3 Methods

2.3.1 Research questions

a) What is the proportion of patients paying out of pocket for the majority of the cost of cancer surgery? Does this vary across income country groups?

Considering that OOPP rates are expected to be higher in low and middle income countries (L&MIC), a second research question seems important to inform decision making:

b) What are the features independently associated with OOPP for cancer surgery in L&MIC?

These two research questions are mapped to this chapter's aims, driving the primary and secondary analysis.

2.3.2 Study design

This chapter focuses on a pre-planned analysis of the SurgWeek study, that was designed to address a few different research questions. The SurgWeek study was a prospective international cohort study conducted by the NIHR Global Health Research on Global Surgery and I was part of the study's central management team.

2.3.2.1 Background to the study design and development

The SurgWeek study was delivered in October 2020, following another international cohort study (COVIDSurg) that assessed postoperative outcomes in patients undergoing surgery and who had a diagnosed SARS-CoV-2 infection within 7 days before and 30 days after surgery. I was also part of the central management team for this study, participating in design, delivery, interpretation of findings and publication. The COVIDSurg study showed that patients undergoing surgery and who had a SARS-CoV-2 infection has unexpectedly high rates of mortality and pulmonary complication rates, being published in The Lancet in June 2020(74). Simultaneously, our central management team coordinated another study (COVIDSurg-Cancer) focused on patients with a decision for curative cancer surgery. This study concluded that lockdowns had a negative

effect in cancer surgery cancellations (79, 80) and assessed the impact of pre-operating swab testing and COVID-free surgical pathways (75, 76) on postoperative outcomes, providing evidence for their implementation worldwide.

As the first COVID-19 waves were coming to an end in many countries, there was an appetite among the research network to research new questions, not all related to COVID-19, which were the focus of the SurgWeek study. One of these questions underpins this study:

- What is the global variation in out-of-pocket payments for surgery?

Other questions addressed SARS-CoV 2 management related to surgery.

This study seemed a unique opportunity to address this topic that has been prioritised by The Lancet Commission on Global Surgery and for which global real-world data does not exist(21). The fact that consecutive patients undergoing surgery (with and without a SARS-CoV-2 infection) needed to be included to study the COVID-19 related research questions, allowed this network to contribute to relevant topics in Global Health research. For the purpose of this chapter, only cancer surgery was included, for the benefit of co-interpretation with the following chapters of this thesis.

2.3.3 Study setting

Any hospital where surgery was performed could participate in the SurgWeek study. Surgery was defined as any procedure routinely performed in an operating theatre by a surgeon. The study was disseminated to an international network of

surgeons, anaesthetists, trainees and medical students to promote inclusive and wide participation. The study was led by the central management team from Birmingham (UK), of which I was part. Hospitals were required to collect data from consecutive patients undergoing surgery of any type, for a minimum period of one week (maximum four weeks) during October 2020. Each participating site could include patients being operated on for one or more surgical specialties. Mini-teams of local collaborators were formed to collect data from each included speciality within the participating hospitals. A hospital lead was designated locally to coordinate study approval submissions and manage data collection teams, ensuring reliable study processes. The hospital leads were then connected with national leads who were in direct contact with the central management team on study set-up, delivery and problem solving. National leads and leads of international and country specific surgical societies and groups were part of the study's Dissemination Committee, of which I was the chair.

2.3.3.1 My role in the central management team

As a chair of the Dissemination Committee, I coordinated the communication with these overarching leads and study promoters, to enhance participation. I also took part in the study protocol development, data base building, team registration and local troubleshooting, data cleaning tasks, data analysis and interpretation and, finally in the publication of the results, being a corresponding author on one of the papers.

2.3.4 Study approvals

The study was registered on clinicaltrials.gov (registration number NCT04509986) and approvals were obtained as per country level and local regulations. Being an observational cohort study without changes to normal care pathways, some countries do not require ethical approval (e.g. approved as a clinical audit in the United Kingdom), some require only local ethical approval at hospital level (e.g. Portugal, Spain) and other require national level approval (e.g. Australia, Sweden, Brazil, India). National leads oversaw national approval submission whenever needed and hospital leads had ultimate responsibility of ensuring the necessary approvals were granted at the time of data entry. Informed consent for data collection was obtained whenever required according to regulations in place.

2.3.5 Site enrolment

All the participating sites registered through a REDCap platform and were issued logins for data upload after confirming that the appropriate approvals were in place. The hospital lead was responsible for local training and monitoring of data collection, namely inclusion of consecutive eligible patients and data entry by the deadlines. In order to help local teams understanding methods and definitions, a handbook was made available by the central management team, where all the datapoints and categories were defined, included and excluded procedures were listed and frequently asked questions were included.

2.3.6 Sample size considerations

As explained above, the research question addressed in this chapter was not the primary aim of the SurgWeek study and therefore a sample size calculation was not performed ahead of this analysis. However, I present an ad-hoc sample size calculation, based on the OOPP rates found in the study to estimate the minimum number of patients that would have been needed to detect those differences across groups. This chapter explores OOPP rates across four country income groups and therefore a sample size estimation can be drawn for comparing any combination of two income groups. Table 1 shows the minimum number of patients needed to detect the observed differences between all combinations of two of the four income groups. According to these estimations, the ad-hod estimated sample size is 567 patients, with a 90% power and 95% confidence level.

Table 1: Ad-hoc sample size estimations for the analysis of OOPP across country income groups.

	HIC	UMIC	LMIC	LIC
HIC	--	229	18	12
UMIC	229	--	29	18
LMIC	18	29	--	567
LIC	12	18	567	--

2.3.7 Patient inclusion and exclusion criteria

Consecutive patients undergoing elective or emergency operations for cancer were included, during at least one week in each participating hospital. This included day-case and inpatient surgery, adults and children.

A list of excluded procedures was circulated to all collaborators, including procedures performed for diagnostic purposes only (e.g. breast biopsy) and endoscopic procedures (e.g. colonoscopy) (full list available in Supplementary Table 1). These procedures were excluded as they were either classified as minor and/or not routinely performed in theatre by a surgeon at a global level.

2.3.8 Study outcome

2.3.8.1 Out-of-pocket payments for cancer surgery

The primary outcome of this study was out-of-pocket payments for cancer surgery, defined as the majority of the cost of surgery being paid out-of-pocket by patients (datapoint collected as described in the box below). Out-of-pocket payments were defined as payments made directly by the patients at the time-of-service use i.e. at the time of the cancer surgery. The cost of cancer surgery included the cost of the infrastructure use, staff time and other items necessary to deliver surgical care during the admission for surgery. Non-medical (travel, accommodation, food), indirect costs (income loss) and costs of subsequent admissions were not included in this definition.

Other funding sources to pay for the majority of cancer surgery, including government funds (e.g. national health system), health insurance (pre-paid by the patient or their employer), external funds and grants or other providers. This was collected within the same datapoint, as shown below:

How was the majority of the cost of surgery covered?
[a] Insurance provided by the government (national or regional level)
[b] Insurance provided by employer (or household members' employer)
[c] Insurance that the patient has privately arranged and paid for
[d] Insurance but unknown how this was arranged
[e] External funds or grants awarded by charities/NGOs
[f] Out of pocket payments (patient paid the hospital directly)
[g] Other

Only one payment method was reported for each patient, as the funding source to pay for the majority of the cost of cancer surgery. This was reported by the research teams collecting data locally, at the time of surgery. By default, the research teams were expected to know how the surgery was paid for, but in case of doubt the teams were encouraged to check with the patient and/or their relatives.

2.3.9 Schedule of assessments

Patients were identified for inclusion in the study and baseline data was collected at the time of surgery. Follow-up data was collected at 30 days after surgery, from clinical records whenever possible, or by direct patient assessment if this best met local treatment pathways.

2.3.10 Data variables and definitions

Patient characteristics: age at the time of surgery, categorised into <40 years, 40 to 69 and 70 or above; sex (male or female); pre-operative risk according to the ASA physical status(84) (grades are described in Table 2 and were grouped into grades 1-2 [no comorbidities or minor comorbidities] and grades 3-5 [severe comorbidities]); peri-operative cardiac risk assessment as per the revised cardiac risk index(85) (full score parameters in Table 3, categorised into 0 for low cardiac risk, 1-2 for mild cardiac risk and >/=3 for high cardiac risk).

Characteristics of surgery: urgency of surgery (defined as elective when performed during a planned admission or emergency when performed during an unplanned admission); surgical procedures were categorised into Bupa grades as major (if major and complex major surgery) and minor/intermediate otherwise; surgical intent (curative or palliative), surgical approach (planned open surgery, planned and performed as laparoscopic, minimally invasive surgery converted to open, hybrid surgery) and surgical specialty (categorised as per surgical oncology disciplines: colorectal, hepatobiliary, oesophagogastric, urology, gynaecology,

head & neck, neurosurgery, spinal, vascular, cardiac, thoracic, orthopaedics, plastic, breast, endocrine, ophthalmology, dentistry, other procedures within general surgery, other surgeries).

Table 2: ASA physical status grades.

ASA grade	Definition
Grade 1	Healthy person
Grade 2	Mild systemic disease
Grade 3	Severe systemic disease
Grade 4	Severe systemic disease that is a constant threat to life
Grade 5	A moribund person who is not expected to survive without the operation

Table 3: Revised Cardiac Risk Index score.

RCRI score items	Weight on total score
Intraperitoneal or intrathoracic surgery	1 point for patients undergoing cardiac, gastrointestinal, general, gynaecology, hepatobiliary, thoracic, urology, or vascular surgery.
History of ischemic heart disease	1 point
History of congestive heart failure	1 point
History of cerebrovascular disease	1 point
History of diabetes mellitus treated with insulin	1 point
History of chronic kidney disease (creatinine > 176 µmol/l^{-1})	1 point

If the RCRI score is zero, the risk of a major cardiac complication in the first 30 days after surgery is 0.5%, being 1.3% in patients with a score of one, 4% for a score of two and 9% for score of three or more (85).

2.3.11 Data handling and analysis

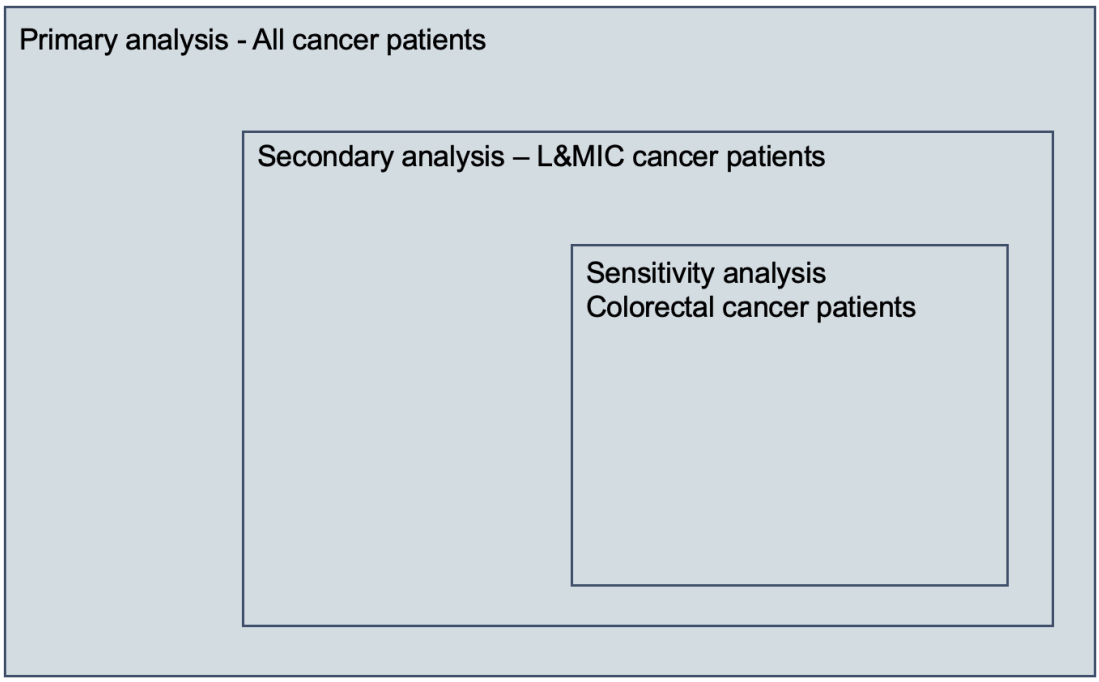
Given the nature of multicentric international data, several checks were performed to chase completeness and ensure consistency across datapoints. This was done through semi-automatised data reports generated on REDCap and sent to local collaborators for data checking and completion. The data was then handled and analysed in *R studio* and statistical software (version 4.1.1).

Primary analysis - Payments for cancer surgery globally: Out-of-pocket payments and other funding sources to pay for cancer surgery presented by income group. Categorical data were presented with absolute frequencies and percentages. 95%CI around the main outcome (OOPP) were given for the different income groups. This dataset did not include any continuous variables.

Secondary analysis - Characteristics of patients paying out-of-pocket in L&MIC: Characteristics of patients paying out-of-pocket in low-middle income countries (unadjusted and adjusted analysis). Unadjusted analysis of the association between categorical variables was performed with Chi-square tests. Random effects logistic regression models were used for adjusted analysis, as I considered that fixing effects on a variable wasn't necessary. However, in future analysis, fixing effects on country or hospital might be considered. The models looked at OOPP as an outcome and included pre-specified patient, disease and settings' features that could be influencing the fact that the outcome is observed in a particular patient.

Sensitivity analysis: an analysis of colorectal cancer patients was conducted to explore OOPP in this type of cancer, which will be the focus of the next two chapters. Figure 13 shows the denominators for each analysis.

Figure 13: Diagram of the patients included in each analysis in chapter 1 (primary, secondary and sensitivity).



2.4 Results

2.4.1 Patients

A total of 24498 cancer patients were included from 1332 hospitals in 108 countries. Most of the patients were adults, with only 1.5% (370/24498) being children (aged under 18 years). The majority of the patients were aged between 40 and 69 years old (57.8% [14173/24498]). Approximately half of the patients were female (54.5% [13355/24498]) and the remaining were male (45.5% [11143/24498]). Patient pre-operative risk was assessed through the ASA grade and the Revised Cardiac Risk Index. 64.9% [15909/24498] of the patients were classified as ASA grade 1-2 (mild comorbidities) and 34.7% [8508/24498] as ASA grade 3-5 (severe or life-threatening comorbidities) (missing n=9). The revised cardiac risk index was zero in 8432 patients (34.4%), one to two in 15256 patients (62.3%) and three or higher in 803 patients (3.3%) (missing n=7).

2.4.2 Settings

Data was collected from all country income groups, with 68.1% (16680/24498) being from high-income countries, 19.5% (4784/24498) from upper-middle income countries, 10.7% (2614/24498) from lower-middle income countries and 1.7% (420/24498) in low-income countries. The number of patients and hospitals

by country income groups is shown in Table 4. The highest recruiting countries per income group were: United Kingdom, Italy and the United States of America (high-income group); Turkey, Brazil and Colombia (upper-middle income group); India, Egypt and Pakistan (lower-middle income group) and Ethiopia, Syria and Sudan (low income group).

2.4.3 Type of cancer and procedures

The most common type of cancer was colorectal cancer (4576/24498 [18.7%]), followed by breast (3994/24498 [16.3%]) and urological cancers (3099/24498 [12.7%]). A full list of the included surgical procedures is available in Supplementary Table 2. The majority of the surgeries were elective (92.2% [22580/24498], missing data n=1) and major procedures (72.9% [17868/24498], missing data n=3). The intent of the surgery was curative or diagnostic in 89.0% of the patients (21803/24498) and palliative in 11.0% (2672/24498) (missing data n=23). The operative approach was planned and performed as open in 65.1% of the patients (15946/24498), as minimally invasive in 31.5% (7716/24498) and as hybrid approach in 1.2% (285/24498), with 2.2% of the patients (549/24498) seeing their minimally invasive surgery converted to an open procedure (missing data n=2).

Table 5 displays the urgency of surgery, surgical grade and surgical intent by specialty. Of note, emergency surgery was most frequent in spinal surgery

(33.7% [61/180]), neurosurgery (22.5% [186/822] and cardiac surgery (20.7% [6/29]), whereas dentistry, breast, endocrine and plastic surgery had the highest rates of elective surgery (100%, 99.5%, 99.1% and 99.1%, respectively). The specialties where curative/diagnostic surgery was most frequent were breast, endocrine and plastics (98.1%, 97.5% and 96.5% respectively), with higher rates of palliative surgery in spinal, orthopaedics and vascular surgeries (48.9%, 33.3% and 24.6% respectively).

Table 4: Number of patients included from each country and income group, ordered by the total amount of patients included per country.

Country	High income	Upper middle income	Lower middle income	Low income	Total of patients per country
Un ted K ngdom of Gr eat Br ta n and Northe rn Ire and	3506 (21.0)				3506 (14.3)
Ita y	2374 (14.2)				2374 (9.7)
Un ted States of Amer ca	1817 (10.9)				1817 (7.4)
Spa n	1705 (10.2)				1705 (7.0)
Germany	1015 (6.1)				1015 (4.1)
Ind a			913 (34.9)		913 (3.7)
Turkey		847 (17.7)			847 (3.5)
Japan	788 (4.7)				788 (3.2)
Portuga	633 (3.8)				633 (2.6)
Braz		584 (12.2)			584 (2.4)
France	560 (3.4)				560 (2.3)
Canada	519 (3.1)				519 (2.1)
Saud Arab a	492 (2.9)				492 (2.0)
Austra a	490 (2.9)				490 (2.0)
Co omb a		482 (10.1)			482 (2.0)
Egypt			466 (17.8)		466 (1.9)
Serb a		463 (9.7)			463 (1.9)
Argent na		367 (7.7)			367 (1.5)
Roman a	343 (2.1)				343 (1.4)
Pak stan			323 (12.4)		323 (1.3)
Greece	286 (1.7)				286 (1.2)
Mex co		272 (5.7)			272 (1.1)
Russ an Federat on		271 (5.7)			271 (1.1)
Peru		270 (5.6)			270 (1.1)
Austr a	257 (1.5)				257 (1.0)
Ph pp nes			249 (9.5)		249 (1.0)
Indones a		231 (4.8)			231 (0.9)
Sweden	183 (1.1)				183 (0.7)
Nether ands	181 (1.1)				181 (0.7)
Ire and	164 (1.0)				164 (0.7)
N ger a			164 (6.3)		164 (0.7)
Eth op a				155 (36.9)	155 (0.6)

Country	High income	Upper middle income	Lower middle income	Low income	Total of patients per country
Ma ays a		147 (3.1)			147 (0.6)
Morocco			145 (5.5)		145 (0.6)
New Zea and	142 (0.9)				142 (0.6)
Croat a	140 (0.8)				140 (0.6)
Syr an Arab Repub c				126 (30.0)	126 (0.5)
Lebanon		123 (2.6)			123 (0.5)
Jordan		118 (2.5)			118 (0.5)
Sw tzer and	108 (0.6)				108 (0.4)
Ukra ne			103 (3.9)		103 (0.4)
Ch e	85 (0.5)				85 (0.3)
S ngapore	85 (0.5)				85 (0.3)
Paraguay		79 (1.7)			79 (0.3)
Iran (Is am c Repub c of)		76 (1.6)			76 (0.3)
Ghana			74 (2.8)		74 (0.3)
Be g um	73 (0.4)				73 (0.3)
Hungary	70 (0.4)				70 (0.3)
Hong Kong	69 (0.4)				69 (0.3)
Ch na		69 (1.4)			69 (0.3)
South Afr ca		63 (1.3)			63 (0.3)
Sr Lanka			60 (2.3)		60 (0.2)
F n and	59 (0.4)				59 (0.2)
Czech a	55 (0.3)				55 (0.2)
S oven a	55 (0.3)				55 (0.2)
L thuan a	51 (0.3)				51 (0.2)
L bya		51 (1.1)			51 (0.2)
Israe	49 (0.3)				49 (0.2)
Sudan				49 (11.7)	49 (0.2)
Bu gar a		45 (0.9)			45 (0.2)
Repub c of North Ma cedon a		45 (0.9)			45 (0.2)
Denmark	42 (0.3)				42 (0.2)
Dom n can Repub c		38 (0.8)			38 (0.2)
Rwanda				35 (8.3)	35 (0.1)
Guatema a		34 (0.7)			34 (0.1)
Ma ta	31 (0.2)				31 (0.1)
Latv a	29 (0.2)				29 (0.1)
Kuwa t	28 (0.2)				28 (0.1)

Country	High income	Upper middle income	Lower middle income	Low income	Total of patients per country
Kazakhstan		28 (0.6)			28 (0.1)
Bahra n	26 (0.2)				26 (0.1)
Un ted Arab Em rates	26 (0.2)				26 (0.1)
Pa est ne, State of			25 (1.0)		25 (0.1)
Cyprus	23 (0.1)				23 (0.1)
Z mbabwe			23 (0.9)		23 (0.1)
Bosn a and Herzegov na		21 (0.4)			21 (0.1)
Tha and		21 (0.4)			21 (0.1)
Yemen				21 (5.0)	21 (0.1)
Qatar	20 (0.1)				20 (0.1)
Kenya			19 (0.7)		19 (0.1)
Madagascar				19 (4.5)	19 (0.1)
Korea (the Repub c o f)	18 (0.1)				18 (0.1)
Iraq		18 (0.4)			18 (0.1)
S ovak a	16 (0.1)				16 (0.1)
Oman	15 (0.1)				15 (0.1)
Uganda				15 (3.6)	15 (0.1)
Po and	14 (0.1)				14 (0.1)
Tun s a			14 (0.5)		14 (0.1)
Luxembourg	11 (0.1)				11 (0.0)
Barbados	10 (0.1)				10 (0.0)
Azerba jan		8 (0.2)			8 (0.0)
Bang adesh			8 (0.3)		8 (0.0)
Mo dova (the Repub c of)			7 (0.3)		7 (0.0)
Mongo a			7 (0.3)		7 (0.0)
Panama	6 (0.0)				6 (0.0)
A ger a			6 (0.2)		6 (0.0)
Uruguay	5 (0.0)				5 (0.0)
Nam b a		5 (0.1)			5 (0.0)
Georg a		4 (0.1)			4 (0.0)
E Sa vador			4 (0.2)		4 (0.0)
Cameroon			3 (0.1)		3 (0.0)
Aruba	2 (0.0)				2 (0.0)
Ta wan (Prov nce of Ch na)	2 (0.0)				2 (0.0)
Ecuador		2 (0.0)			2 (0.0)

Country	High income	Upper middle income	Lower middle income	Low income	Total of patients per country
Eston a	1 (0.0)				1 (0.0)
Tr n dad and Tobago	1 (0.0)				1 (0.0)
A ban a		1 (0.0)			1 (0.0)
Gabon		1 (0.0)			1 (0.0)
Ben n			1 (0.0)		1 (0.0)
Total	**16680**	**4784**	**2614**	**420**	**24498**

Data presented as n(%). Missing data for country and income group n=0.

Table 5: Number of cancer patients by surgical specialty, with urgency of surgery, surgical grade and surgical intent by specialty.

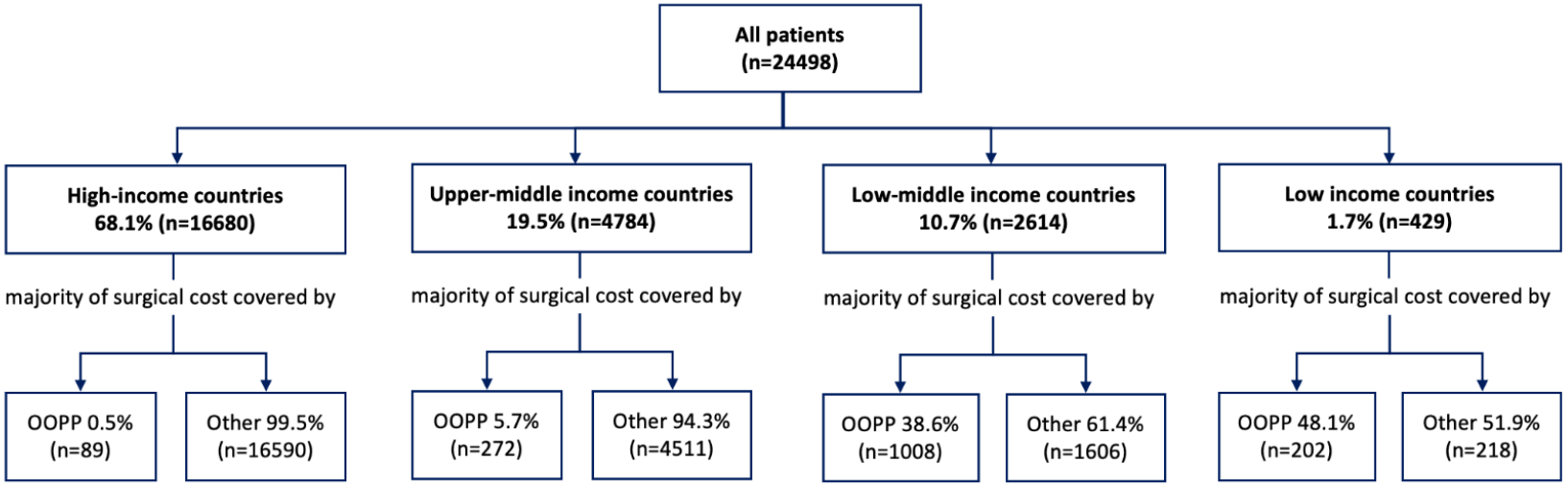
Surgical specialty	Urgency of surgery		Surgical grade		Surgical intent		Total
	Emergency	Elective	Major	Minor/Intermediate	Curative or diagnostic	Palliative	
Co orecta	864 (18.9)	3712 (81.1)	4466 (97.6)	110 (2.4)	3718 (81.3)	855 (18.7)	4573
Breast	21 (0.5)	3973 (99.5)	2445 (61.2)	1549 (38.8)	3916 (98.1)	75 (1.9)	3991
Uro ogy	125 (4.0)	2974 (96.0)	1540 (49.7)	1559 (50.3)	2726 (88.0)	371 (12.0)	3097
Head & Neck	100 (5.2)	1841 (94.8)	1124 (57.9)	817 (42.1)	1821 (94.0)	117 (6.0)	1938
Gynaeco ogy	30 (1.7)	1728 (98.3)	1556 (88.5)	202 (11.5)	1652 (94.0)	106 (6.0)	1758
Hepatob ary	62 (4.1)	1453 (95.9)	1513 (99.9)	2 (0.1)	1374 (90.8)	139 (9.2)	1513
Thorac c	52 (4.0)	1240 (96.0)	1255 (97.1)	37 (2.9)	1146 (88.8)	144 (11.2)	1290
Genera	213 (18.0)	973 (82.0)	523 (44.1)	663 (55.9)	986 (83.2)	199 (16.8)	1185
P ast c	11 (0.9)	1160 (99.1)	72 (6.1)	1099 (93.9)	1130 (96.5)	41 (3.5)	1171
Endocr ne	9 (0.9)	1023 (99.1)	1032 (100.0)	0 (0.0)	1004 (97.5)	26 (2.5)	1030
Oesophagogastr c	76 (8.3)	844 (91.7)	917 (99.6)	4 (0.4)	770 (83.6)	151 (16.4)	921
Neurosurgery	186 (22.5)	639 (77.5)	825 (100.0)	0 (0.0)	623 (75.8)	199 (24.2)	822
Other	29 (6.0)	458 (94.0)	130 (26.7)	357 (73.3)	461 (94.7)	26 (5.3)	487
Orthopaed cs	49 (15.0)	278 (85.0)	207 (63.3)	120 (36.7)	218 (66.7)	109 (33.3)	327
Sp na	61 (33.7)	120 (66.3)	180 (99.4)	1 (0.6)	92 (51.1)	88 (48.9)	180
Ophtha mo ogy	13 (13.3)	85 (86.7)	0 (0.0)	98 (100.0)	93 (94.9)	5 (5.1)	98
Vascu ar	9 (15.8)	48 (84.2)	54 (94.7)	3 (5.3)	43 (75.4)	14 (24.6)	57
Card ac	6 (20.7)	23 (79.3)	29 (100.0)	0 (0.0)	23 (79.3)	6 (20.7)	29
Dent stry	0 (0.0)	6 (100.0)	0 (0.0)	6 (100.0)	5 (83.3)	1 (16.7)	6

Data presented as n(%). M ss ng data: surg ca spec a ty n=3; urgency of surgery n=1; surg ca grade n=3; surg ca ntent n=23. Percentages g ven by row to represent % of emergent, e ect ve, curat ve and pa at ve surgery by surg ca spec a ty.

2.4.4 Primary analysis: Payments for cancer surgery globally

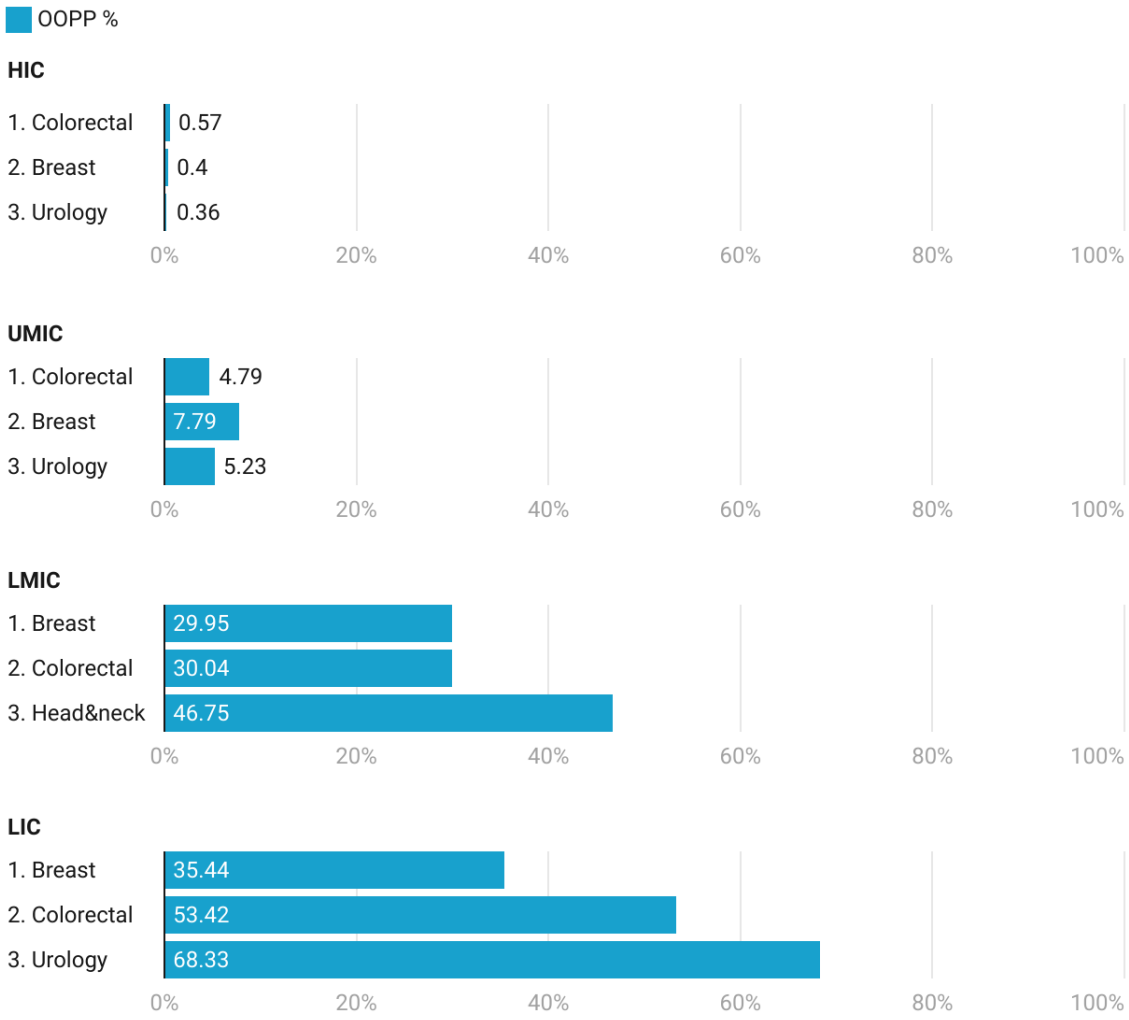
From all the patients included in the study, 6.4% (1571/24498, 95%CI 6.1-6.7%) paid out-of-pocket payments (OOPP) for the majority of their cancer surgery. The proportion of surgeries where the majority of payment was OOPP was different across income settings, being 0.5% (89/16680, 95%CI 0.4-0.6%) in high income countries, 5.7% (272/4784, 95%CI 5.1-6.4%) in upper-middle income, 38.6% (1008/2614, 95%CI 36.7-40.5%) in lower-middle income and 48.1% (202/429, 95%CI 42.3-51.9%) in low-income (Figure 14). Figure 15 shows the rates of OOPP across the three most common surgery types in each income setting, which are always higher in lower income settings.

Figure 14: Rates of out-of-pocket payments to pay for the majority of cancer surgery cost, by country income group.



Missing data for method of payment n=2.

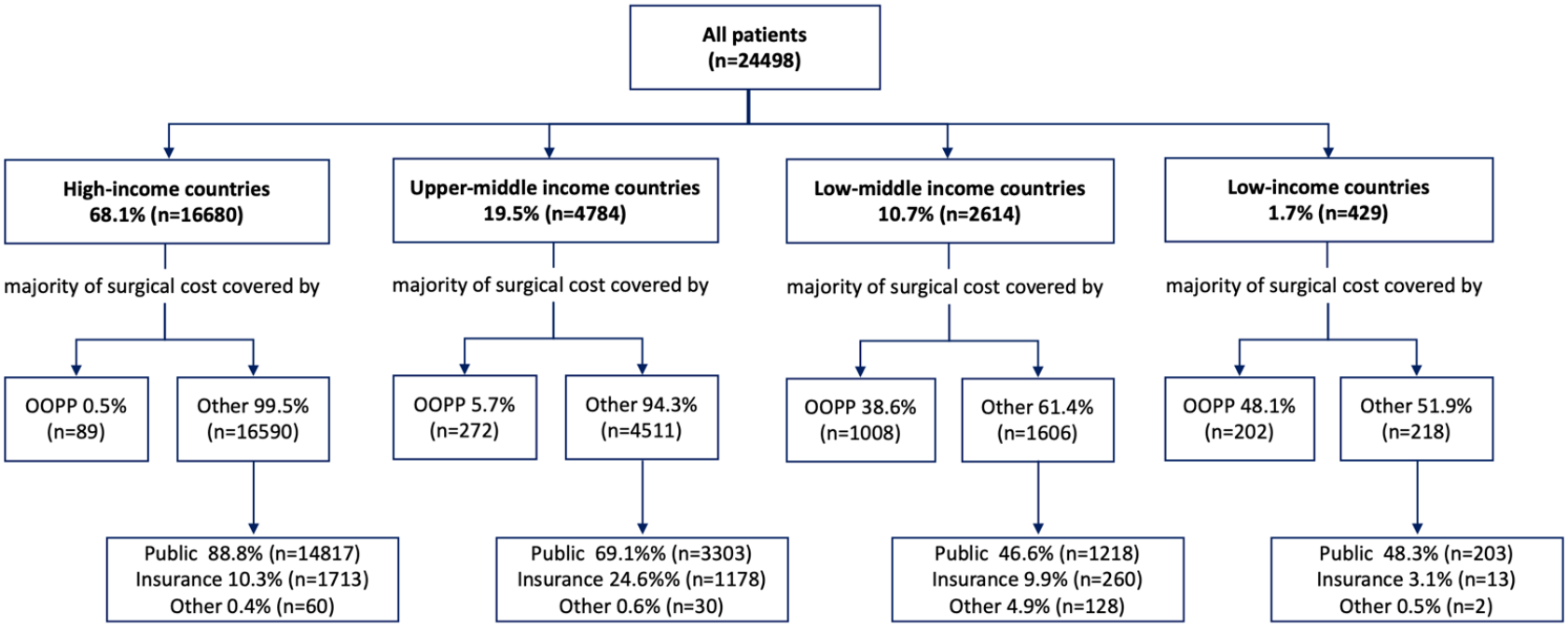
Figure 15: OOPP rates for the three most common types of surgery across country income groups.



Missing data for method of payment n=2 and for type of surgery n=3.

Other funding sources were used to pay for the majority of cancer surgery, with public or government funds being the most common at global level (79.8% [19541/24498]), followed by insurance (12.9% [3164/24498]) and other providers (0.9% [220/24498]) (missing data n=2). The use of these public and insurance funds to pay for cancer surgery was variable across income groups, with high-income countries having the highest use of public funds (87.8% [14646/16680]) and upper-middle income countries using insurance more commonly (24.2% [1158/4784]). Figure 16 and 17 demonstrate the frequency of each funding source by income group. The rates of OOPP were consistently higher in L&MIC regardless the urgency and the intent of the procedures (Figures 18 (A) and (B), respectively).

Figure 16: Funding sources to pay for the majority of the cost of cancer surgery, by country income group.



Missing data for method of payment n=2.

Figure 17: Mosaic plot of funding sources to pay for the majority of the cost of cancer surgery, by country income group.

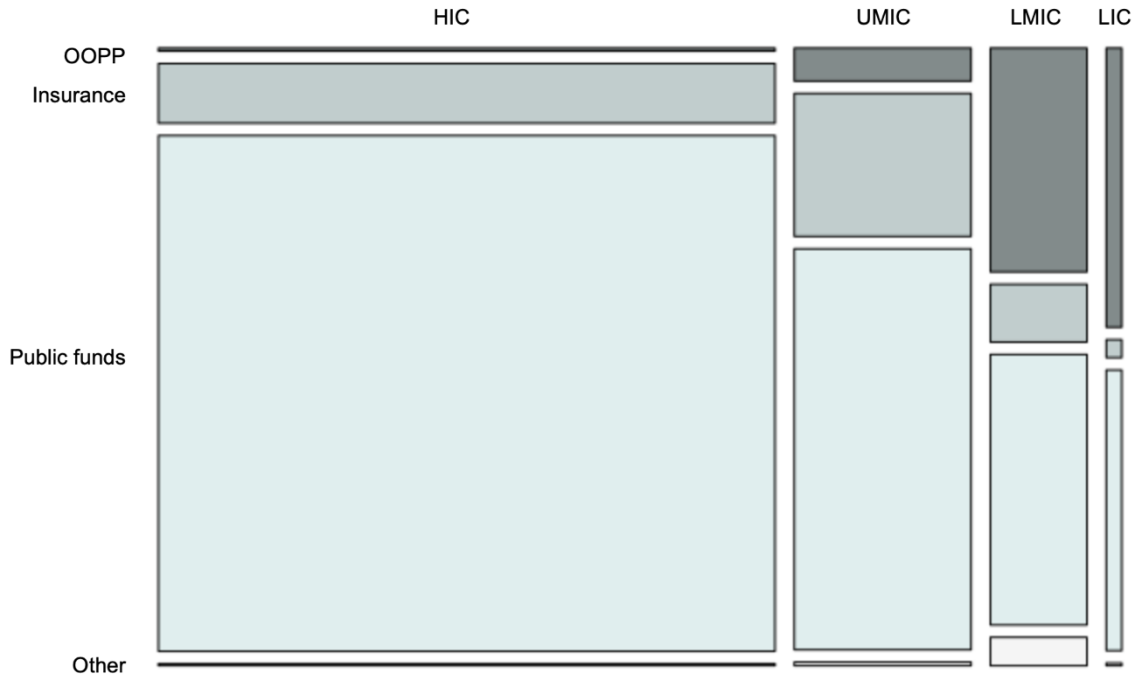
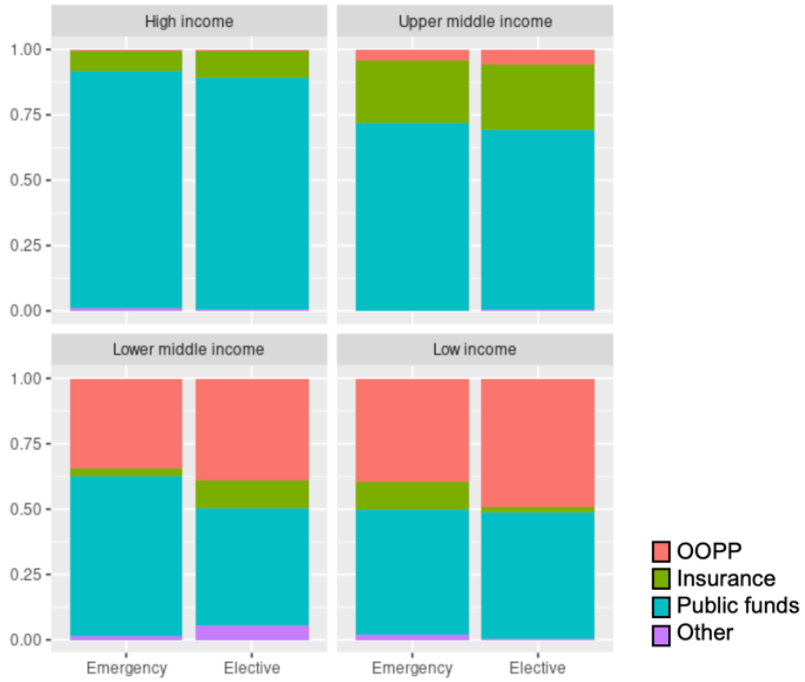


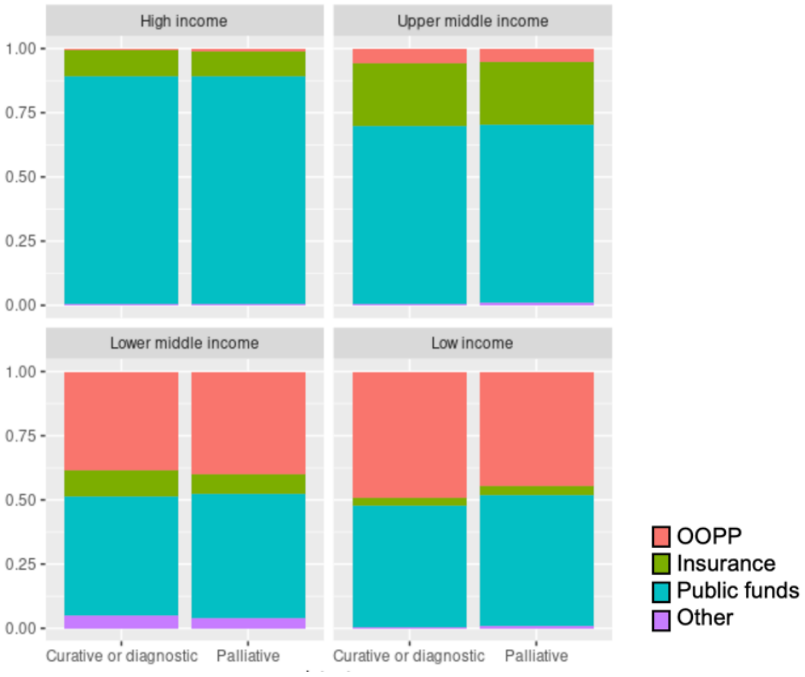
Chart displays the proportion of patients within each setting who pay for the majority of their cancer surgery through OOPP, insurance, public funds or other funding sources. Actual percentages are shown in the previous flowchart (Figure 16). HIC = high income countries, UMIC = upper middle income countries, LMIC = low middle income countries, LIC = low income countries. Missing data for method of payment n=2.

Figure 18: OOPP rates by urgency (A) and intent (B) of the surgical procedure, across country income groups.

(A) OOPP by urgency of surgery



(B) OOPP by surgical intent



2.4.5 Secondary analysis: Characteristics of patients paying out-of-pocket in L&MIC

Patients being treated in low-middle income countries were distinct of those from HIC. Of note, cancer surgery patients in L&MIC were younger (18.4% vs 7% were aged under 40 years old), lower comorbidities (75.5% vs 60.0% were ASA grade 1-2), had a higher number of palliative (14.9% vs 9%) and open surgeries (77.8% vs 59.1%). See Table 6 for full the patient characteristics in L&MIC and HIC.

Table 6: Patient and surgery characteristics in patients from HIC and L&MIC.

		HIC	L&MIC	p-value
Age	<40 years	1165 (7.0)	1440 (18.4)	<0.001
	40-69 years	9111 (54.6)	5062 (64.7)	
	>70 years	6404 (38.4)	1316 (16.8)	
Sex	Female	8774 (52.6)	4581 (58.6)	<0.001
	Male	7906 (47.4)	3237 (41.4)	
ASA grade	Grades 1-2	10008 (60.0)	5901 (75.5)	<0.001
	Grades 3-5	6663 (40.0)	1917 (24.5)	
Cardiac risk (RCRI)	0	5335 (32.0)	3097 (39.6)	<0.001
	1-2	10755 (64.5)	4501 (57.6)	
	≥3	585 (3.5)	218 (2.8)	
	Missing	1	2	
Urgency	Emergency	1205 (7.2)	712 (9.1)	<0.001
	Elective	15474 (92.8)	7106 (90.9)	
	Missing	1	0	
Surgical grade	Major	11779 (70.6)	6089 (77.9)	<0.001
	Minor/Intermediate	4900 (29.4)	1727 (22.1)	
	Missing	1	2	
Intent	Curative or diagnostic	15160 (91.0)	6643 (85.1)	<0.001
	Palliative	1507 (9.0)	1165 (14.9)	
	Missing	13	10	
Operative approach	Open	9861 (59.1)	6085 (77.8)	<0.001
	Minimally invasive	6219 (37.3)	1497 (19.2)	
	Hybrid	198 (1.2)	87 (1.1)	
	Converted to open	401 (2.4)	148 (1.9)	
	Missing	1	1	
Specialty	Breast surgery	2481 (14.9)	1513 (19.4)	<0.001
	Cardiac surgery	23 (0.1)	6 (0.1)	
	Colorectal surgery	3179 (19.1)	1397 (17.9)	
	Dentistry	4 (0.0)	2 (0.0)	
	Endocrine surgery	554 (3.3)	478 (6.1)	
	General surgery	831 (5.0)	355 (4.5)	
	Gynaecology	1133 (6.8)	625 (8.0)	
	Head & Neck surgery	1248 (7.5)	693 (8.9)	
	Hepatobiliary surgery	1131 (6.8)	384 (4.9)	

	Neurosurgery	515 (3.1)	310 (4.0)	
	Oesophagogastric surgery	588 (3.5)	333 (4.3)	
	Ophthalmology	67 (0.4)	31 (0.4)	
	Orthopaedics	183 (1.1)	144 (1.8)	
	Other procedures	358 (2.1)	129 (1.7)	
	Plastic surgery	914 (5.5)	257 (3.3)	
	Spinal surgery	134 (0.8)	47 (0.6)	
	Thoracic surgery	1077 (6.5)	215 (2.8)	
	Urology	2215 (13.3)	884 (11.3)	
	Vascular surgery	44 (0.3)	13 (0.2)	
	Missing	1	2	

Data presented as n(%). RCRI = Revised Cardiac Risk Index.

Of the 7818 patients included from low and middle income countries, 19.0% (1482/7818) paid out-of-pocket for the majority of their cancer surgery cost. Majority OOPP rates were higher in young patients (24% in under 40 years old, 18.8% in patients 40-69 years old and 13.9% in patients above 70 years old, $p<0.001$) and in males (20.1% versus 18.1% in female patients, $p=0.027$). Patients with fewer comorbidities were more likely to pay for the majority of their surgery by OOPP (20.2% for ASA grade 1-2 and 15.1% for ASA grades 3-5, $p<0.001$), with similar trends for patients with low cardiac risk (OOPP for majority of surgery rates 20.1% when RCRI was 0, 18.4% for RCRI 1-2 and 13.3% for RCRI ≥ 3, $p=0.014$). OOPP for majority of surgery rates were not significantly different by urgency or surgical grade but were higher in patients undergoing palliative surgery (22.2% vs 18.4% in curative/diagnostic surgery, $p=0.002$) and open procedures (19.6% versus 17.2% in minimally invasive, 16.1% in hybrid and 12.2% in converted procedures, $p=0.022$). See Table 7 for full unadjusted results.

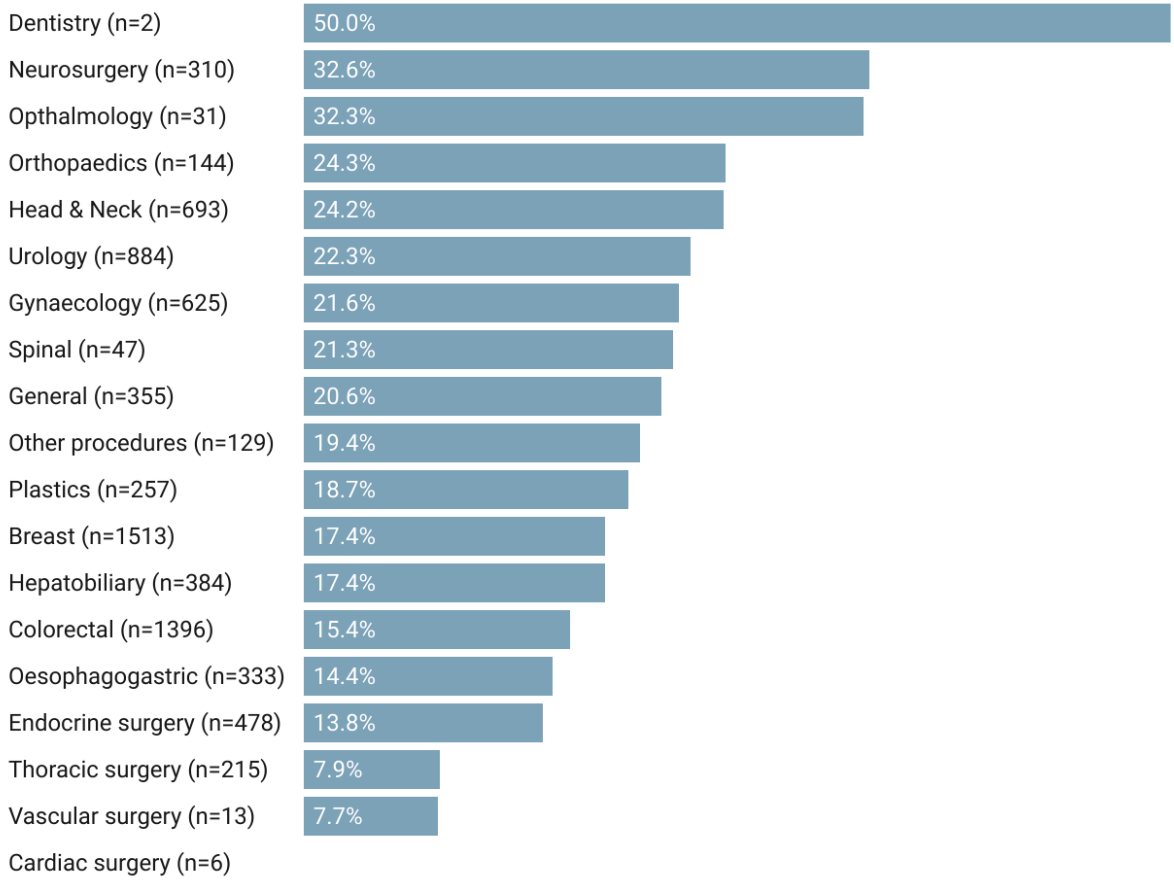
The surgical procedures for which L&MIC patients more often make OOPP are dentistry (50.0%), neurosurgery (32.6%) and ophthalmology (32.3%), whereas cardiac, vascular and thoracic surgery had the lowest rates of OOPP (0.0%, 7.7%, 7.9%) (see Figure 19 for percentages for all specialties). Figure 20 shows the absolute number of patients undergoing surgery per surgical specialty, with absolute number of OOPP for each specialty. The most common surgeries in L&MIC were breast surgery (majority OOPP rate of 17.4%), colorectal surgery (OOPP rate of 15.4%) and urology (OOPP rate of 22.3%).

Table 7: Patient and surgical features associated with out-of-pocket payments for the majority of the cost of surgery in L&MICs (unadjusted analysis).

		Non-OOPP	OOPP	p-value
Age	<40 years	1094 (76.0)	346 (24.0)	<0.001
	40-69 years	4108 (81.2)	953 (18.8)	
	>70 years	1133 (86.1)	183 (13.9)	
Sex	Female	3750 (81.9)	830 (18.1)	0.027
	Male	2585 (79.9)	652 (20.1)	
ASA grade	Grades 1-2	4708 (79.8)	1192 (20.2)	<0.001
	Grades 3-5	1627 (84.9)	290 (15.1)	
Cardiac risk (RCRI)	0	2472 (79.8)	625 (20.2)	0.014
	1-2	3673 (81.6)	827 (18.4)	
	≥3	189 (86.7)	29 (13.3)	
	Missing	1	1	
Urgency	Emergency	584 (82.0)	128 (18.0)	0.515
	Elective	5751 (80.9)	1354 (19.1)	
Surgical grade	Major	4934 (81.0)	1154 (19.0)	1.000
	Minor/Intermediate	1400 (81.1)	327 (18.9)	
	Missing	1	1	
Intent	Curative or diagnostic	5421 (81.6)	1221 (18.4)	0.002
	Palliative	906 (77.8)	259 (22.2)	
	Missing	8	2	
Operative approach	Open	4892 (80.4)	1192 (19.6)	0.022
	Minimally invasive	1240 (82.8)	257 (17.2)	
	Hybrid	73 (83.9)	14 (16.1)	
	Converted to open	130 (87.8)	18 (12.2)	
	Missing	0	1	

Data presented as n(%). RCRI = Revised Cardiac Risk Index.

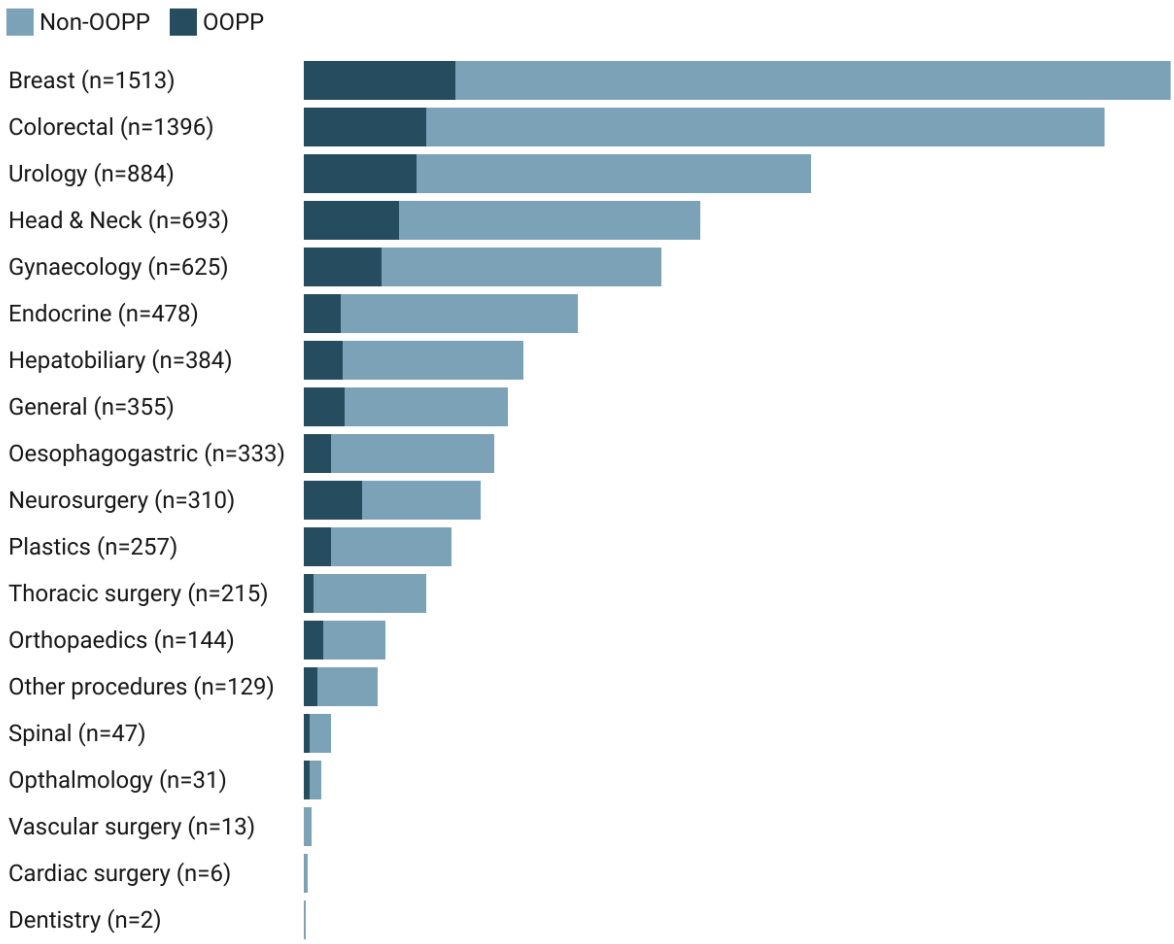
Figure 19: Rates of out-of-pocket payment rates for the majority of the cost of cancer surgery in L&MIC, by surgical specialty.



Bar chart is ordered by the percentage of patients paying out-of-pocket per specialty.

Missing data for OOPP n=1 and for surgical specialty n=2.

Figure 20: Absolute frequency of OOPP to pay for the majority of the cost of cancer surgery in L&MIC, by surgical specialty.

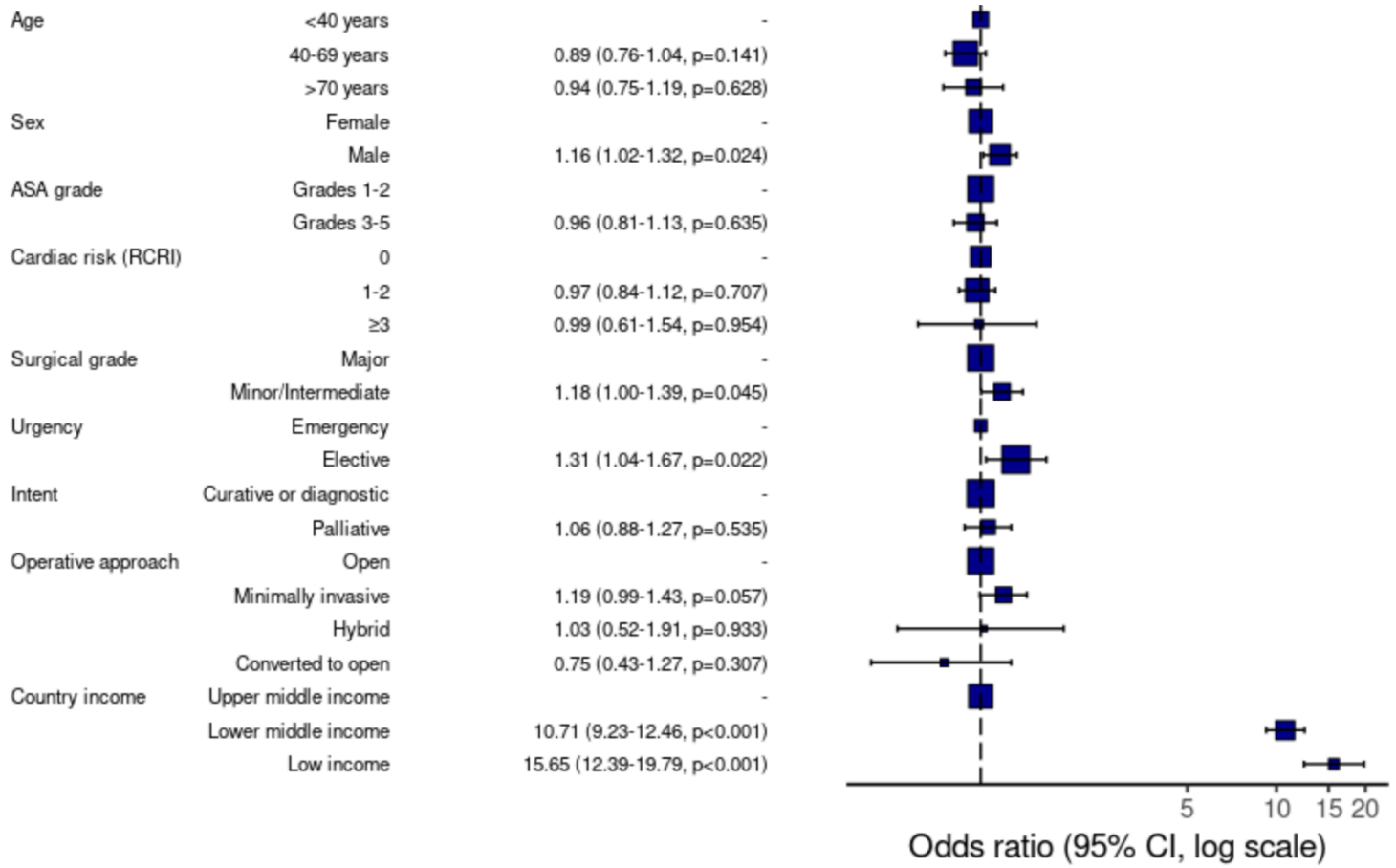


Bar chart is ordered by the total number of patients per surgical specialty.

Missing data for OOPP n=1 and for surgical specialty n=2.

After adjustment, the characteristics independently associated with OOPP for the majority of cancer surgery were male sex (OR 1.16, 95%CI 1.02-1.32, p=0.024), elective surgery (OR 1.31, 1.04-1.67, p=0.022), and lower country income groups (OR 10.71, 95%CI 9.23-12.46, p<0.001 for lower-middle income countries and OR 15.65, 95%CI 12.39-19.79, p<0.001 for low income countries, compared to upper-middle income countries). The forest plot of the adjusted model is shown in Figure 21 and the full model is available on Table 8.

Figure 21: Forest plot of the logistic regression model of characteristics associated with OOPP for the majority of cancer surgery.



Model metrics: Number in dataframe = 7818, Number in model = 7804, Missing = 14, AIC = 6144.9, C-statistic = 0.783, H&L = Chi-sq(8) 16.20 (p=0.040). RCRI = Revised Cardiac Risk Index.

Table 8: Full logistic regression model of characteristics associated with OOPP for the majority of cancer surgery.

		Non-OOPP	OOPP	OR (univariable)	OR (multivariable)
Age	<40 years	1094 (76.0)	346 (24.0)	-	-
	40-69 years	4108 (81.2)	953 (18.8)	0.73 (0.64-0.84, p<0.001)	0.89 (0.76-1.04, p=0.141)
	>70 years	1133 (86.1)	183 (13.9)	0.51 (0.42-0.62, p<0.001)	0.94 (0.75-1.19, p=0.628)
Sex	Fema e	3750 (81.9)	830 (18.1)	-	-
	Ma e	2585 (79.9)	652 (20.1)	1.14 (1.02-1.28, p=0.025)	1.16 (1.02-1.32, p=0.024)
ASA grade	Grades 1-2	4708 (79.8)	1192 (20.2)	-	-
	Grades 3-5	1627 (84.9)	290 (15.1)	0.70 (0.61-0.81, p<0.001)	0.96 (0.81-1.13, p=0.635)
RCRI	0	2472 (79.8)	625 (20.2)	-	-
	1-2	3673 (81.6)	827 (18.4)	0.89 (0.79-1.00, p=0.050)	0.97 (0.84-1.12, p=0.707)
	≥3	189 (86.7)	29 (13.3)	0.61 (0.40-0.89, p=0.015)	0.99 (0.61-1.54, p=0.954)
Surg ca grade	Ma or	4934 (81.0)	1154 (19.0)	-	-
	M nor/Intermed ate	1400 (81.1)	327 (18.9)	1.00 (0.87-1.14, p=0.985)	1.18 (1.00-1.39, p=0.045)
Urgency	Emergency	584 (82.0)	128 (18.0)	-	-
	E ect ve	5751 (80.9)	1354 (19.1)	1.07 (0.88-1.32, p=0.484)	1.31 (1.04-1.67, p=0.022)
Intent	Curat ve or d agnost c	5421 (81.6)	1221 (18.4)	-	-
	Pa at ve	906 (77.8)	259 (22.2)	1.27 (1.09-1.47, p=0.002)	1.06 (0.88-1.27, p=0.535)
Operat ve approach	Open	4892 (80.4)	1192 (19.6)	-	-
	M n ma y nvas ve	1240 (82.8)	257 (17.2)	0.85 (0.73-0.99, p=0.033)	1.19 (0.99-1.43, p=0.057)
	Hybr d	73 (83.9)	14 (16.1)	0.79 (0.42-1.35, p=0.415)	1.03 (0.52-1.91, p=0.933)
	Converted to open	130 (87.8)	18 (12.2)	0.57 (0.33-0.91, p=0.026)	0.75 (0.43-1.27, p=0.307)
Country ncome	UMIC	4511 (94.3)	272 (5.7)	-	-
	LMIC	1606 (61.4)	1008 (38.6)	10.41 (9.01-12.06, p<0.001)	10.71 (9.23-12.46, p<0.001)
	LIC	218 (51.9)	202 (48.1)	15.37 (12.25-19.30, p<0.001)	15.65 (12.39-19.79, p<0.001)

2.4.6 Sensitivity analysis of colorectal cancer patients

From the patients included from L&MIC, 1108 patients had colorectal cancer, of which 14.3% (158/1108) paid out-of-pocket for the majority of their surgery. In this subgroup of patients, the variables independently associated with OOPP for cancer surgery were revised cardiac risk index ≥3 (OR 0.20, 95%CI 0.03-0.68, p=0.030) and country income group (OR 8.78, 95% CI 5.72-13.78, p<0.001) in lower-middle and OR 22.59, 95% CI 11.49-45.12, p<0.001 in low income countries). See Table 9 for the full adjusted model.

Table 9: Logistic regression model: variables associated with OOPP for the majority of cancer surgery cost, colorectal cancer only.

		Non-OOPP	OOPP	OR (univariable)	OR (multivariable)
Age	<40 years	96 (81.4)	22 (18.6)	-	-
	40-69 years	597 (84.7)	108 (15.3)	0.79 (0.48-1.34, p=0.360)	1.28 (0.74-2.30, p=0.383)
	>70 years	256 (90.1)	28 (9.9)	0.48 (0.26-0.88, p=0.017)	1.18 (0.59-2.38, p=0.638)
Sex	Fema e	438 (85.2)	76 (14.8)	-	-
	Ma e	511 (86.2)	82 (13.8)	0.92 (0.66-1.30, p=0.650)	0.98 (0.67-1.43, p=0.919)
ASA grade	Grades 1-2	646 (84.0)	123 (16.0)	-	-
	Grades 3-5	303 (89.6)	35 (10.4)	0.61 (0.40-0.90, p=0.014)	1.00 (0.62-1.58, p=0.997)
RCRI	0-2	877 (84.9)	156 (15.1)	-	-
	≥3	72 (97.3)	2 (2.7)	0.16 (0.03-0.50, p=0.010)	0.20 (0.03-0.68, p=0.030)
Urgency	Emergency	185 (84.9)	33 (15.1)	-	-
	E ect ve	764 (85.9)	125 (14.1)	0.92 (0.61-1.41, p=0.684)	1.17 (0.71-1.96, p=0.548)
Intent	Curat ve or d agnost c	773 (87.1)	114 (12.9)	-	-
	Pa at ve	175 (80.3)	43 (19.7)	1.67 (1.12-2.44, p=0.010)	1.20 (0.75-1.89, p=0.439)
Operat ve approach	Open	659 (84.4)	122 (15.6)	-	-
	M n ma y nvas ve	238 (89.1)	29 (10.9)	0.66 (0.42-1.00, p=0.057)	1.13 (0.68-1.84, p=0.625)
	Hybr d	16 (88.9)	2 (11.1)	0.68 (0.11-2.41, p=0.604)	1.43 (0.19-6.34, p=0.679)
	Converted to open	36 (87.8)	5 (12.2)	0.75 (0.25-1.79, p=0.555)	0.99 (0.31-2.59, p=0.982)
Country ncome	Upper m dd e ncome	697 (95.3)	34 (4.7)	-	-
	Lower m dd e ncome	227 (70.1)	97 (29.9)	8.76 (5.82-13.47, p<0.001)	8.78 (5.72-13.78, p<0.001)
	Low ncome	25 (48.1)	27 (51.9)	22.14 (11.68-42.52, p<0.001)	22.59 (11.49-45.12, p<0.001)

Model metrics: Number in dataframe = 1108, Number in model = 1105, Missing = 3, AIC = 755.3, C-statistic = 0.793, H&L = Chi-sq(8) 4.70 (p=0.790).
RCRI = Revised Cardiac Risk Index.

2.5 Discussion

2.5.1 Main findings

This study showed that cancer patients in low-middle income countries were more likely to pay out-of-pocket for the majority of the cost of surgery, with rates of OOPP ranging from 0.5% in high income countries, to 5.7% in upper-middle income, 38.6% in lower-middle income and 48.1% in low-income countries. Country income was associated with OOPP for cancer surgery in all analyses and subgroups, suggesting that patients who live in economically challenged contexts lack financial protection more often.

The distribution of pre-paid mechanisms used across income groups to pay for cancer surgery is likely to reflect the organization of their healthcare systems. Public funds are more often used in high income countries, where national health systems funded through taxes are more common. Although publicly funded healthcare systems have their own limitations, particularly when responding to a high volume of patients, they seem to be one of the most reliable ways to avoid financial instability due to healthcare costs(41, 86). Upper-middle countries had the highest rate of insurance use, reflecting the well-developed private health sector but perhaps also that employer provided insurance is more common or that individuals choose or are forced to purchase private insurance(86).

2.5.2 Secondary findings

Although young age, male sex, comorbidity scores, palliative and open surgery were associated with OOPP in the unadjusted analysis, only male sex and elective surgery remained significant after adjustment, meaning that these are independently associated with OOPP, with potential implications for health policy. While this supports advocacy for more investment in financing elective care, the ratio of elective/emergency surgery in this study (more then 90% elective) makes this finding difficult to interpret. A possible selection bias needs to be acknowledged as patients requiring emergency surgery could have been treated more often in non-participating hospitals, being underrepresented in this study. It is also possible that patients requiring emergency surgery are more frequently from disadvantaged backgrounds, with higher odds of advanced disease, and might struggle to access surgical treatment, therefore being selected out of the study.

Similarly, careful considerations need to be drawn from the fact that men pay more frequently out-of-pocket for the majority of their cancer surgery. This result can reflect that men have a higher income, disposable money or a better ability to raise funds for their cancer care. However, I can not exclude that male patients could eventually carry disease patterns that require more expensive treatments(87) or that they would indeed be a vulnerable group, with less financial protection at the time of cancer service use.

Decision making on the types of surgery that require more financial support going forwards needs to balance OOPP rates but also the burden of the disease and how common surgery is required. For example, whereas the highest rate of OOPP was seen in dentistry and neurosurgery, the absolute number of procedures in this sample of patients was relatively low and therefore an improvement in financing these surgeries would probably not have a huge public health benefit. Similar OOPP rates were observed in the most commonly performed surgeries (breast 17.4%, colorectal 15.4% and urology 22.3%), positioning them as good areas for public investment. The fact that these were the most common procedures in this study is a result of the incidence of cancer types but also the surgical case mix of the participating hospitals network, which can be different at whole population levels.

2.5.3 Key strengths

To my knowledge, there is no previous study reporting out-of-pocket payments for surgical care in more than 100 countries, likely because this is difficult to collect at a global scale. This difficulty influenced the design of the study, with methodological limitations that are acknowledged below. The findings of this study are widely applicable given that it captured data from a broad range of clinical settings. Although it can introduce heterogeneity, the fact that several types of cancers were included allows wide generalisability of findings, making this data more useful to advocate for additional funding towards multiple cancers.

2.5.4 Key limitations

Several limitations need to be acknowledged in this study. The main limitation is that although the study sample size is large, the granularity of the data is low. This limits the conclusions that can be drawn from the data. More details on the type of disease (e.g. stage) and costs of treatment parcels (e.g. theatre costs, admission costs, etc) would be useful to identify the most vulnerable subgroups of patients or types of treatment benefiting from investment. Secondly, the inclusion criteria constitute a selection feature in itself, as patients requiring surgery but unable to afford or access it were not included in the study and might be the most disadvantaged of all. The fact that most patients underwent elective and curative surgery probably reflects the profile of patients being treated in the participating hospitals, introducing an inevitable selection bias that is commonly seen in global studies (88). Thirdly, the representation of low income settings in this study is not optimal, with fewer patients being included as country income decreased. Although the findings of the study are strongly related to income groups, the fact that representation of all groups was not balanced brings limitations in relation to generalisability.

The methodological decision to exclude HIC patients from the models identifying predictors of OOPP aimed to avoid confounding, as the rate of OOPP in HIC was expected to be very low and patients accessing surgery to have quite different characteristics. This could influence the results and make them less interpretable in the L&MIC setting, where OOPP for cancer surgery were expected to be a

larger problem. However, I acknowledge that it reduces to generalisability of the findings.

The rates of catastrophic expenditure for cancer care are expected to range from 5 to 84% depending on study definitions, type of cancer and treatment setting (89). The fact that the OOPP rates in this study were relatively low is probably related to the way that the data was collected. In theory, any OOPP can put households at risk of financial toxicity, depending on the scale of the OOPP compared to household income. However, OOPP made for the majority of the cost of surgery are more likely to be high and have an impact on household finances, working as a better marker of financial burden than OOPP in general. Ideally, the total cost of treatment and household income would have been collected but this is very challenging at an international level, especially when the sources of funding for surgery are a secondary outcome of the main study. Additionally, this study didn't include indirect nor cost opportunity costs of surgical care.

2.5.5 Implications for policy

This data calls for action in policy in primary and secondary/tertiary care.

At a secondary and tertiary care levels, increased investment in pre-paid mechanisms to protect cancer patients from OOPP is needed, particularly in low-income settings. Governments need to be informed that a high number of patients requiring cancer surgery in L&MIC pay out-of-pocket for most of it,

potentially compromising the economic and social stability of the whole household. Besides out-of-pocket payments, other studies have reported various financial distress strategies that can impact several generations (e.g. loans and property selling)(47).

At a primary care level, given the rising incidence of cancer, international health organisations, governmental and non-governmental, should up-prioritise cancer care. The detection of cancer at a stage where it is still curable through surgery, improving not only health outcomes, but also having with socio-economic benefits in population productivity and mitigation against long-term disability.

Health reforms are challenging in L&MICs, where multiple providers have competing interests within the health system and payment sources are usually not centralised in the government. Regulation of providers and reorganisation of payment mechanisms is needed, with an initial focus on the poorest which are at highest risk of adverse health and economic outcomes. This has been done successfully in other countries, namely in southeast Asia(34, 90).

2.5.6 Future research

Patients' ability or choice to pay OOPP for cancer surgery is probably influenced by multiple factors that are not yet fully understood. A patient-facing study assessing patients' perspectives on methods to pay for cancer care is needed to implement health improvement projects tailored to patients' needs.

As this study did not assess the consequences of the OOPP for households, a study exploring catastrophic expenditure rates or financial hardship is needed to understand the real financial impact of these costs. A more generic inclusion of OOPP is desirable in a future study, as the minority of the cost of surgery can still have a relevant impact on patients' finances.

Finally, future research should include patients who are eligible for cancer treatments, rather than only the ones receiving it, to capture the financial struggles of a wider groups of patients and also their consequences to treatment completeness.

3 Catastrophic expenditure and treatment attrition in patients seeking comprehensive colorectal cancer treatment in India

3.1 Link to the previous chapter

The previous chapter showed global variation in out-of-pocket payments for cancer surgery, with out-of-pocket payments (OOPP) as the predominant funding of surgery being higher in low- and middle-income countries. The impact of these OOPP on household finances is unknown, and a study looking at household income and catastrophic expenditure is needed to explore that impact. To research the relationship between catastrophic spending and treatment drop-out, a study including patients with a treatment plan (as opposed to a completed treatment course) is needed. In this chapter, a prospective cohort of patients with a colorectal cancer treatment plan is used to explore the impact of out-of-pocket payments in household finances and treatment attrition.

3.2 Abstract

Introduction: Treatment for cancer is one of the most expensive among non-communicable diseases. Colorectal cancer is increasing in India and its costs are unknown. This study aimed to assess catastrophic expenditure and treatment attrition in patients with a treatment plan for colorectal cancer in tertiary hospitals in India. As a secondary aim, the feasibility of using the International Wealth Index (IWI) and the Gapminder tool, compared to self-reported income was assessed.

Methods: Prospective, multicentre, cohort study was conducted in five tertiary care hospitals in India (December 2020 to March 2022), including patients with a new treatment plan for colorectal cancer, who were followed-up for six months. Absolute costs, catastrophic expenditure and treatment attrition rates were reported. A Bland-Altman analysis was performed to compare the self-reported income with the IWI and the Gapminder incomes.

Results: Of 226 patients included, 20 died within six months of being offered a treatment plan and four were lost to follow-up. The average total cost of colorectal cancer treatment was 475,781 Indian Rupees (INR, equivalent to 6069 United States Dollars [USD]), to which the biggest contributor was the patient's OOPP (mean 365,768 INR / 4667 USD). The overall catastrophic expenditure rate was 90.1% (182/202) and the treatment attrition rate was 9.4% (19/202).

Overall, 99.5% patients completed the IWI and the Gapminder tool. The IWI showed better agreement with the self-reported income than the Gapminder tool. For both instruments, the agreement was better for low income earning households.

Discussion: Most treatment costs for colorectal cancer were paid out-of-pocket by patients and catastrophic expenditure was common. Treatment attrition rates at tertiary centres were low, suggesting greater attrition at previous stages of care. Better financial protection may allow more patients to receive cancer treatment while avoiding household financial catastrophe. The IWI and the Gapminder are promising tools to assess household income but need refining before their use in future studies.

3.3 Introduction

Colorectal cancer is currently the 7th most common cancer in India with 65 358 new cases in 2021(91). The incidence of colorectal cancer has been increasing worldwide currently being 19.5 per 100 000 population globally and 15.2 in India(91, 92). From 2004 to 2014, the age-sex adjusted rates of colorectal cancer in India have raised by 20.6%, with a steeper increase in adults aged under 50 years (92-94). Although not yet included in early detection programs, colorectal cancer is the 6th type of cancer contributing to disability-adjusted life years loss in India (95).

Treatment for cancer is one of the most expensive among non-communicable diseases, with catastrophic expenditure rates reported between 34% and 84% (41, 47, 96-105). Acute cardiovascular conditions such as stroke and myocardial infarct show catastrophic rates of 70-90% with cancer being slightly lower and more varied, from 30 to 70%(41). Reducing catastrophic health spending is a Sustainable Development Goal (3.8.2), defined as health expenditure being higher than 25% or 10% of household income (the 25% threshold was used in this study, see methods). The latest WHO report on financial protection states that 996 million people were undergoing catastrophic expenditure in 2017 and 70 million being pushed into poverty due to healthcare costs (31). Patients from low- and middle-income countries are particularly vulnerable due to low governmental spending on healthcare, insufficient insurance coverage and high out-of-pocket payments (83, 96, 106). India's public health expenditure is less than 2% of the

GDP, resulting in high out-of-pocket payments and 6.53% of the whole population experiencing catastrophic healthcare spending (7th highest in the world)(47, 107). Cancer care in India is funded by public funds, private or employer-provided insurances, out-of-pocket payments, non-profit organisations, and other funds (grants or loans)(28). It is estimated that government funds only cover a quarter to a third of cancer treatment cost, forcing patients to make out-of-pocket payments ranging from 19,494 to 295,679 Indian Rupees (INR, 235 to 3573 USD) depending on the type of cancer(47, 108). To date, no data exists on absolute costs nor out-of-pocket payments for colorectal cancer in India.

Healthcare funding systems in India fail to account for the complexity of cancer and catastrophic spending is more likely when multiple treatment modalities are required, which is often the case in colorectal cancer(68). Catastrophic expenditure for colorectal cancer has been reported in Malaysia and China, with very different rates of 17.8% and 75% respectively, but there are no studies reporting financial toxicity in colorectal cancer in India(109, 110). The current costs of colorectal cancer treatment in India and its consequences for patients' treatment courses and their household financial stability are unknown. This study aimed to describe catastrophic expenditure and treatment attrition in patients with a diagnosis and a treatment plan for colorectal cancer.

Simultaneously, this study was set to research a methodological question on alternative tools to assess household income. Self-reported income is widely

used to assess household income (e.g. household surveys) but is exposed to several biases and limitations. Data from previous studies showed that patients do feel reluctant to answer questions about income and that this can lead to high rates of non-response(111). Individual characteristics can influence the likelihood of accurate income reporting and surveyed people often have difficulty in interpreting formulated questions about income(112, 113). Additionally, social desirability bias is commonly present in household surveys responses, introducing over or underestimations depending on the socio-economic and cultural setting, as well as individual circumstances at the point of data collection(114, 115). These limitations of self-reported income can have an impact on population-level estimations (e.g. poverty lines) and policy decision making at national and global level(116, 117). To the best of my knowledge, direct income reporting is the standard method to assess income and there are no alternatives. The secondary aim of this study was to assess the feasibility of the International Wealth Index (IWI) and the Gapminder tool as indirect measures of household income, comparing them to self-reported income.

3.4 Methods

3.4.1 Research questions

i) What are the catastrophic expenditure and treatment attrition rates in patients accessing tertiary care for colorectal cancer treatment in India? (primary analysis)

ii) Is it feasible to use International Wealth Index (IWI) and the Gapminder tool as indirect measures of household income?

3.4.2 Study co-design

CROCODILE was a prospective multicentric cohort study including consecutive patients with a new treatment plan for colorectal cancer was designed to address the proposed research question. This study was co-designed with the Global Surgery Unit research partners in India whose input was crucial for the protocol development and the delivery of the study. This exchange of ideas and knowledge started in February 2020 on a scoping visit to India. As explained below, the need for a qualitative component to this study was identified at the time of design and this component is explored further in the next chapter of this thesis.

3.4.2.1 Scoping visit to India

In February 2020 I was able to visit the NIHR Global Surgery Unit research Hub in India, at the Christian Medical College and Hospital in Ludhiana, and also two

other hospitals with a particular expertise in colorectal cancer, Christian Medical College and Hospital (Vellore) and Tata Medical Centre (Kolkata). The Christian Medical College in Vellore was an existing spoke of the research network in India and the Tata Medical Centre in Kolkata was made a spoke after this visit to India, CROCODILE being the first study that they took part on. I also visited three district hospitals in Ludhiana and Vellore, which represent a different level of care and provided me with a broader perspective of the healthcare system.

During this two-week visit, I learned about local research priorities, patient pathways within the hospital and the healthcare system and gathered thoughts on the most appropriate and feasible methods to be conducted. I met colorectal surgeons, medical oncologists, radiation oncologists, social workers, hospital finance offices and research assistants that helped me understand the feasibility of the study delivery.

3.4.2.2 Key learning points from the visit

3.4.2.2.1 Network interests and priorities

There is a growing interest in colorectal cancer research in India, given the increase in its incidence and the fact that it hasn't been a priority for the healthcare system, given that other cancers are more common. There is an expanding network of surgeons and oncologists interested in colorectal cancer,

developing expertise in its treatment and a rising interest in high quality research to improve care. Hopefully the CROCODILE study helped strengthening this network and will foster enthusiasm for future studies. There was an obvious interest among the partners in India to understand the economic impact of colorectal cancer costs for patients and their families. But there was also a general opinion that some patients might avoid making the unaffordable payments and give up on treatment at all. This was reflected on the study goals and outcomes.

3.4.2.2.2 Patient pathways

Most of the cancer care professionals who I talked to were based at tertiary care hospitals, where patients are usually referred, with a diagnosis or a strong suspicion of colorectal cancer. It was felt that in the community, patients don't always know how to recognise symptoms of colorectal cancer or how to seek help to investigate them. It was conveyed to me that at local healthcare practices and district hospitals, the investigation and treatment of changes in bowel habits and bleeding per rectum are not always considered as possible symptoms of cancer, being often assumed to be a benign condition. These and other challenges, together with the absence of a screening programme for colorectal cancer, inevitably meant that patients would usually present at an advanced stage to tertiary care. Therefore, it would probably be more feasible to include patients with a diagnosis of colorectal cancer rather than a suspicion of colorectal cancer in the study. It was also perceived that it was important to capture the

costs of previous investigations or treatments that patients had undergone as they were often high.

The pathways of care varied across hospitals and that influenced how patients were identified, recruited and assessed within the study. Not all hospitals had a formal multidisciplinary meeting where all colorectal cancer patients are discussed and therefore, identification of patients from outpatient clinics or wards (in the case of emergency admissions) would be necessary. It was also highlighted that some patients would come to these tertiary care hospitals to get a second opinion on their cancer care plan and then continue treatment elsewhere. Given the level of detail about costs that the research group was aiming to collect, it was agreed that including patients intending to get treated at a participating site would be the best.

3.4.2.2.3 Financing of cancer treatment

The way patients pay for their care in India depends broadly on the type of hospital, type / existence of insurance and on the patient's choice on which type of care they want. It was explained to me that at government hospitals, treatment tends to be free of cost or at least much cheaper but patients might need to buy drugs or other items from outside the hospital. In charity and private hospitals, patients usually pay more but part of the cost can be covered by an insurance (private or provided by an employer) or a government funding scheme. Patients were eligible for government funding schemes depending on where they live,

which hospital they are getting treated at, which type of disease they have and their income too. The funding could be given to patients upfront or as a reimbursement. Also, in most charity hospitals, patients could choose between general fees and private fees, the latter more expensive and including a different type of care (e.g. private ward room or consultant care only). It was agreed that collecting costs from the hospital bills wouldn't be enough as many patients end up completing parts of the treatment in other hospitals and the bills for those wouldn't be available. The information gathered has fed directly into the study design, please see Table 10 for a summary. The study protocol was published in April 2021 in *Colorectal Disease* (118).

Table 10: Impact of the information gathered during the scoping visit on the CROCODILE study protocol development.

	Information gathered during scope visit to India	Impact on the study protocol
Study design	• Absence of good qua ty records may mpa r retrospect ve data co ect on. • Research partners w ng to part c pate n a study w th good data qua ty.	Prospect ve des gn.
	• Var ous factors affect treatment uptake and comp ance by cancer pat ents. • Genera percept on that educat on, awareness and pr mary care qua ty are cruc a to cancer care.	Qua tat ve component a ongs de the prospect ve cohort, for a deeper understand ng.
Sites	• There s a geograph ca var at on n pat ents character st cs and access to care. • Some hosp ta s prov de most y treatment to oca pat ents, others to d stant pat ents wh ch m ght nf uence presentat on, treatment and cost.	In favour of enro ng hosp ta s n d fferent reg ons n Ind a and co ect on of d verse cost sources.
	• D str ct hosp ta s may comp ement tert ary hosp ta s both n d agnos s and parts of cancer treatment but pat ent dent f cat on and data co ect on wou d be very d ff cu t, sacr f c ng the data qua ty and the def n t on of a feas b e denom nator.	Focus on tert ary centres.
Population	• Co orecta pat ents are not the major ty of the cancer pat ents n Ind a but co orecta cancer s an ncreas ng and unexp ored top c that s becom ng more mean ngfu .	Focus on co orecta cancer pat ents.

Patient inclusion and recruitment	• Pat ents who reach the end of the r treatment m ght undergo catastroph c expend ture but some of them m ght drop out, not on y for f nanc a but for other reasons and that s an mportant deta to capture.	Study denom nator: co orecta cancer pat ents w th a new dec s on for treatment. Treatment drop-out as a ma n a m.
	• Pat ent pathways vary across hosp ta s.	Pat ent dent f cat on from mu t d sc p nary meet ngs but a so outpat ent and npat ent adm ss ons.
Data collection	• Pat ent ncome s assessed n d fferent ways n the d fferent hosp ta s. • Pat ents tend to underreport the r ncome.	D rect and nd rect pat ent ncome assessment methods were nc uded n the study.
	• Hosp ta b s and f nance records don t cover a the cancer-re ated expenses.	Add t ona cost sources were co ected, to ach eve the most re ab e f gures poss b e.

3.4.3 Study setting and approvals

This study was conducted in five tertiary care hospitals who showed interest in participating, in five different states of India. More hospitals showed interest in participating but as the national approvals had been submitted, this wasn't possible.

The study was registered (ClinicalTrials.gov 04517032; Central Trials Registry of India CTRI/2020/09/027896). Ethical approval from the University of Birmingham was granted in April 2020 and from the Indian Council of Medical Research in October 2020. The study was reviewed by hospital level ethical review boards in all participating sites. Individual patient consent for data collection and use was obtained for all patients, as per local regulations in India (Participant Information Sheets and Informed Consent Forms are available in Supplementary documents 1).

3.4.4 Site enrolment and sample size

The participating hospitals obtained ethical approval at different points in time and were enrolled as soon as these approvals were granted. The sample size was calculated for the whole study and the number of patients per hospital was planned to allow the most balanced sample possible. As per the published protocol, the planned sample size was 200 patients, based on an expected catastrophic expenditure rate of 45% (119, 120), absolute precision margins of 10% and 5% (United Nations recommendation for household surveys) and a

confidence interval of 95%(121). A balanced sample with the same number of patients from each one of the five hospitals, however the participating hospitals are diverse in their baseline number of colorectal cancer cases, hence different recruitment volume was expected from the five sites.

3.4.4.1 Site set up

A virtual site initiation visit was performed with each site, with two sessions per site.

- Site initiation visit – session 1:
    - Introduction to the NIHR Global Surgery Unit (for new spoke sites);
    - CROCODILE study components and aims;
    - Concept of catastrophic expenditure and out-of-pocket payments;
    - Inclusion criteria and patient identification for enrolment;
    - Timing and method for face-to-face assessment and telephone follow-up.
- Site initiation visit – session 2:
    - Baseline datapoints on demographics and tumour details;
    - Face-to-face income assessment;
    - Telephone follow-up:
        - Treatment status details from clinical files and clinical teams;
        - Medical costs details from hospital bills;
        - Other costs details from telephone follow-up with patients.
    - Cross learning hub-spokes on strategies to improve data quality.

Additionally, an online resource was built in collaboration with the NIHR Global Surgery India Hub and made available to all sites, where an example of a baseline patient assessment and a telephone follow-up, together with a summary of study and all the necessary documents. Link available here: https://redcap.link/crocodiletraining.

3.4.5 Patient inclusion

Consecutive patients with a new treatment plan (curative or palliative) for colorectal cancer made at the participating hospitals were included. Hospitals identified patients for inclusion from multidisciplinary meetings whenever possible or colorectal dedicated outpatient clinics or inpatient wards, at hospitals where routine multidisciplinary decisions are not held for all patients. After identification, patients were invited to participate in the study during their following visit to the hospital (or during the same visit if admitted), where informed consent and baseline data were collected.

3.4.6 Exclusion criteria

3.4.6.1.1 Tumour related criteria

Patients with suspected cancer but for whom histopathological proof of colorectal cancer was not available were excluded. Pre-malignant colorectal lesions (e.g. adenomas) were also excluded.

3.4.6.1.2 Data collection related criteria

Patients who were seen at the participating hospitals with a diagnosis of colorectal cancer but whose plan was not to undergo treatment at that hospital were excluded as the feasibility of out-of-pocket payments data collection would be compromised. Patients for whom the telephone follow-up at six weeks, three months or six months wasn't possible were also excluded.

3.4.7 Study outcomes

3.4.7.1 Primary analysis - catastrophic expenditure and treatment attrition

3.4.7.1.1 Costs of colorectal cancer treatment

The total costs of colorectal cancer treatment, paid by patients as OOPP (patient perspective) or covered by any third parties (healthcare system perspective) were reported. Out-of-pocket payments were defined as payments made by patients at the time of cancer service use that were not covered by any other third party (details below, under the definition of catastrophic expenditure). Costs covered by third parties included insurance companies (pre-paid by the patient or their employer), central or state government funding schemes (e.g. Ayuhsman Bharat, Swastha Sathi) or covered by hospitals at free cost for patients (concessions or discounts). These data were collected from hospital bills and from patient-reported expenses via telephone, at six weeks, three months and six months after a new treatment plan. These three timepoints were used to mitigate against

recall bias and loss to follow-up, but research teams were trained to collect costs from the specified time-window to avoid double counting.

3.4.7.1.2 Funding support and distress financing strategies

Patients reported if they were accessing or applying any funding support from third parties, including government funding schemes (central government or state government), medical insurance (private or employer-provided) or free-care and discounts provided by the hospital.

Besides the described third parties that could have covered patients' treatment costs, distress financing strategies were reported, money loans, property selling and donations from relatives or friends. The money raised through distress financing strategies was not considered to be cancer care coverage by a third party, as they are not systematic pathways of financial protection.

3.4.7.1.3 Catastrophic Expenditure

The primary outcome was catastrophic expenditure at six months after a new treatment plan, defined as out-of-pocket payments (OOPP) for colorectal cancer being higher than 25% of patient's annual household income.

$$Catastrophic\ expenditure =$$

$$out\ of\ pocket\ payments > 25\%\ of\ household\ income$$

Although there is no consensus on the ideal threshold for the definition of catastrophic expenditure, this threshold was chosen from the options made available by the World Health Organisation. The proportion of population with large household expenditures on health as a share of total household expenditure or income is the indicator of the Sustainable Development Goal 3.8.2, within the Goal 3: Good health and well-being (44). Other definitions exist and have been used by the WHO, such as:

- Catastrophic expenditure defined as out-of-pockets for healthcare being higher than 10% of annual household income (43)
- Catastrophic expenditure defined as out-of-pockets for healthcare being higher than 40% of annual household capacity to pay, with capacity to pay equating non-subsistence income (income left after paying for subsistence needs like housing and food) (42)

Multiple other definitions have been used in publications on catastrophic costs of healthcare, and an ideal definition hasn't been agreed on(41). The use of different thresholds to define catastrophic expenditure results makes the rates reported in different studies difficult to compare and interpret in the context of previous literature. Therefore, I have decided to use the definition most recently and widely used by the WHO.

Out-of-pocket payments

Out-of-pocket payments were defined as payments made by patients at the time of cancer service use that were not covered by any other third party and included medical, non-medical and indirect expenses. Medical OOPP included payments made at the participating hospitals (collected from hospital bills, confirmed with patients), at other healthcare facilities if patients received part of the treatment elsewhere (reported by patients) and for other healthcare services (e.g. pharmacy, nursing services, dressings, colostomy bags). Non-medical OOPP included travel, accommodation and food expenses necessary to receive treatment at the participating hospitals. Indirect OOPP reflect patient income loss while being absent of work due to receiving treatment. Full details on how OOPP were collected are available in Table 11. The average proportion of medical, non-medical and indirect expenses from the total OOPP for colorectal cancer was reported.

Table 11: Details of out-of-pocket payment: definitions, data source and timing of data collection.

Type of OOPP for colorectal cancer care	Definition	Examples	Data source	Timing of collection
Direct Costs	Out-of-pocket payments to d rect y pay for co orecta cancer treatment			
Direct Medical	Out-of-pocket payments for co orecta cancer d agnos s and treatment			
In the hospital	D rect payments at the part c pat ng hosp ta	e.g. surg ca fees, rad otherapy fees	Hosp ta b s	Fo ow up
Outside the hospital	D rect payments to other hosp ta / hea thcare fac ty / prov der (prev ous y and wh e be ng treated at the part c pat ng hosp ta)	e.g. drugs from the pharmacy, dress ng costs	Pat ent	F rst assessment Fo ow up
Direct Non-medical	Out-of-pocket payments re ated to the use of cancer care serv ces at the part c pat ng hosp ta			
Travelling	Payments made by pat ent s househo d for: - Da y commut ng to the hosp ta (pat ent and/or compan ons) - Long d stance trave ng (pat ent and/or househo d members)	e.g. bus or tax to the hosp ta e.g. f ght or tra n to the hosp ta	Pat ent	Fo ow up
Accommodation	Payments made by the pat ent s househo d for accommodat on near the hosp ta n order to access treatment (pat ent and/or compan ons)	e.g. stay ng n a hote near the hosp ta to attend mu t p e outpat ent v s ts	Pat ent	Fo ow up
Food	Payments made by the pat ent s househo d for food near the hosp ta n order to access treatment (pat ent and/or compan ons)	e.g. food bought by pat ent s re at ves wh e stay ng away from home	Pat ent	Fo ow up
Indirect Costs	Income osses re ated work absence due to co orecta cancer care, ncurred by the pat ent (th s exc udes eave days when sa ary s not pena sed)	e.g. ncome not earned by the pat ent dur ng hosp ta adm ss on	Pat ent	Fo ow up

3.4.7.1.3.1 Household income (self-reported)

Patients' annual household income was defined as the total amount earned by all the earning members of the household over the one year, in Indian Rupees (INR). The monthly household income was reported by patients at the time of first assessment (face-to-face) and multiplied by twelve to achieve an annual income figure.

3.4.7.1.4 Treatment attrition

Treatment attrition at six months after a treatment plan was the secondary outcome, defined as an interruption of the treatment course that was not planned or recommended by the clinical team. Treatment interruption due to side effects, clinical events or clinical decisions on treatment plans were not included in this definition. The reasons for treatment drop-out were reported by patients whenever possible, at the time of follow-up.

3.4.7.2 Secondary analysis - comparison of the use of the self-reported, international wealth index and Gapminder incomes:

According to the feedback obtained by the local research partners, two other indirect measure of income were collected, and their use was compared to the self-reported income.

3.4.7.2.1 Self-reported household income

Patients' annual household income was defined as the total amount earned by all the earning members of the household over the one year, in Indian Rupees (INR). The monthly household income was reported by patients at the time of first assessment (face-to-face) and multiplied by twelve to achieve an annual income figure. This definition is given above but is repeated for convenience of the reader.

3.4.7.2.2 International Wealth Index income

The International Wealth Index (IWI) is a twelve-point questionnaire where patients reported whether they owned a number of consumer durables (television, refrigerator, phone, car, bicycle, cheap utensils e.g. chair and expensive utensils e.g. air conditioner) and described their household characteristics (floor material, toilet facility, number of rooms, access to electricity and water source)(122). Based on the responses to these questions, a final score is calculated, ranging from 0 to 100 where a low score relates to lower wealth levels and a high score relates to a wealthier household. The full score is available in the Table 12. This tool was validated in multiple national and international population based datasets(122).

Table 12: International Wealth Index.

International Wealth Index		
Consumer durables	**Do you own this item?**	**Weight of the item in overall score**
Television	Yes/No	8.612657
Refrigerator	Yes/No	8.429076
Phone	Yes/No	7.127699
Car	Yes/No	4.651382
Bike	Yes/No	1.84686
Do you have one or more of these utensils? Chair, table, clock, watch, water cooker, radio, fan or mixer.	Yes/No	4.118394
Do you have one or more of these utensils? Washer, dryer, computer, motorbike, motorboat, air conditioner, or generator.	Yes/No	6.507283
Housing characteristics		
Which is your **floor** material? (choose **one** of the options below)		
Earth, dung, sand	☐	-7.558471
Cement, concrete, raw wood	☐	1.227531
Finished floor with parquet, carpet, tiles, ceramic	☐	6.107428
How is your **toilet** facility? (choose one of the options below)		
Traditional pit latrine, hanging toilet, or no toilet facility	☐	-7.439841
Public toilet, improved pit latrine	☐	-1.090393
Private flush toilet	☐	8.140637
How many rooms are there in your house? (choose **one** of the options below)		
Zero or one	☐	-3.699681
Two	☐	0.38405
Three or more	☐	3.445009
Public utilities		
Access to **electricity**	Yes/No	8.056664
Water source: (choose **one** of the options below)		
Spring, surface water, unprotected well	☐	-6.306477
Public tap, protected well or tanker truck	☐	-2.302023
Bottled water or water piped into dwelling or premises	☐	7.952443
	Constant	25.00447

The final IWI score was translated into an income figure using a previously available formula that explains the relationship between income and the IWI score in 2015 United States Dollars (USD)(123). The following formula was obtained by computing the IWI in multiple population-based households (including the India Human Development Survey).

*IWI income (per day, in USD) = 1.489056*exp(0.02918)*

In order to obtain a figure that is comparable to the reported income in 2021 Indian Rupees, the IWI income in 2015 United States Dollars (USD) was multiplied by purchase power parities (PPP) for USD-INR exchange and by the consumer price index to account for inflation between 2015 and 2021(124).

3.4.7.2.3 Gapminder income

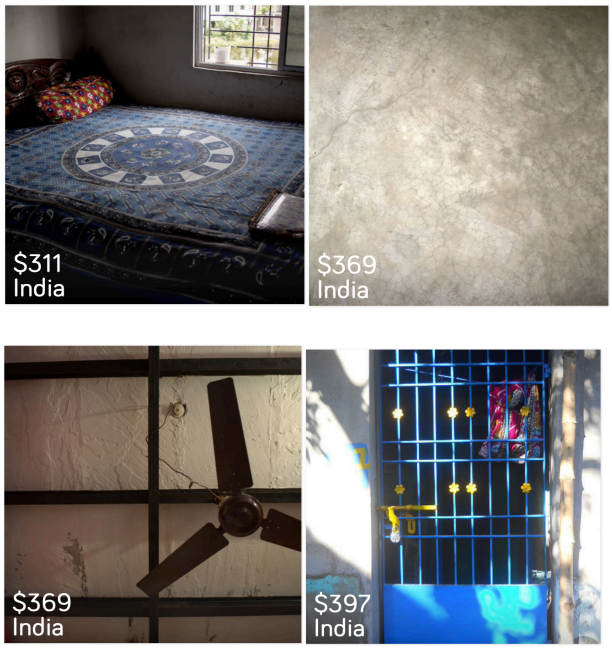
The Gapminder Foundation has created the Dollar Street project where a pool of pictures of household and personal goods are available and matched to an income reported by the household members to the Gapminder team (125). The patients were shown five categories of pictures from Indian households (all the available at the time of study design): houses, kitchens, floors, toilets and beds. The patient was invited to select the house, kitchen, floor, toilet and bed that looked more similar to the one their own, to which an income was then matched (see Figure 22). The mean average of the income matched to the selected

pictures was obtained and converted from USD to INR using purchase power parities, as follows:

$$Gapminder\ income = \frac{(Income\ matched\ to\ house + kitchen + floor + toilet + bed)}{5} * PPP$$

This tool has never been validated.

Figure 22: Illustrative example of Gapminder pictures chosen by a patient.

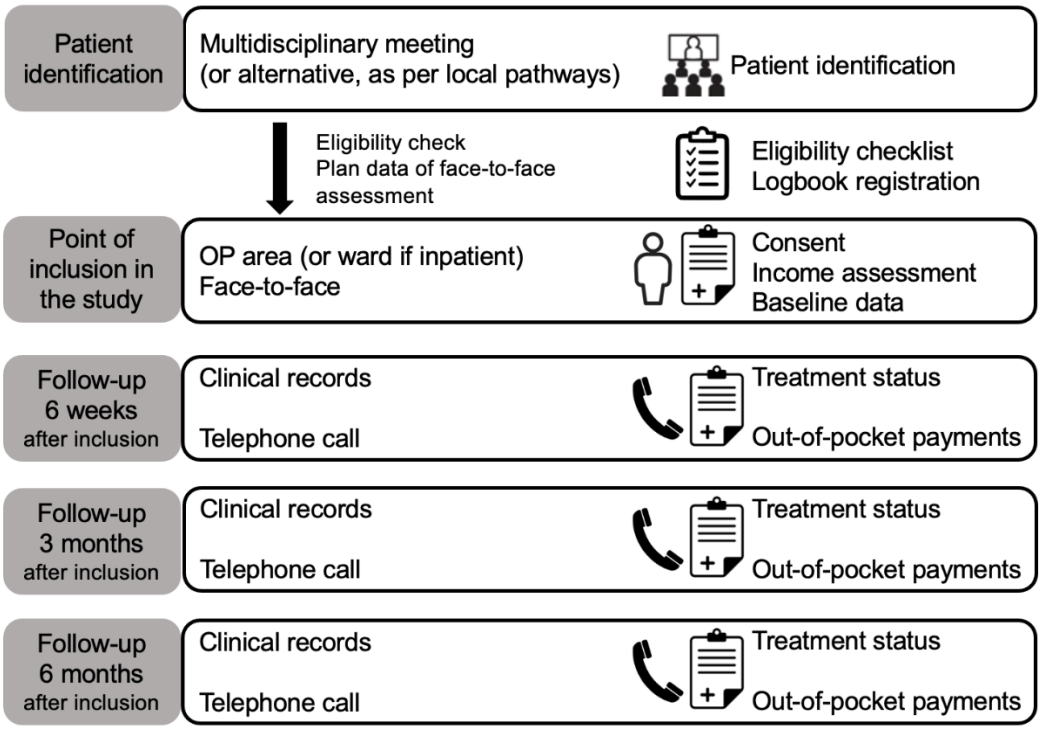


The income calculation in this case would be: (311+369+369+369+397) / 5 = 363 US dollars (conversion to Indian Rupees performed after).

3.4.8 Schedule of assessments

After patient identification, the baseline assessment was planned for their next visit to the hospital. This was a face-to-face assessment where demographic data, baseline tumour and treatment details were collected, and during which the income assessment was performed (including self-reported, IWI and Gapminder). The first follow-up timepoint was performed at 6 weeks, where costs of treatment and treatment attrition were collected. Costs of treatment were collected from hospital bills and via a telephone call with patients, and included payments made out-of-pocket and covered by any third parties. Treatment attrition was collected from clinical files and confirmed with patients during the telephone call. Similar processes were used for 3 months and 6 months follow-up. A diagram of the assessments included in the study is shown in Figure 23.

Figure 23: Diagram of the study flow with the timepoints of patient assessment for baseline and outcome data.



3.4.9 Other data variables and definitions

The collected demographic variables included age, sex, patient education (highest completed level: graduate, secondary, primary or none), household size (number of adults and children sharing the same house unit), employment status (categorized into employed, non-employed [housewives/students/other] and retired) and distance from the patient's house to the hospital (in kilometres (km), categorised into <100, 100-500, >500 km). Cancer stage was defined according to the TMN classification (8th edition of the AJCC guidelines(126)), being categorised into local (T1-3 without nodal or metastatic invasion) or advanced (T4 or with positive nodes or with metastatic spread). Treatment intent was defined as curative or palliative at the time when the treatment plan was made. Treatment status at follow-up was collected, including at least one of the following: surgical resection, chemotherapy, radiotherapy, diverting stoma and targeted therapy. The treatment status was categorised into surgical resection and no surgical resection for the analysis, as this was expected to be a key determinant of oncological and study outcomes. Hospital types reflect the funding system of the hospital where the patients were recruited, being defined as public if funded by the government and private if privately owned (profit or non-profit).

3.4.10 Data handling and analysis

The analysis was performed using the R statistical software (version 4.1.1). Categorical variables were described with frequency tables and percentages. Continuous variables were summarised with appropriate metrics: mean and

standard deviation when normally distributed or with median and interquartile range otherwise. Although costs data are usually skewed by nature, policy making typically requires average means to be presented the extremes of populations need to be accounted for in decision making(127). Chi-square tests were used for unadjusted analysis of categorical variables, T-tests for comparison of normally distributed continuous variables between groups, and Mann-Whitney U tests for when the distribution was non-normal. Logistic regression models were used for adjusted analysis. Missing data was reported in all figures and tables.

- Primary analysis - catastrophic expenditure and treatment attrition:

  Mean costs of treatment, with a split by OOPP and costs covered by third parties were presented. Rates and characteristics of patients with catastrophic expenditure and treatment attrition were described. The mean OOPP made by patients with and without these outcomes were presented and compared. A logistic regression model was used to identify independent predictors of catastrophic expenditure.

- Secondary analysis - comparison of the use of the self-reported, international wealth index and Gapminder incomes:

  Median self-reported, IWI and Gapminder incomes were reported and plotted. A Bland-Altman analysis was performed to describe the agreement between (1) self-reported and IWI income and (2) self-reported and Gapminder income. In the Bland-Altman plots, the difference between reported and estimated incomes was plotted against the mean average of those the same incomes(128). A standard Bland-Altman analysis with

agreement limits based on 95% confidence intervals for the observations was not possible, because the income data did not comply with normality assumptions. I opted for the description of the proportion of patients for whom the differences between reported and estimated incomes were within a particular range (methodology suggested by Bland and Altman for non-parametric data(129). This allows an understanding of the range of differences between reported and estimated incomes, as well as the description of any patterns in the Bland-Altman plots.

This study followed the reporting guidelines for observational studies (STROBE) (see checklist in Supplementary Table 3).

3.5 Results

3.5.1 Patients and households

A total of 226 patients were included from five hospitals. Recruitment numbers and study periods per hospital (anonymised data) are shown in Table 13. The included hospitals served diverse patient populations, as demonstrated in Table 14, e.g. Hospital C included more older and colon cancer patients, who lived closer to the hospital, whereas Hospital D had patients with low education and large households. Of 226 patients, 20 died within six months of being offered a treatment plan and four were lost to follow-up. Detailed number of deaths and losses to follow-up at each follow-up timepoint are given in Figure 24. Patients receiving treatment with palliative intent were more likely to die within six months of a treatment decision (27% vs 5.4% mortality in patients with palliative and curative treatment plans, $p<0.001$). Low education levels were also associated with higher mortality rates, being 16.4% in patients with primary or no education vs 6.3% in patients with secondary or graduate education). The remaining characteristics were similar between patients who were alive and dead at six months follow-up. Of the twenty patients who died, only two had not received any treatment before the time of death. Full details are shown in in Table 15.

Table 13: Study inclusion period and total recruitment numbers in each participating hospital.

Hospital	Patient recruitment period	Last date of follow-up	Number of patients enrolled	Type of hospital
Hospital A	Dec 2020 - Aug 2021	March 2022	6	Charity/private
Hospital B	Dec 2020 - July 2021	Jan 2022	70	Charity/private
Hospital C	Jan 2021-July 2021	Jan 2022	70	Charity/private
Hospital D	Dec 2020 - July 2021	Jan 2022	60	Government
Hospital E	Aug 2021	March 2022	20	Government

Table 14: Patient characteristics by participating hospital.

		Hospital A	Hospital B	Hospital C	Hospital D	Hospital E
Age	18-40 years	4 (80.0)	20 (29.4)	7 (10.9)	16 (32.7)	5 (31.2)
	41-60 years	1 (20.0)	27 (39.7)	25 (39.1)	22 (44.9)	7 (43.8)
	>60 years	0 (0.0)	21 (30.9)	32 (50.0)	11 (22.4)	4 (25.0)
Sex	Fema e	2 (40.0)	24 (35.3)	29 (45.3)	15 (30.6)	2 (12.5)
	Ma e	3 (60.0)	44 (64.7)	35 (54.7)	34 (69.4)	14 (87.5)
Pat ent educat on	Secondary/ Graduate	4 (80.0)	49 (72.1)	55 (85.9)	27 (55.1)	16 (100.0)
	Pr mary/none	1 (20.0)	19 (27.9)	9 (14.1)	22 (44.9)	0 (0.0)
Emp oy-ment	Emp oyed	4 (80.0)	36 (52.9)	22 (34.4)	28 (57.1)	11 (68.8)
	Unemp oyed	1 (20.0)	23 (33.8)	23 (35.9)	15 (30.6)	2 (12.5)
	Ret red	0 (0.0)	9 (13.2)	19 (29.7)	6 (12.2)	3 (18.8)
Househo d s ze	< 4 peop e	3 (60.0)	31 (45.6)	43 (67.2)	14 (28.6)	9 (56.2)
	>= 4 peop e	2 (40.0)	37 (54.4)	21 (32.8)	35 (71.4)	7 (43.8)
Cancer ocat on	Co on	2 (40.0)	33 (48.5)	37 (57.8)	19 (38.8)	6 (37.5)
	Rectum	3 (60.0)	35 (51.5)	27 (42.2)	30 (61.2)	10 (62.5)
Cancer stage	Loca	0 (0.0)	10 (14.9)	8 (12.7)	8 (16.3)	2 (12.5)
	Advanced	5 (100.0)	57 (85.1)	55 (87.3)	41 (83.7)	14 (87.5)
Treatment ntent	Curat ve	2 (40.0)	59 (86.8)	56 (87.5)	42 (85.7)	16 (100.0)
	Pa at ve	3 (60.0)	9 (13.2)	8 (12.5)	7 (14.3)	0 (0.0)
D stance to hosp ta	0-100 km	2 (40.0)	7 (10.3)	36 (56.2)	15 (30.6)	6 (37.5)
	100-500 km	3 (60.0)	8 (11.8)	17 (26.6)	33 (67.3)	3 (18.8)
	>500km	0 (0.0)	53 (77.9)	11 (17.2)	1 (2.0)	7 (43.8)

Data presented as n(%). Percentages by column. Missing data for cancer stage n=2, for treatment intent n=1.

Figure 24: Flowchart of deaths and losses of follow-up, at each follow-up timepoint.

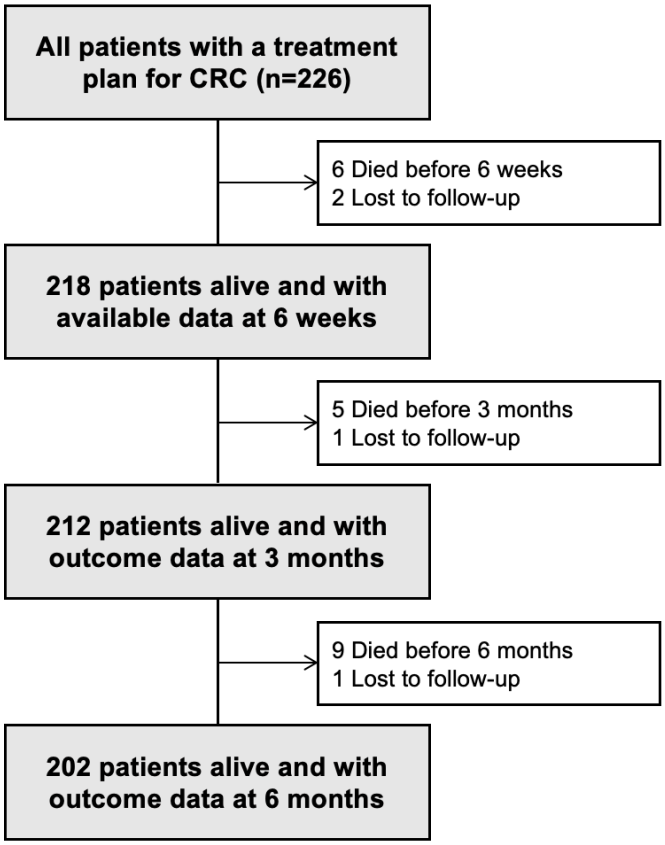


Table 15: Characteristics of patients who were alive and dead at six months follow-up.

		Mortality at 6 months		
		No	Yes	p-value
Age	18-40 years	52 (92.9)	4 (7.1)	0.705
	41-60 years	82 (89.1)	10 (10.9)	
	>60 years	68 (91.9)	6 (8.1)	
Sex	Female	72 (88.9)	9 (11.1)	0.558
	Male	130 (92.2)	11 (7.8)	
Patient education	Secondary/Graduate	151 (93.8)	10 (6.2)	0.035
	Primary/none	51 (83.6)	10 (16.4)	
Employment	Employed	101 (92.7)	8 (7.3)	0.075
	Unemployed	64 (85.3)	11 (14.7)	
	Retired	37 (97.4)	1 (2.6)	
Income category	High	101 (92.7)	8 (7.3)	0.536
	Low	101 (89.4)	12 (10.6)	
Household size	< 4 people	100 (88.5)	13 (11.5)	0.277
	>= 4 people	102 (93.6)	7 (6.4)	
Cancer location	Colon	97 (90.7)	10 (9.3)	1
	Rectum	105 (91.3)	10 (8.7)	
Cancer stage	Local	28 (96.6)	1 (3.4)	0.431
	Advanced	172 (90.1)	19 (9.9)	
Treatment intent	Curative	174 (94.6)	10 (5.4)	<0.001
	Palliative	27 (73.0)	10 (27.0)	
Distance to hospital	0-100 km	66 (86.8)	10 (13.2)	0.138
	100-500 km	64 (90.1)	7 (9.9)	
	>500km	72 (96.0)	3 (4.0)	
Hospital type	Government	65 (85.5)	11 (14.5)	0.071
	Charity / Private	137 (93.8)	9 (6.2)	
Funding scheme	No	115 (87.8)	16 (12.2)	0.078
	Yes	87 (95.6)	4 (4.4)	
Insurance	No	174 (90.6)	18 (9.4)	0.889
	Yes	28 (93.3)	2 (6.7)	

Data presented as n(%). Percentages by row. Missing data for cancer stage n=2, for treatment intent n=1.

From the 202 patients included in the main analysis (alive at six months), more than half were male (63.3%), and the mean age was 52 years (standard deviation 14.8). Overall, 36.3% of the patients held a graduate degree, 36.3% attended secondary school and 27% attended primary school or had no school education. Around half of the patients were employed (48.7%), with the remaining being either unemployed (34.1%) or retired (17.3%). The median household size was 5 people (IQR 4-6 people), the median distance to hospital was 200 km (IQR 51.5-1622.5 km) and the median household income per year was 228,000 Indian rupees (IQR 120,000-501,000).

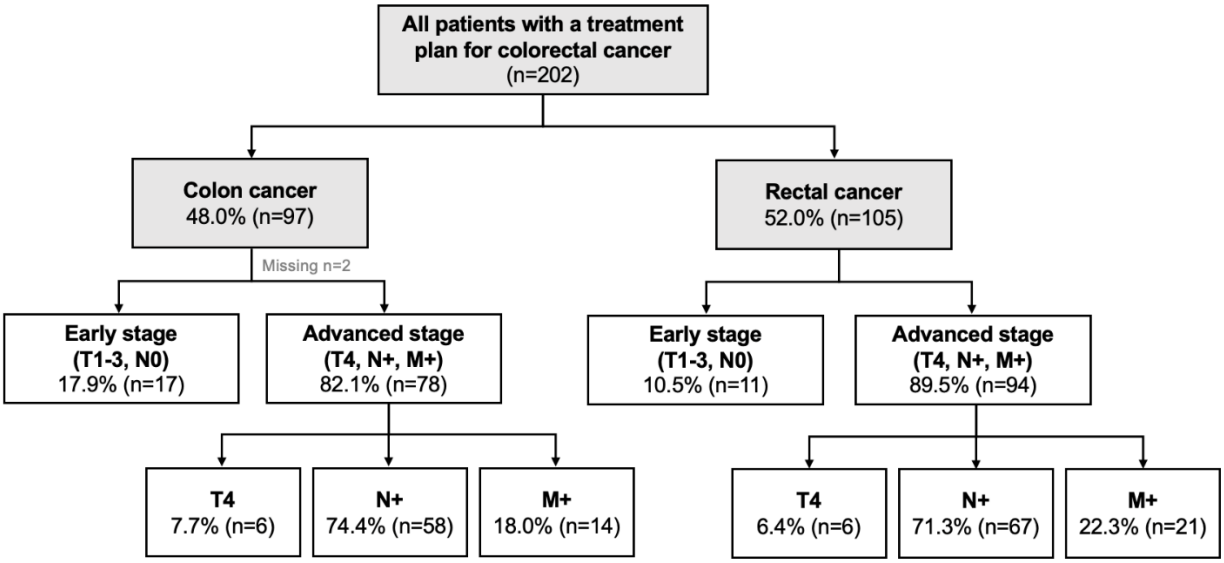
3.5.2 Tumour and treatment characteristics

Overall, 48.0% (97/202) had colon cancer and 52.0% (105/202) had rectal cancer. Advanced disease stage was predominant, with only 17.9% of colon cancer patients and 10.5% of the rectal cancer patients presenting with early disease (Figure 25). Most patients in this cohort had a plan for curative treatment, both in colon cancer (93.8%) and rectal cancer (79.8%) (Figure 26).

Regarding the type of treatment that patients received, around half of the patients (48.5%) received both resection surgery and radio/chemotherapy, whereas 35.5% of the patients received chemo or radiotherapy only and 16.3% received resection surgery only. Figure 27 shows the types of treatment by cancer location, demonstrating that the proportion of patients not receiving resection

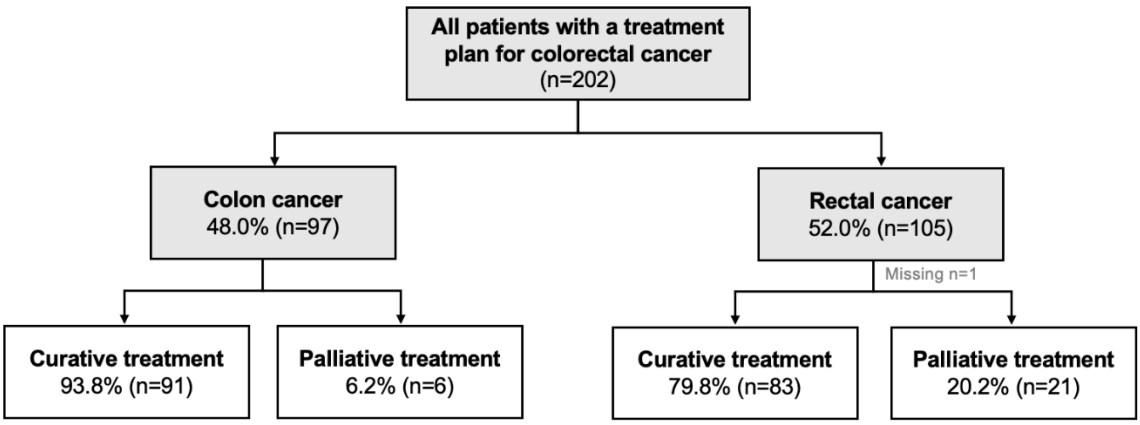
surgery is higher in rectal cancer, whereas colon cancer patients have a higher proportion of patients undergoing resection only.

Figure 25: Flowchart of disease stage by cancer location, in patients alive at 6 months after a treatment plan.



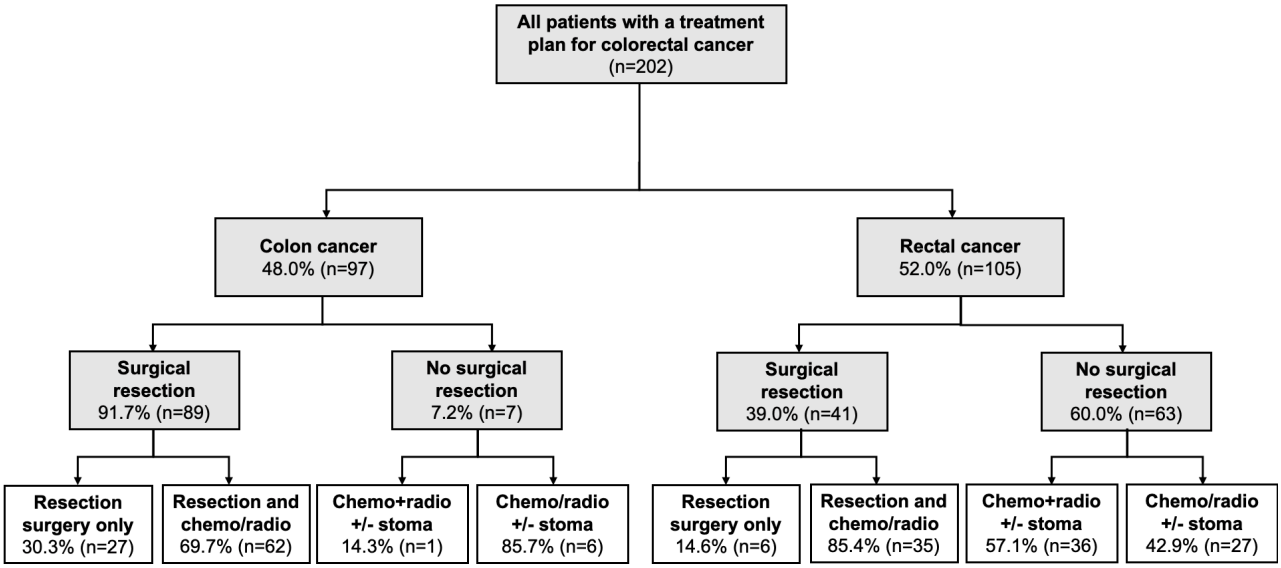
Missing data for cancer stage n=2. T describes the extension of the tumour in the visceral wall. N describes lymph node affection. M describes the existence of metastases.

Figure 26: Flowchart of treatment intent by cancer location, in patients alive at 6 months after a treatment plan.



Missing data for treatment intent n=1.

Figure 27: Type of treatment by cancer location.



Two of the patients (1 colon and 1 rectal cancer patient) are missing in this diagram as the patients reached the six months follow-up without receiving any treatment.

3.5.3 Primary analysis – catastrophic expenditure and treatment attrition

3.5.3.1 Cost of colorectal cancer treatment

The mean total cost of colorectal cancer treatment was 475,781 INR (SD 292,944) and the largest proportion of these were medical costs (mean 392,611 INR, SD 275,020). Medical costs paid out-of-pocket (mean 283,142 INR, SD 219,498) were higher than the medical expenses covered by third parties (mean 109,469 INR, SD 194,839). See Figure 28 for a full breakdown of average total costs and OOPP. From the total costs at the index hospital, surgery and anaesthesia fees (mean 102,864 [SD 88,987]) were higher than radiotherapy (mean cost 66,753 [SD 69,283]) and chemotherapy (mean 47,824 [SD 78,159]). Charged fees for other items at the index hospital are shown in Table 16.

Table 16: Mean cost of hospital items collected from the hospital bills.

Items on hospital bills	Mean cost (standard deviation)
Main cancer treatment items	
Surgery and anaesthes a (n=138)	102,864 INR (88,987)
Rad otherapy (n=62)	66,753 INR (69,283)
Chemotherapy (n= 160)	47,824 INR (78,159)
Other items	
Adm ss on (ward/ITU)	23,534 INR (30,920)
Outpat ent fees	1,219 INR (3,700)
Invest gat ons (mag ng, aboratory and patho ogy)	37,088 INR (36,577)
Other (other drugs or tems)	50,283 INR (62,580)

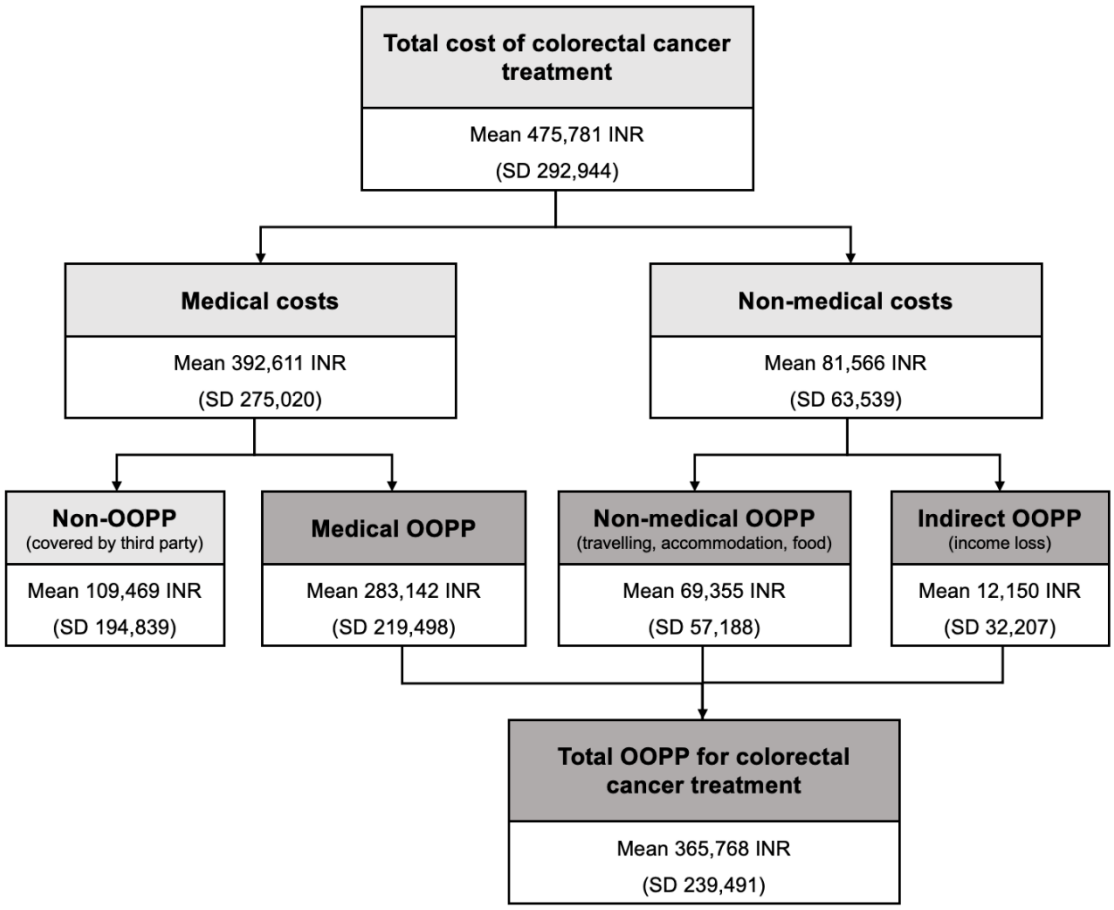
Table displays the average cost of the reported items, from hospital bills only. Costs paid outside the hospital or that are not reported in the bills are not included in this table (e.g., chemotherapy drugs bought outside the hospital). ITU = Intensive Treatment Unit. Missing data for the cost of colorectal cancer treatment n=1.

The average OOPP made by patients for colorectal cancer care was 365,768 INR (SD 239,491). This included the OOPP for medical expenses but also non-medical expenses such as travelling, accommodation and food (mean 69,355 INR (SD 57,188)) and indirect expenses in the form of income loss (mean 12150 INR (SD 32,207)) (see Figure 28). On average, 73.4% of the total OOPP made by patients were direct medical expenses, 22.4% were non-medical expenses and 4.1% was income loss.

3.5.3.2 Funding support and distress financing strategies

From all patients, 43.1% (87/202) applied for government funding schemes, 13.9% (28/202) had private or employer-provided insurance and 20.8% (42/202) benefited from discounts/concessions provided by the hospital. Funding support options were reported by patients, with 43.1% (87/202) having applied for government funding schemes, 13.9% (28/202) having private or employer-provided insurance and 20.8% (42/202) benefiting from discounts provided by the hospital. Distress financing strategies included donations from friends or relatives in 12.8% (26/202) of the patients, money loans in 10.9% (22/202) and property selling in 1.9% (4/202).

Figure 28: Total costs and out-of-pocket payments (OOPP) for colorectal cancer treatment.



Missing data for the cost of colorectal cancer treatment n=1.

3.5.3.3 Catastrophic expenditure

The overall rate of catastrophic expenditure was 90.1% (182/202). In the unadjusted analysis, catastrophic expenditure was associated with employment status, distance from the patient's home to hospital and insurance coverage. The catastrophic expenditure rates were higher in employed (94.1%) and unemployed patients (93.7%), compared to patients who were retired (75.7%, p=0.003). Patients who lived farther from the hospital had higher catastrophic expenditure rates (81.5% in patients living up to 100km, 93.8% if living within 100-500 km and 95.8% if living more than 500 km from the hospital, p=0.01). Patients with insurance coverage had lower rates of catastrophic expenditure (75.0% vs 93.1%, p=0.007). The full unadjusted results are shown in Table 17.

Catastrophic expenditure was independently associated with male sex (OR 13.16, 95%CI 2.05-105.09, p=0.009), primary or no education (OR 40.88 95%CI 2.88-1870.70, p=0.021), treatment in private hospitals (OR 6.74, 95%CI 1.32-41.75, p=0.027), rectal cancer (OR 5.31, 95%CI 1.08-31.27, p=0.049) advanced cancer stage (OR 5.94, 95%CI 1.11-34.95, p=0.038), and receiving surgical resection (OR 11.0, 95%CI 1.27-119.37, p=0.036). Patients who were retired (0.12, 95%CI 0.01-0.87, p=0.047) and who had medical insurance (OR 0.10, 94%CI 0.01-0.56, p=0.012) were less likely to have catastrophic expenditure. The full adjusted model is available in Table 18.

Table 17: Characteristics of patients with and without catastrophic expenditure.

		Catastrophic Expenditure		
		No	Yes	p-value
Age	18-40 years	3 (5.8)	49 (94.2)	0.066
	41-60 years	5 (6.2)	76 (93.8)	
	>60 years	11 (16.2)	57 (83.8)	
Sex	Female	8 (11.3)	63 (88.7)	0.691
	Male	11 (8.5)	119 (91.5)	
Patient education	Secondary/Graduate	18 (11.9)	133 (88.1)	0.072
	Primary/none	1 (2.0)	49 (98.0)	
Employment	Employed	6 (5.9)	95 (94.1)	0.003
	Unemployed	4 (6.3)	59 (93.7)	
	Retired	9 (24.3)	28 (75.7)	
Household size	< 4 people	8 (8.0)	92 (92.0)	0.646
	>= 4 people	11 (10.9)	90 (89.1)	
Cancer location	Colon	11 (11.5)	85 (88.5)	0.491
	Rectum	8 (7.6)	97 (92.4)	
Cancer stage	Local	5 (17.9)	23 (82.1)	0.201
	Advanced	14 (8.1)	158 (91.9)	
Treatment intent	Curative	17 (9.8)	156 (90.2)	0.963
	Palliative	2 (7.4)	25 (92.6)	
Distance to hospital	0-100 km	12 (18.5)	53 (81.5)	0.01
	100-500 km	4 (6.2)	60 (93.8)	
	>500km	3 (4.2)	69 (95.8)	
Hospital type	Government	10 (15.4)	55 (84.6)	0.084
	Charity / Private	9 (6.6)	127 (93.4)	
Funding scheme	No	11 (9.6)	103 (90.4)	1
	Yes	8 (9.2)	79 (90.8)	
Insurance	No	12 (6.9)	161 (93.1)	0.007
	Yes	7 (25.0)	21 (75.0)	

Missing data for catastrophic expenditure n=1, for cancer stage n=2, for treatment intent n=1.

Table 18: Adjusted model exploring factors associated with catastrophic expenditure.

		Catastrophic expenditure			
		No	Yes	OR (univariable)	OR (multivariable)
Treatment attrition	No	16 (8 8)	166 (91 2)	-	-
	Yes	3 (15 8)	16 (84 2)	0 51 (0 15-2 37 p=0 329)	0 23 (0 03-2 28 p=0 186)
Age	18-40 years	3 (5 8)	49 (94 2)	-	-
	41-60 years	5 (6 2)	76 (93 8)	0 93 (0 18-3 97 p=0 924)	0 68 (0 10-4 18 p=0 683)
	>60 years	11 (16 2)	57 (83 8)	0 32 (0 07-1 08 p=0 091)	0 89 (0 09-8 96 p=0 923)
Sex	Female	8 (11 3)	63 (88 7)	-	-
	Male	11 (8 5)	119 (91 5)	1 37 (0 51-3 57 p=0 517)	13 16 (2 05-105 09 p=0 009)
Patient education	Secondary/Graduate	18 (11 9)	133 (88 1)	-	-
	Primary/none	1 (2 0)	49 (98 0)	6 63 (1 31-120 89 p=0 069)	40 88 (2 88-1870 70 p=0 021)
Household size	< 4 people	8 (8 0)	92 (92 0)	-	-
	>= 4 people	11 (10 9)	90 (89 1)	0 71 (0 26-1 84 p=0 485)	0 53 (0 12-2 17 p=0 383)
Employment	Employed	6 (5 9)	95 (94 1)	-	-
	Unemployed	4 (6 3)	59 (93 7)	0 93 (0 26-3 77 p=0 915)	1 95 (0 25-15 55 p=0 516)
	Retired	9 (24 3)	28 (75 7)	0 20 (0 06-0 59 p=0 004)	0 12 (0 01-0 87 p=0 047)
Distance to hospital	0-100 km	12 (18 5)	53 (81 5)	-	-
	100-500 km	4 (6 2)	60 (93 8)	3 40 (1 11-12 73 p=0 044)	4 31 (0 94-24 70 p=0 075)
	>500km	3 (4 2)	69 (95 8)	5 21 (1 56-23 70 p=0 014)	3 94 (0 64-34 18 p=0 166)
Hospital type	Public	10 (15 4)	55 (84 6)	-	-
	Private	9 (6 6)	127 (93 4)	2 57 (0 98-6 80 p=0 053)	6 74 (1 32-41 75 p=0 027)
Cancer location	Colon	11 (11 5)	85 (88 5)	-	-
	Rectum	8 (7 6)	97 (92 4)	1 57 (0 61-4 23 p=0 356)	5 31 (1 08-31 27 p=0 049)
Cancer stage	Local	5 (17 9)	23 (82 1)	-	-
	Advanced	14 (8 1)	158 (91 9)	2 45 (0 74-7 11 p=0 113)	5 94 (1 11-34 95 p=0 038)
Treatment intent	Curative	17 (9 8)	157 (90 2)	-	-
	Palliative	2 (7 4)	25 (92 6)	1 35 (0 36-8 86 p=0 697)	1 55 (0 20-17 14 p=0 692)
Surgical resection	No Resection	7 (10 0)	63 (90 0)	-	-
	Resection	12 (9 2)	119 (90 8)	1 10 (0 39-2 88 p=0 846)	11 00 (1 27-119 37 p=0 036)
Funding scheme	No	11 (9 6)	103 (90 4)	-	-
	Yes	8 (9 2)	79 (90 8)	1 05 (0 41-2 84 p=0 913)	0 52 (0 10-2 66 p=0 428)
Insurance	No	12 (6 9)	161 (93 1)	-	-
	Yes	7 (25 0)	21 (75 0)	0 22 (0 08-0 66 p=0 005)	0 10 (0 01-0 56 p=0 012)

Number in dataframe = 202, Number in model = 200, Missing = 2, AIC = 113, C-statistic = 0.899, H&L = Chi-sq(8) 4.34 (p=0.825). Missing data for catastrophic expenditure n=1, for cancer stage n=2, for treatment intent n=1.

The mean OOPP made by patients who suffered catastrophic expenditure was 387,536 INR (SD 235,980), being lower in those without catastrophic expenditure 157,253 INR (SD 163,232). Patients who didn't suffer from catastrophic expenditure had no income losses and had a higher proportion of OOPP for non-medical expenses (29.1% vs 22.8%) (see Figure 29 and Table 19).

Figure 29: Out-of-pocket payments in patients with and without catastrophic expenditure.

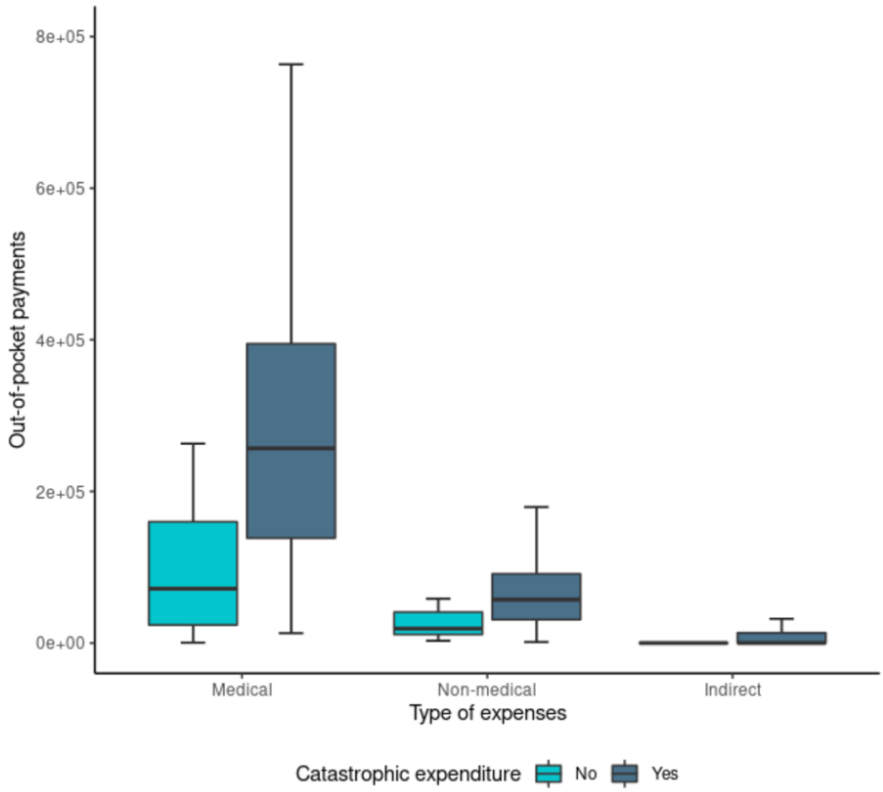


Chart displays OOPP (in India Rupees) for medical, non-medical and indirect expenses by catastrophic expenditure. Absolute figures for all types of OOPP are given in Table 19. Missing data for the cost of cancer treatment n=1.

Table 19: Absolute OOPP by catastrophic expenditure, with a breakdown of medical, non-medical and indirect as a proportion of total OOPP.

	Mean total OOPP (INR)	p-value	Average proportion (%) of OOPP		
			Medical OOPP	Non-medical OOPP	Indirect OOPP
All patients	365,768	--	73.4%	22.4%	4.1%
Catastrophic expenditure					
Yes	387,536	p<0.001	72.3%	22.8%	4.8%
No	157,253		70.9%	29.1%	0%

Missing data for the cost of colorectal cancer treatment n=1.

3.5.3.4 Treatment attrition

Of all patients, 9.4% (19/202) had attrition of treatment, the majority because they declined treatment (n=10) or opted for Ayurvedic medicine (n=4), with the remaining mentioning inability to pay (n=3), inability to travel (n=1) or other reasons (n=1). The reasons for treatment attrition reported by patients with and without catastrophic expenditure are reported in Table 20.

Treatment attrition was more common in patients with lower education levels (17.6% for primary or non-educated patients versus 6.6% for secondary or higher education, p=0.04). The rates of attrition varied with distance from the patient's home to the hospital, being 10.6% in patients living within 100km, 15.6% in patients living within 100-500 km and 2.8% in patient living beyond 500 km from the hospital. Patients being treatment in government hospitals were more likely to drop out of treatment than in private / charity hospitals (18.5% vs 5.1%, p=0.005). Full unadjusted results are shown in Table 21.

Table 20: Reasons for treatment attrition by catastrophic expenditure.

Reasons for treatment attrition	Catastrophic expenditure		Total
	No	Yes	
Opted for Ayurvedic medicine	1	3	4
Declined surgery	1	3	4
Declined chemotherapy		5	5
Declined whole treatment		1	1
Unable to pay		3	3
Unable to travel		1	1
Unknown reasons	1		1

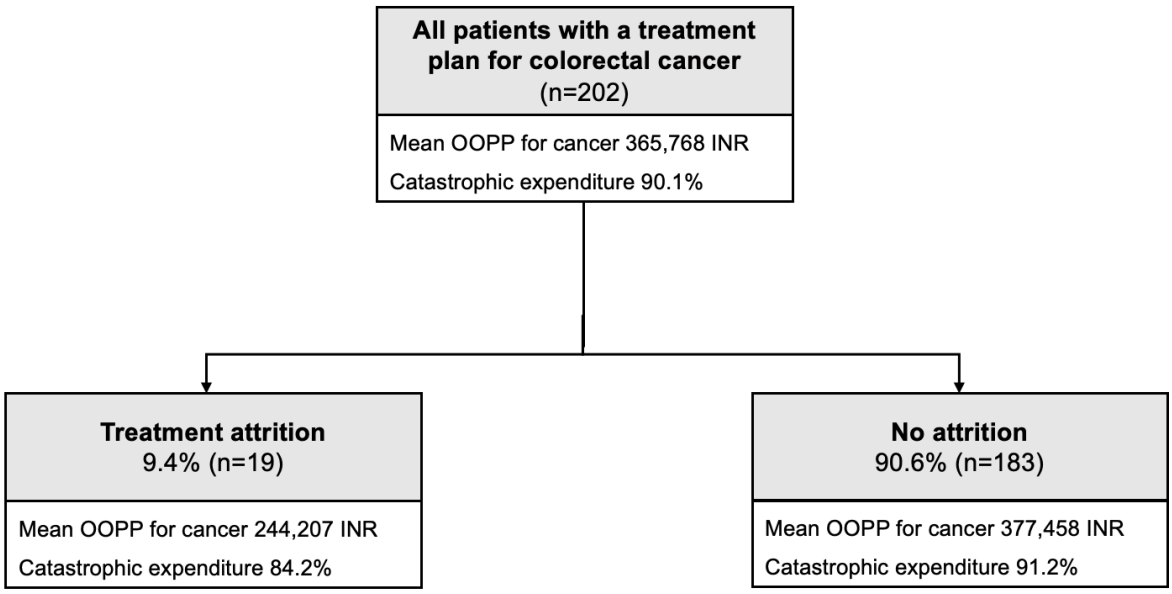
Table 21: Characteristics of patients with and without treatment attrition.

		Treatment attrition		
		No	**Yes**	**p**
Age	18-40 years	49 (94.2)	3 (5.8)	0.177
	41-60 years	76 (92.7)	6 (7.3)	
	>60 years	58 (85.3)	10 (14.7)	
Sex	Female	62 (86.1)	10 (13.9)	0.170
	Male	121 (93.1)	9 (6.9)	
Patient education	Secondary/Graduate	141 (93.4)	10 (6.6)	0.040
	Primary/none	42 (82.4)	9 (17.6)	
Employment	Employed	94 (93.1)	7 (6.9)	0.465
	Unemployed	56 (87.5)	8 (12.5)	
	Retired	33 (89.2)	4 (10.8)	
Household income	High	93 (92.1)	8 (7.9)	0.630
	Low	90 (89.1)	11 (10.9)	
Household size	< 4 people	91 (91.0)	9 (9.0)	1.000
	>= 4 people	92 (90.2)	10 (9.8)	
Cancer location	Colon	91 (93.8)	6 (6.2)	0.206
	Rectum	92 (87.6)	13 (12.4)	
Cancer stage	Local	27 (96.4)	1 (3.6)	0.420
	Advanced	154 (89.5)	18 (10.5)	
Treatment intent	Curative	159 (91.4)	15 (8.6)	0.953
	Palliative	24 (88.9)	3 (11.1)	
Distance to hospital	0-100 km	59 (89.4)	7 (10.6)	0.035
	100-500 km	54 (84.4)	10 (15.6)	
	>500km	70 (97.2)	2 (2.8)	
Hospital type	Government	53 (81.5)	12 (18.5)	0.005
	Charity / Private	130 (94.9)	7 (5.1)	
Funding scheme	No	106 (92.2)	9 (7.8)	0.522
	Yes	77 (88.5)	10 (11.5)	
Insurance	No	155 (89.1)	19 (10.9)	0.137
	Yes	28 (100.0)	0 (0.0)	

Data presented as n(%). Percentages by row. Missing data for cancer stage n=2, for treatment intent n=1.

Patients with treatment attrition made lower OOPP than those who completed treatment (mean 244,207 INR vs 378,458 INR, p=0.008) but had a similar risk of catastrophic expenditure (84.2% vs 91.2%, p=0.562, Figure 30), including after adjustment (OR 0.23, 95%CI 0.03-2.28, p=0.186, full model in Table 18). The proportion of OOPP spent as medical, non-medical and indirect expenses were similar in patients with and without treatment attrition (Figure 31 and Table 22).

Figure 30: Catastrophic expenditure rates and OOPP made by patients with and without treatment attrition.



Missing data for the cost of cancer treatment n=1.

Figure 31: Out-of-pocket payments in patients with and without treatment attrition

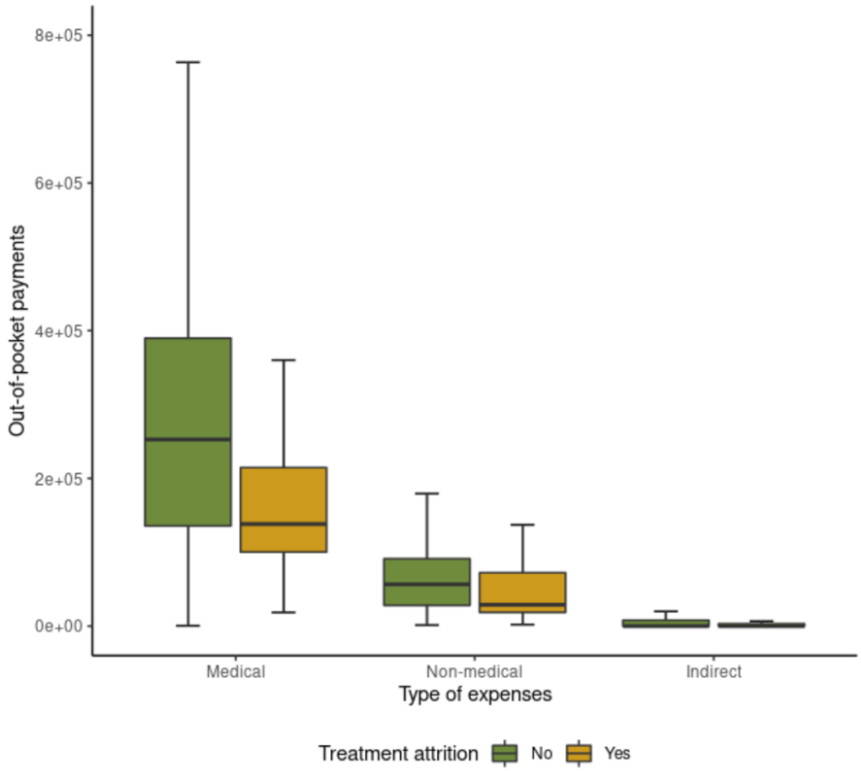


Chart displays OOPP(in India Rupees) for medical, non-medical and indirect expenses by treatment attrition. Absolute figures for all types of OOPP are given in Table 22. Missing data for the cost of cancer treatment n=1.

Table 22: Absolute OOPP by treatment attrition, with a breakdown of medical, non-medical and indirect as a proportion of total OOPP.

	Mean total OOPP (INR)	p-value	Average proportion (%) of OOPP		
			Medical OOPP	Non-medical OOPP	Indirect OOPP
All patients	365,768	--	73.4%	22.4%	4.1%
Treatment attrition					
Yes	244,207	p=0.008	71.1%	25.7%	3.2%
No	377,458		73.7%	22.0%	4.2%

Missing data for the cost of colorectal cancer treatment n=1.

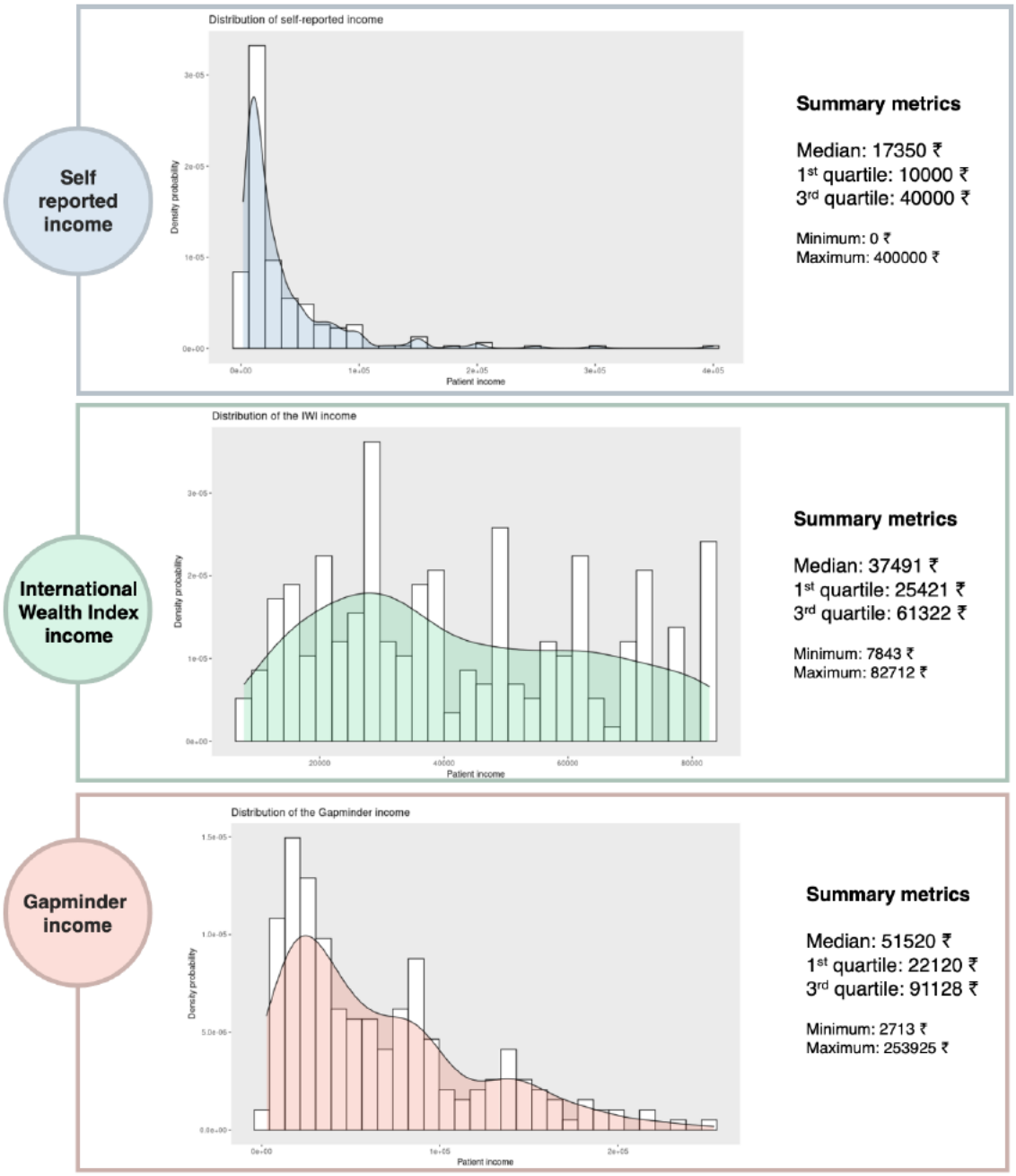
3.5.4 Secondary analysis – Comparison of the use of the self-reported, international wealth index (IWI) and Gapminder incomes

3.5.4.1 Self-reported, IWI and Gapminder income distribution

From the 226 patients included, 98.7% (223/226) completed all the three instruments of income assessment. Only one patient did not complete the IWI and another patient didn't respond to the Gapminder tool either. Overall, the median reported monthly income (17350 INR, (IQR 10000-40000)) was lower than median monthly income assessed using the IWI (37491 INR, (IQR 25421-61322)) and the Gapminder tool (51520 INR, (IQR 22120-91128)). The distribution and metrics of the self-reported IWI and Gapminder incomes are shown in Figure 32.

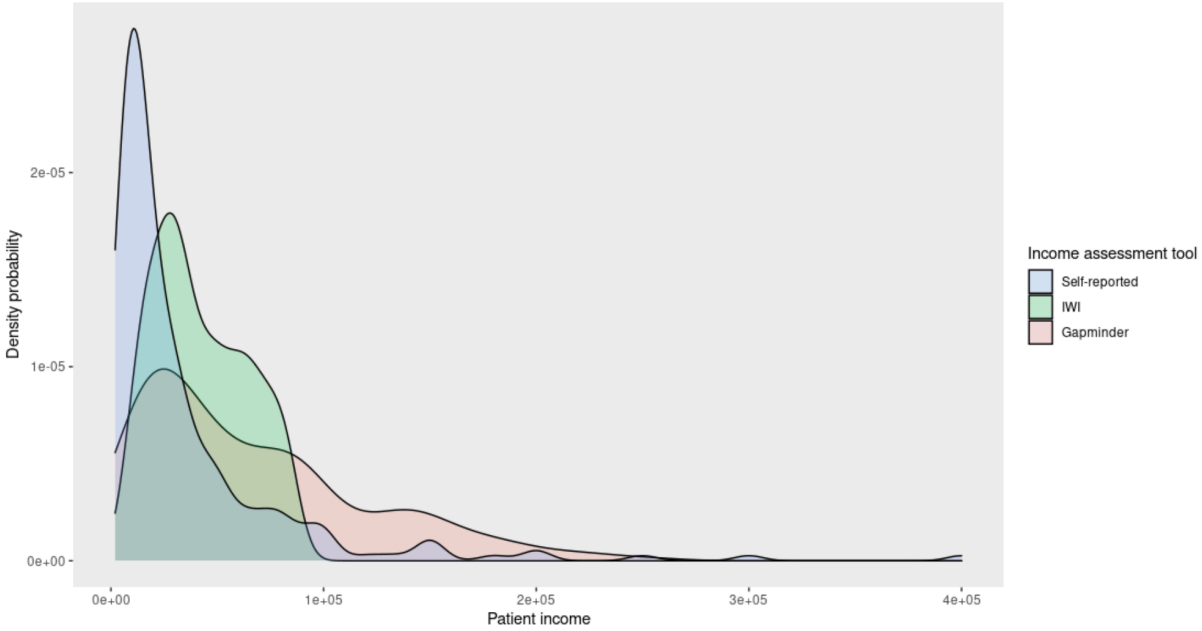
The distribution of the self-reported incomes was more skewed to the left (lower incomes), meaning that more patients reported a lower income directly, when compared to the incomes estimated with the IWI and the Gapminder tool (Figure 33). The distribution of IWI income figures is more homogeneous, and the figures are contained within a narrower range, when compared to the Gapminder or the self-reported income where more outliers exist. The Gapminder income follows a similar distribution when compared to the reported income but with a flattened density curve, where the results are not as skewed towards low incomes as they are for self-reported income.

Figure 32: Distribution and summary metrics of patient household monthly income, assessed by self-reporting, the International Wealth Index and the Gapminder tool.



The graphs display histograms of the self-reported, IWI and Gapminder incomes, with overlapped Kernel density plots showing the overall distribution of income figures in the three types of assessment. Summary metrics of the three income assessments are provided to allow comparison. All incomes are reported in Indian Rupees (INR, ₹). Missing data for IWI income n=1 and for Gapminder income n=2).

Figure 33: Distribution of all patient household income assessments (self-reported, IWI and Gapminder) in a combined density plot.

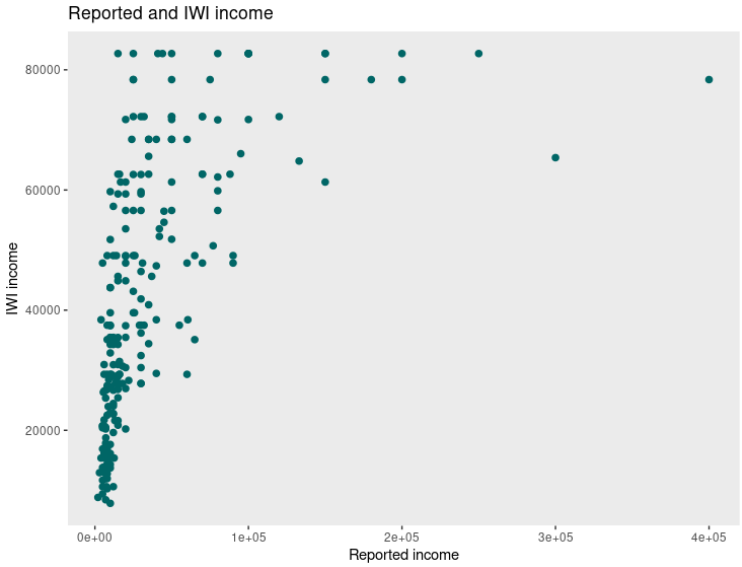


Combined Kernel density plot graph displaying the distribution of incomes assessed by the three income assessment tools (self-reported, IWI and Gapminder tool). Patient income is reported in Indian Rupees (INR). Missing data for IWI income n=1 and for Gapminder income n=2).

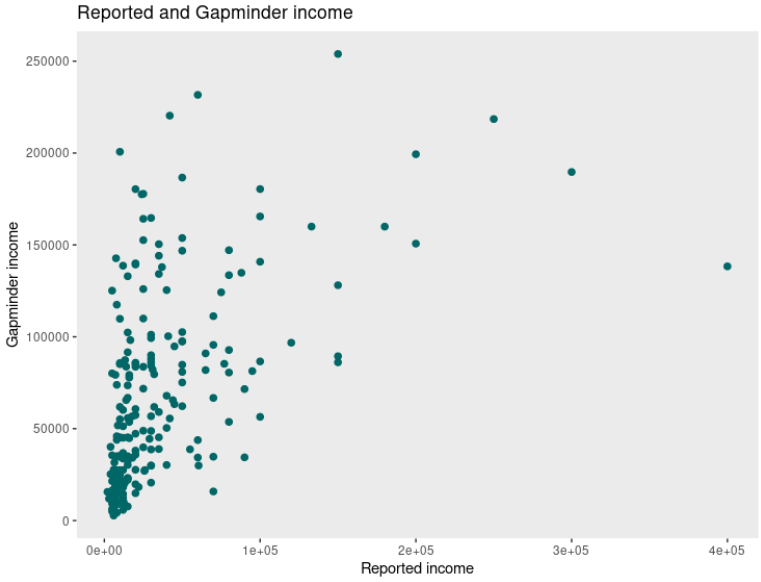
Figure 34 (A) and (B) shows scatter plots exploring the association between the self-reported income and estimated incomes using the IWI and the Gapminder tool respectively. Both estimated incomes show a positive non-linear association with self-reported incomes. The association is strong for low reported incomes, becoming weaker as the reported income increases.

Figure 34: Scatter plots of self-reported income against the IWI and the Gapminder incomes.

(A) IWI and self-reported income



(B) Gapminder and self-reported income



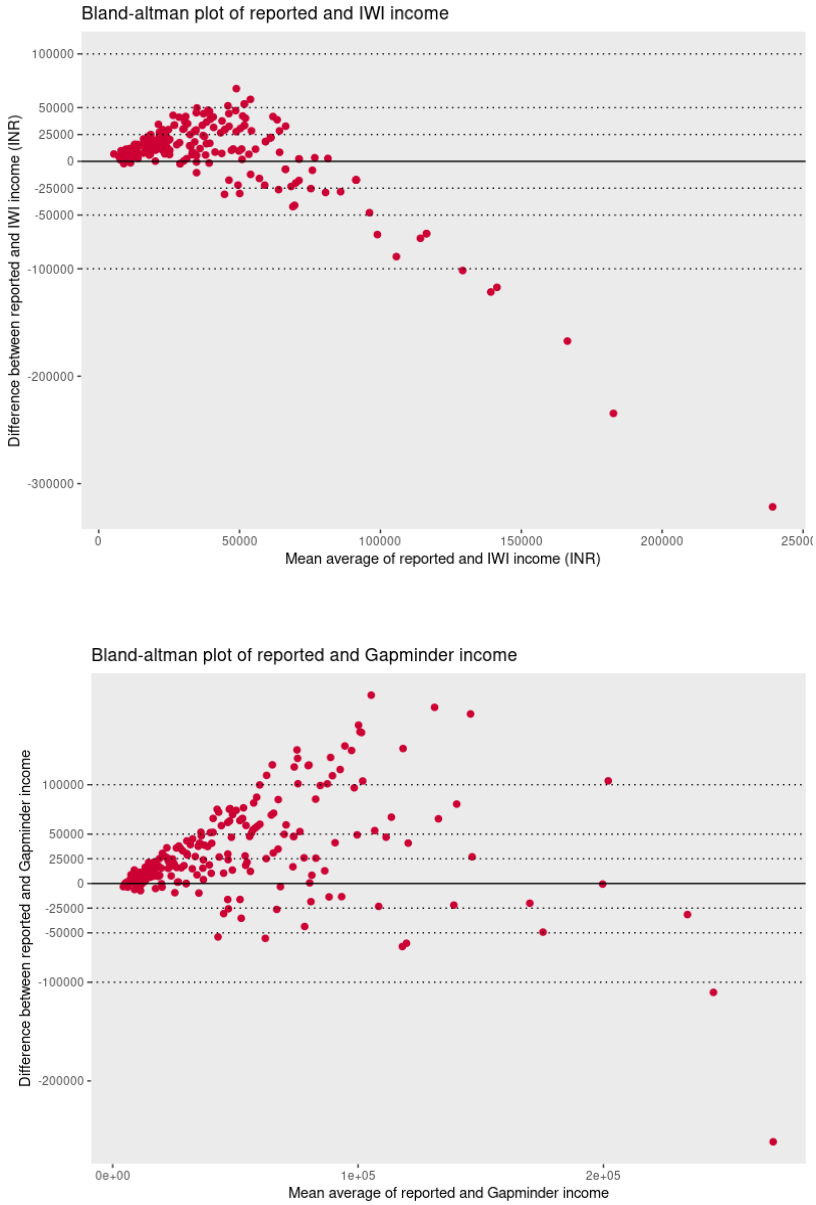
IWI = International wealth index. Missing data for IWI income n=1 and for Gapminder income n=2.

3.5.4.2 Agreement between self-reported, IWI and Gapminder incomes

The differences between reported and estimated incomes show lower dispersion for the IWI, compared to the Gapminder income (Figure 35). The proportion of patients for whom the estimated income is within 50000 INR of the self-reported income is 92.8% for the IWI and 70.2% for the Gapminder tool. Similar trends are observed for differences within lower limits (25000 INR) and higher limits (100000 INR), reinforcing better agreement for the IWI (Table 23).

In the Bland-Altman plots describing agreement for both the IWI and the Gapminder tool (Figure 35), there is a funnel shaped distribution of the differences between self-reported and estimated incomes. The differences are closer to zero for low income earning households and farther from zero as the household income increases, demonstrating a worse degree of agreement for high income earning households. Standard 95% confidence interval for agreement can't be drawn for this data as the differences between income assessments didn't follow a normal distribution (Q-Q plots shown in Supplementary Figure 1, in the Appendix).

Figure 35: Bland-Altman analysis exploring agreement between the self-reported income and the International Wealth Index and the Gapminder incomes.



Bland Altman plots describing the agreement patterns between the self-reported income and the International Wealth Index and the Gapminder incomes, respectively. Plots display difference between measured incomes against mean average of measured incomes. The dotted lines represent a difference between income measurements of 25000, 50000 and 100000 INR, respectively. The full line represents perfect agreement (no difference between reported and estimated income). Missing data for IWI income n=1 and for Gapminder income n=2.

Table 23: Proportion of patients whose the IWI and Gapminder index is contained within 25000, 50000 and 100000 INR of the self-reported income.

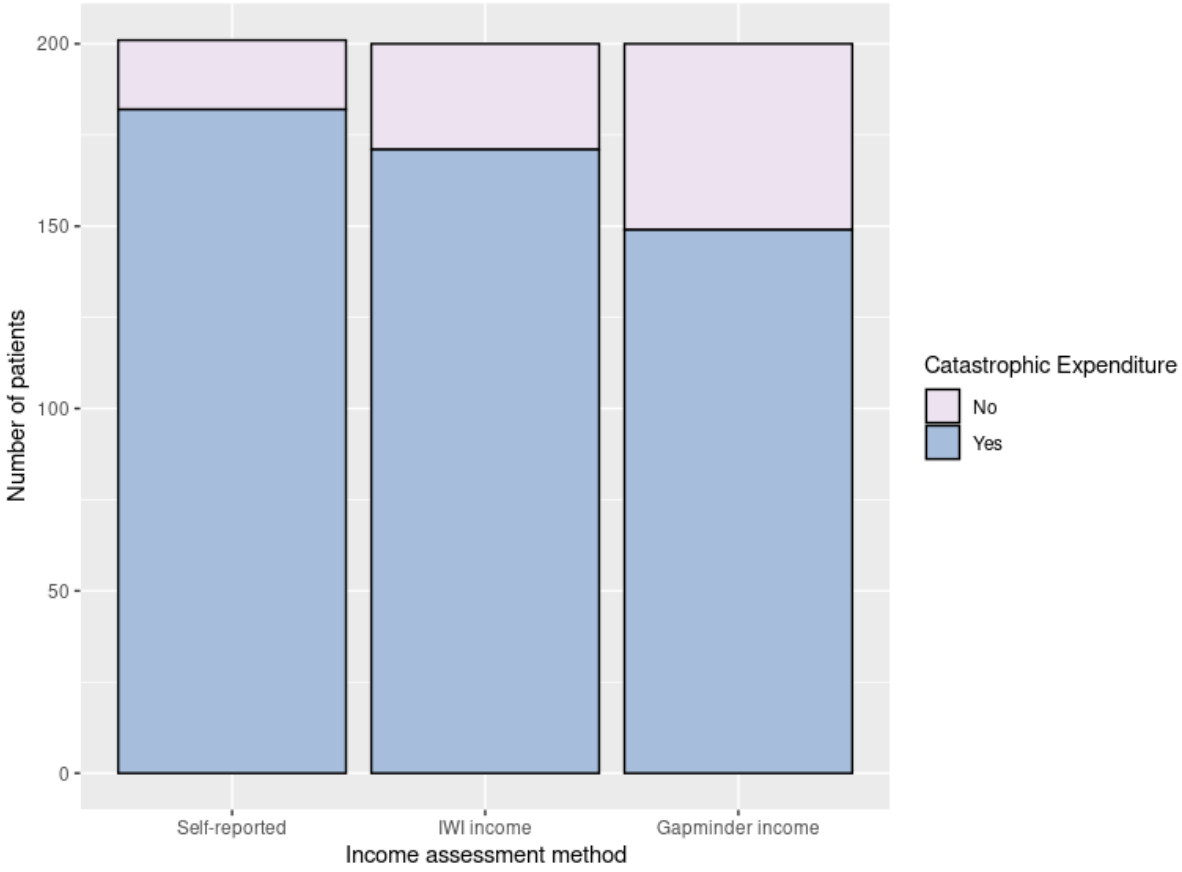
	Proportion of patients for whom the difference between the assessed incomes is		
	within a 25000 INR interval	**within a 50000 INR interval**	**within a 100000 INR interval**
Reported and IWI income	67.1% (151/225)	92.8% (209/225)	97.3% (219/225)
Reported and Gapminder income	49.3% (111/225)	70.2% (158/225)	88.9% (200/225)

Missing data for IWI income n=1 and for Gapminder income n=2.

3.5.4.3 Illustration of catastrophic expenditure rates using self-reported, IWI and Gapminder income

An illustration of the impact of the income reporting tools on catastrophic expenditure rates was performed using the data from the patients who were alive at 6 months (n=202). Within six months of having received a new decision for treatment, this cohort of patients had a median out-of-pocket expenditure for cancer care of 365,768 INR (SD 239,491). The rates of catastrophic expenditure calculated using self-reported and estimated incomes were different (Figure 36). The rate of catastrophic expenditure for this cohort of patients was highest when the self-reported income was used (90.1%), when compared to the rates obtained with the IWI income (84.7%) or the Gapminder tool (73.8%). The patients who were categorised as undergoing catastrophic expenditure when using the self-reported income but not when using the IWI income, lived closer to the hospital and were more likely to be treated in government hospitals. The patients who shifted category when using Gapminder had higher income but no other significant differences in their characteristics.

Figure 36: Catastrophic expenditure rates for colorectal cancer care, when using self-reported household income versus the International Wealth Index income or the Gapminder income.



The bar chart compares the number of patients undergoing catastrophic expenditure, when the income is self-reported, assessed through the IWI or the Gapminder tool. Missing data for IWI income n=1, for Gapminder income n=2, for the cost of cancer treatment n=1.

3.6 Discussion

3.6.1 Main findings

This study demonstrated that most of the costs of colorectal cancer treatment were supported by patients through out-of-pocket payments, with 90% of households subject to catastrophic expenditure within six months of a new treatment plan. Surgical and anaesthesia fees were among the most expensive items of treatment and tumour resection was independently associated with catastrophic expenditure. Surgery for colorectal cancer was previously identified as a risk factor for catastrophic expenditure in Malaysia but not in India, and this can have direct policy implications(110). Treatment attrition rates in tertiary care were low, raising the hypothesis that attrition is a bigger problem at other levels of the healthcare system (e.g. district and community facilities). Patients with treatment attrition made fewer OOPPs, which might be a cause or a consequence of attrition but suggests that financial barriers might impact treatment completion.

3.6.1.1 Primary analysis – catastrophic expenditure and treatment attrition

The 90% catastrophic expenditure rate found in this study is high, compared to previous studies. A systematic review showed a pooled catastrophic expenditure rate for cancer of 67.9% in countries with low HDI and an international study in Southeast Asia (not including India) showed that 48% of the patients experienced

financial catastrophe at one year after a cancer diagnosis(96, 120). Among Indian households, cancer was proven to be the disease causing highest catastrophic expenditure rates but no data previously existed for colorectal cancer(72). The high catastrophic expenditure rates can mirror a quite unique level of detail and effort made to source OOPP and suggests that colorectal cancer treatment might be particularly expensive, especially when surgery is needed. Although we acknowledge that the cost of treatment in the participating hospitals can be higher than average, some patients were probably awaiting money reimbursements from insurance companies and government funding schemes, at the time of follow-up. Other explanations for any overestimation of catastrophic expenditure rates can be related to sources of household wealth that weren't captured in the study as well as a degree of income underreporting. Biases in income reporting have been described before (114) and might have been exacerbated by the fact that the income assessment took place just after a decision for treatment, while patients often seek funding support through the hospital pathways.

Surgical resection was one of the factors associated with catastrophic expenditure in the adjusted model, which is aligned with the finding that surgery being one of the most expensive items in hospital bills. Surgical costs usually include theatre time fees, instruments and devices, anaesthetic drugs and theatre staff, which can sum up to a high financial burden. On the other hand, surgical resection is needed for cure in most colorectal cancer patients, especially in settings like India where advanced stage is very common. The investment in surgery can therefore bring individual and societal benefits that outweigh the

immediate costs, if surgery is done timely and safely. The Lancet Commission for Global Surgery published that without an accelerated investment in surgery, L&MIC will continue to experience losses in economic productivity that was estimated to be of 12.3 trillion USD until 2030 (21).

Patients with rectal cancer, advanced disease and being treated in charity/private hospitals were at increased risk of catastrophic expenditure, possibly reflecting their eligibility for expensive surgery or multimodal treatment. Of note, the included centres all have expertise in rectal cancer, making minimally invasive surgery available to their patients and perhaps other costly health technologies in order to enhance clinical care. Although these technologies improve recovery and complication rates, justifying a cost-effectiveness argument to their implementation, their cost is high for patients' pockets at the time of surgery.

Following surgery, radiotherapy was the main contributor to colorectal cancer costs, reinforcing previous recommendations for cost-effectiveness research on radiotherapy strategies in India(73). Patients in India often purchase chemotherapy drugs from external suppliers, to be administered at the hospital, explaining the apparent low cost of chemotherapy collected from hospital bills in this study(130). Cancer care in India is often funded through budgets that are common to other non-communicable diseases and fail to account for the complexity and high cost of cancer treatments(68). This study emphasizes the need for tailored cancer care funding, highlighting that patients with advanced

disease and who require surgery require additional funding. Having medical insurance seemed to protect patients from catastrophic spending, reinforcing that pre-paid mechanisms are a better strategy of financial protection and that costs covered government schemes need to be expanded.

The demographic features associated with catastrophic expenditure need careful interpretation, as there might be wider group of vulnerable patients who did not reach tertiary care. Whereas male patients can be more exposed to catastrophic expenditure, they might also have better ability to raise funds beyond their income and higher chances of accessing appropriate healthcare (105, 131). The fact that men are only breadwinners for many households in India, makes those families particularly susceptible to financial trouble when men need to stop working. Lower education has been identified as a risk factor for catastrophic health expenditure across settings and types of care, reinforcing the need for investment in education and health literacy to improve health outcomes (47). The demographics of the patients who were included in the main analysis are also influenced by the fact that these excluded the patients who died before six months of a treatment plan. Patients could have died due to disease progression or the lack of access to optimal treatment, which cannot be drawn from this data. This can also be a result of the advanced cancer stage at presentation, which is likely to be associated with the absence of screening but also with a lack of knowledge about colorectal cancer symptoms or inability for swift referrals from frontline healthcare workers (132).

The distance from the patient's home to the hospital was associated with higher rates of catastrophic expenditure but this didn't prevail in the adjusted model, suggesting that the characteristics of patients who travel farther are probably stronger determinants of catastrophic expenditure than the distance itself. However, patients who lived very far from the hospital had lower attrition rates, raising the hypothesis that these might have the resources and the motivation to complete their treatment.

Medical insurance was associated with lower risk of catastrophic expenditure, which is in line with previous studies (120) and highlights the importance of pre-paid financing mechanisms in healthcare. The fact that government funding schemes are still not protecting patients from catastrophic expenditure is in favour of an expansion of these schemes, ensuring the coverage of a larger proportion of treatment costs. Many patients might pay out-of-pocket to be able to start cancer treatment, while awaiting funding approval or reimbursements from these schemes. Faster and more reliable processes for funding approval are needed to protect patients and households.

Treatment attrition was observed only in less than one in ten patients, being associated with low education levels and treatment in public hospitals. Patients with treatment attrition made less out-of-pocket payments for cancer care, but the catastrophic expenditure rates were similar. It is unclear if the lower OOPP are a cause or a consequence of dropping out, but this finding suggests that there is a

vulnerable group of patients who might not be able to gather funds and might sacrifice treatment completion. The most common reason reported by patients for treatment attrition was their choice to decline treatment but the underlying motives behind these decisions need further research. Previous studies in Asian populations have found disproportionate catastrophic expenditure rates in patients with cancer who used complementary medicine and suggested its integration in cancer care funding (133). Some of the patients in this study declined treatment and opted for alternative medicine, which highlights the importance of improving communication across professionals of all types and clear dissemination of effective treatments.

3.6.1.2 Secondary analysis – Comparison of the use of the self-reported, international wealth index and Gapminder incomes

The IWI and the Gapminder tool are feasible and promising instruments to assess household income in global health research studies. The vast majority of this cohort of colorectal patients from India was able to complete both instruments. When using the IWI index to estimate household income, 92.8% of the patients will have an estimated income that differs up to 50000 INR from their self-reported income. The Gapminder tool shows worse agreement, with 88.9% of the patients having an estimated income that differs up to 100000 INR from the self-reported income. The use of different tools to assess income resulted in different catastrophic expenditure rates within the cohort, highlighting that further

research and refinement of methods is needed to monitor this well-established Sustainable Development Goal at global scale.

The fact that self-reported incomes are generally lower than estimated incomes is unsurprising. Firstly, patients might feel uncomfortable revealing their income due to social pressures(114, 115, 117). Secondly, all income data were collected at the point of inclusion in the cohort study which was, by definition, coincident with a new treatment decision for colorectal cancer. At this point in time, many patients could have been seeking funds from the hospital and the government to pay for their cancer care. Given that government and charity funds are usually allocated to patients based on their earnings, this might have played a role in patients underreporting their income (68). Thirdly, the self-reported income was collected from household members wages and did not include any other sources of income (e.g. inheritance). Even though self-reported incomes tended to be lower, the most severe outlying income figures were actually self-reported. This can reflect the inability of the indirect tools to capture these incomes, but we can't exclude a previously described form of social desirability bias where some patients felt like they should overreport their incomes (117).

The International Wealth Index and the Gapminder tool were both designed to allow a comparison of wealth levels across households(122, 125). It is expected that households generate wealth through their income but also through other sources of purchasing power. There is no consensus on the best definition and

threshold for catastrophic expenditure and some authors argue that wealth and expenditure levels might be a better reflection of households' capacity to pay for cancer care (41). The indirect tools have the advantage of assessing wealth more holistically, which might justify why IWI and Gapminder incomes being higher than the self-reported income. Additional factors can contribute to higher income figures with the IWI and the Gapminder tool, such as patients owning donated household goods that typically belong to higher income households or the personal choice to rent versus buy a house (renting requires less short-term investment for a better house).

The authors of the IWI have described that a truncation effect exists in this index, meaning that it has less discriminative power in very low and very high levels of wealth, as the score is limited to the number and value of the included assets(122). This explains why the income figures obtained with the use of the IWI showed a narrower distribution. This can also explain why the agreement between the IWI and the self-reported income is worse for high income earners.

The Gapminder tool showed a less skewed distribution of incomes than self-reporting or the IWI, with more patients having higher incomes. This might reflect a better ability to discriminate wealth but can also be a result of this tool including multiple sources of data to match a household to an income (e.g. minimum and average wages, own food production, average consumption for specific groups of the population) (123). The way that this tool was designed and used in the study

could have contributed to worse agreement with self-reported income when compared to the IWI. Although there was a wide range of house items for the patient to choose from (around 30 items per category), patients could have struggled to find items that look like their own. We also acknowledge that similar pictures could be matched to quite different incomes, e.g. private flush toilets looking quite similarly were owned by households living on 1295 USD / 16 INR a month and 3477 USD / 42 INR a month, potentially resulting in very different income estimations.

A refinement of the IWI and Gapminder tools would be needed to enable their use as income assessment instruments in international studies. From our data, we can conclude that the IWI shows better agreement with self-reported incomes, but high income earning households are underrepresented. The IWI was derived from a set of household surveys from which several items were selected and their association to household income was drawn into a weighted score. A refinement of this index to capture some items typically owned by wealthy households could improve its discriminative power for high-income earners and its overall generalisability. Regarding the Gapminder tool, the estimated incomes follow a distribution shape comparable to the self-reported income but are more dispersed. For future studies using this tool, a selection of fewer pictures for each category (e.g. ten kitchens representative of ten different income levels), representative of well-defined income levels could improve its ability to estimate accurate income figures.

3.6.2 Key strengths

The heterogeneity of how and where patients pay for their cancer treatment is a challenge and this study used a meticulous methodology to capture all sources of expenditure. The co-design with research partners in India, who have a deep knowledge of patient's pathways, enabled the study to capture reliable data from the included patients. This study provides unique prospective real-world data on the costs of colorectal cancer in India and was designed to prevent recall bias, namely with multiple follow-up timepoints and regular data monitoring. Although focusing on catastrophic expenditure, this study also collected in-hospital expenses covered by third parties (public and private funds), allowing an understanding of the proportion of the total cost that is supported by patients as OOPP.

Additionally, this study explored alternative instruments for household income assessment, addressing a quite novel research question. The study demonstrated the feasibility of the use of indirect tools to assess income and was able to identify areas for improvement of these tools, if they are to be used at a larger scale.

3.6.3 Key limitations

A few limitations need to be acknowledged, mainly related to the sample size and type of hospitals included. This is a small sample of patients and there might be some selection bias given the characteristics of the participating hospitals, which were all tertiary care hospitals with colorectal dedicated teams. Although colon cancer is more common than rectal cancer in India(3), in this study rectal cancer was more frequent, which, together with the fact that many patients travelled a long distance to be treated, suggests that patients were seeking specialised care from expert colorectal teams. Palliative treatment plans were only seen in 15% of all patients, which can reflect another source of selection bias, meaning that patients who only need supportive care could have been treated in district hospitals or local healthcare facilities. Although the study included private and public hospitals, it is possible that economically challenged or rural populations struggle to access tertiary care, preventing the detection of barriers for treatment completion in a wider group of patients.

The collection of costs of treatment was an expected challenge, and some of the costs were reported by patients with potential inaccuracies. Regarding in-hospital costs, efforts were made to collect it from the bills to capture the most accurate picture. The hospital bills had many items that were difficult to categorize for clear reporting but allowed the fees of specific treatments of interest to be reported (surgery/anaesthesia, radiotherapy, chemotherapy).

Regarding the secondary analysis, although the completion rates for all income assessment instruments were high, full limitations of the use of the IWI and Gapminder tools were not explored in this study (e.g. biases and barriers for patients to respond). Secondly, although this is a multicentric cohort study, it only included tertiary care hospitals in India, limiting the generalisability for other countries and other levels of care in India. Finally, the IWI and the Gapminder tools revealed better agreement for low-income earning households, compromising the applicability of the results to high-income social strata. The fact that the IWI and the Gapminder tools were designed to reflect wealth, can partially explain why they don't match perfectly with income levels, as sources of household wealth are sometimes distinct of their sources of income.

3.6.4 Implications for policy

As colorectal cancer incidence increases in India, better financial protection is needed, especially for patients who require surgery. Strategies for screening and early diagnosis should be planned, as patients with advanced cancers are more likely to need multimodal expensive treatment and experience catastrophic expenditure. Non-medical expenses should not be neglected in future policies for funding cancer, as these account for a quarter of the OOPP made by patients. A larger investment of public funds in cancer care is needed to achieve the best

chances of cure and strategies for funds to be readily available for vulnerable patients should be up prioritised.

Travelling and accommodation expenses contributed to 20% of the overall OOPP, meaning that providing cheap or free transport and lodging could reduce the financial burden of colorectal cancer(134). Although indirect costs had a low impact on total OOPP, the average income loss was zero in patients without catastrophic expenditure, highlighting the importance of job protection policies to improve financial protection.

3.6.5 Future research

Although reducing catastrophic expenditure is likely to increase healthcare coverage and improve health outcomes for populations, catastrophic expenditure rates should not be interpreted in isolation. The lack of financial protection might not only expose patients to unaffordable payments but might indeed prevent them from entering or completing a treatment pathway. A deeper understanding of the barriers faced by patients with a colorectal cancer diagnosis is needed to develop evidence-based interventions and improve treatment completion. This topic will be the focus of my next chapter.

This study focused on colorectal cancer patients but the challenges faced by patients with other types of cancer might be similar and a larger scale study of multiple types of cancer would inform policy making in India. The National Program for Cancer Control focuses on the three most common types of cancer (breast, oral and cervical cancer) but many other cancers are responsible for an important decrease in DALYs in India and therefore deserve attention to improve outcomes at a country level(95). Ideally, future studies would involve cancer patients being treated at multiple levels of care to capture a more realistic picture of cancer care and reduce the selection bias inherent to tertiary care hospitals.

The costs of NCDs and their impact for patients and households is one of the priorities of the WHO, aiming to improve universal health coverage. An international prospective study of catastrophic expenditure and drivers of cost in cancer care, could help inform health and development goals at a global scale. The design of an international study on this topic would require a simpler and less time-consuming methodology that can be reproduced across settings and for a larger number of patients. The data collection on costs of treatment probably needs to be context specific but will likely rely on patient reported data, as hospital bills don't necessarily exist in all settings, especially when hospitals are funded or owned by the government. There are some learning points on income assessment from this study, that can be useful for future studies. Although it is feasible to use the IWI and the Gapminder at a global level, a qualitative assessment of the use of these tools would be ideal to achieve a better understanding of their strengths, limitations and potential biases. A consensus

process involving patients, researchers and decision makers might be needed ahead of its global use, enabling the development of a tool that matches goals at individual and community levels.

Provided the necessary refinements, these tools have the potential to facilitate real-world assessment and monitoring of healthcare related catastrophic expenditure, without the need for direct income assessment. Moreover, data on house characteristics and household goods is routinely collected in several household surveys, meaning that the IWI and the Gapminder tool could allow large scale modelling of catastrophic expenditure rates from population survey data. Although more research is needed, the high completion rates and the apparent low complexity of both the IWI and the Gapminder tool allows one to conclude that they are promising tools in global health research.

4 Barriers and facilitators of colorectal treatment adherence in India: qualitative assessment of cancer care perspective in four states

4.1 Link to the previous chapter

The previous chapter showed that colorectal cancer catastrophic expenditure rates are high, but treatment attrition is low in tertiary care hospitals. Most of the patients with treatment attrition declined treatment and the reasons for that are not completely understood. A deeper understanding of the reasons for treatment drop-out can inform future interventions to increase patient retention.

4.2 Abstract

Introduction: Barriers for completeness of cancer treatment plans in India haven't been fully explored. In the context of an increase in colorectal cancer incidence, this study aimed to assess the views and perspectives of cancer care professionals on barriers and facilitators for colorectal cancer care adherence.

Methods: Thematic analysis of semi-structured interviews were conducted with fourteen colorectal cancer care professionals in four tertiary care hospitals in India, from April to October 2021. A deductive approach was used to generate codes, themes and key-messages from the data and quotations were used for illustration.

Results: Fourteen interviews were conducted with medical oncologists (four), radiation oncologists (four), surgeons(four), a stoma nurse (one) and a hospital finance manager (one). Barriers and facilitators were identified within five main themes: (1) social background and support, (2) awareness, education and beliefs, (3) healthcare system capacity and organisation, (4) clinical events and (5) financial and job protection.

Discussion: Barriers and facilitators for colorectal cancer treatment adherence were identified at multiple societal levels, which can be targeted in future cancer policy and research to improve the delivery of cancer care in India.

4.3 Introduction

Although the incidence of colorectal cancer in India is increasing, this type of cancer has not yet been considered a public health priority(28). Colorectal cancer patients in India and other low and middle-income countries (L&MIC) are known to present at a more advanced stage when compared to high-income countries, meaning that prompt and complete treatment are needed to achieve the best oncological outcomes(49).

Although a large number of studies have focused on barriers to access to colorectal cancer screening, no data exist on the challenges to reach and receive colorectal cancer treatment. Scarce health resources can limit access to cancer care. In the case of India, the professional/patient ratios are as low as 1 oncologist per 16,000 cancer patients in India (60), there is a shortage of radiotherapy machines with only 545 existing in the country and referral systems are inefficient(19). Additionally, it is possible that high out-of-pocket payments for cancer care prevent patients from entering or completing treatment pathways due to the risk of financial hardship(37). Previous qualitative work on attitudes towards cancer in India revealed that social taboos and nihilistic views exist in communities(28), adding a further barrier. Qualitative research with key stakeholders in colorectal cancer treatment is needed to understand barriers to take-up of comprehensive colorectal cancer treatment, as the increasing incidence is likely to demand new health policies.

The aim of this study was to explore the views and perspectives of colorectal cancer patients and professionals on barriers and facilitators for treatment adherence and delivery. When co-interpreted with drop-out rates and patient-reported reasons for non-adherence, this can provide a comprehensive picture of where problems lie in the treatment pathway. Unfortunately, due to the COVID-19 related travel restrictions, it was not possible for me to visit India during the study. I decided to conduct the interviews with cancer professionals only, as they could more easily be done online. Therefore, this chapter will focus on the views of colorectal cancer care professionals.

4.4 Methods

4.4.1 Context and design

This qualitative study was conducted in four tertiary care hospitals in India from April to October 2021. The study was designed alongside a prospective cohort study looking at expenditure and attrition in colorectal cancer patients (chapter 3). The need for a qualitative assessment of the factors influencing colorectal cancer care delivery was determined during the aforementioned scoping visit to India (see pages 105 to 111 for full details).

4.4.1.1 Rationale for a qualitative study

During my scoping visit to India I visited mainly tertiary care hospitals but also three district hospitals which worked as referring centres of patients with confirmed or suspected colorectal cancer. During my conversations with several practitioners at the different hospitals (general medicine doctors, surgeons, medical oncologists and radiation oncologists), many issues regarding detection, management and treatment of colorectal cancer patients were raised. These ranged from barriers in the community level, namely a lack of knowledge about colorectal cancer symptoms (compromising early detection), to the availability of appropriate diagnostic tests at local facilities, and to difficulties in referring patients to hospitals where cancers can be fully diagnosed and treated, to challenges at the referring facilities.

The barriers for patients to seek, reach and receive colorectal cancer care seemed to be an active concern to fellow physicians and researchers in India. It was clear to me that the volume of patients attending the hospitals in question gave these professionals a rich experience and understanding of the challenges that patients faced. The question of whether a quantitative or a qualitative methodology would be most appropriate to research this topic was discussed with surgeons, oncologists and other clinicians. They felt that a qualitative study would enable the right depth and that interviews with both patients and cancer professionals would be relevant, as patients usually share only their own experience but cancer professionals have contact with many patients' stories. Capturing reasons for treatment drop-out through a quantitative study seemed challenging, as only a low percentage was expected to truly drop out and patients can avoid reporting their true reasons for dropping out.

Qualitative research can be defined as an interpretive, naturalistic approach to describing the world, through which researchers try to make sense or interpret phenomena, in terms of the meanings people bring to them(135). Qualitative methods were appropriate to research the topic of treatment adherence, as they enabled me to study the meaning that the participants bring from their experience of treatment pathways, while empowering local individuals to share their stories and make their voices heard. Finally, treatment barriers and facilitators do not exist in isolation and need to be interpreted as part of a complex problem, for which qualitative methods are best suited.

4.4.1.2 Semi-structured individual interviews

The choice of individual interviews as the data collection method was made together with the research partners in India as it was felt that this would avoid dominance of some individuals (due to their hierarchy or previous professional relationships) over others, compared to focus group methods. Such a dynamic could prevent the participants from fully sharing lived and observed experiences. There was also a logistic angle to this choice, as it seemed difficult to organise group meetings with professionals in India given their busy clinical schedules.

I considered that semi-structured interviews were the most appropriate way of conducting the data collection as they allowed the inclusion of:

- Open questions to obtain unprompted views of the participant;
- Focused questions to explore if factors identified in previous literature as influencing access to cancer care in India would have an impact on receiving colorectal cancer care;
- A dynamic interaction between the interviewer and the interviewee to newly raised topics or details of the participant perspective.

4.4.1.3 COVID-19 impact on the study

The COVID-19 pandemic had two main effects on the delivery of the study: (1) it was not possible to include patient interviews as these were deemed by the research group to require a face-to-face contact, (2) all interviews were conducted online. The conduct of online interviews is further detailed below and might have influenced the data, which needs to be taken account in the

interpretation of the findings. However, there is current evidence that remote video interviews are not materially worse than in-person interviews, as a similar number of topics is usually identified(136).

4.4.2 Registration, approvals and ethical considerations

The study was registered as a mixed-methods study of which this qualitative component was part of (ClinicalTrials.gov 04517032; Central Trials Registry of India CTRI/2020/09/027896) and the protocol was published (118). Ethical approval was obtained from the University of Birmingham (April 2020), the Indian Council of Medical Research (October 2020) and hospital level ethical boards (Supplementary Figure 2 (A) to (E)).

All interviews were planned to be conducted by me, with or without the help of a third person translating questions and answers into local languages and/or dialects. The design of the study and topic guide were sensitive to the fact that I am not from India and have never practiced medicine there. This meant that all the questions needed to be carefully worded to avoid subjective language, promoting trust and respect, when asking about treatment delivery(137).

4.4.3 Topic guide development

4.4.3.1 Research question

The research question guided the development of the topic guide:

What are the barriers and facilitators for patients with a colorectal cancer diagnosis to receive their planned treatment course?

This research question was defined with feedback from the partners in India and after a literature review. Although scarce, some data exist on what might prevent patients from generally accessing cancer care in India, mainly focusing on seeking and reaching care. Given that colorectal cancer patients are mainly treated at tertiary care hospitals, it made sense to focus on barriers faced by patients after a diagnosis (receiving care). The journey up to a diagnosis is often made at previous stages of care and capturing those challenges at a tertiary care level could potentially be inaccurate.

4.4.3.2 Structure of the topic guide

After a brief introduction to the study topic, and an opportunity for questions to be asked by the participant, consent was obtained verbally (with written consent being obtained by email). The first two questions aimed to bring the participant into the scope of the interview, asking them about their professional role and the treatment pathways for colorectal cancer in their setting. The next two questions explored openly what the concerns of a newly diagnosed patient were, and what could be the reasons for a drop-out after treatment initiation. Five other questions/prompts were included to assess the participant's views - specifically on economic, social and cultural factors that could influence treatment drop-out. One last question on barriers for treatment adherence opened the floor for the

participant to raise any other barriers that we would not have explored yet, followed by a question on what could be the facilitators for treatment delivery. The final question meant to give the participant the space to talk about anything else that they would like to raise. The full topic guide is available in Supplementary Table 4.

4.4.4 Interview conduct

Individual, non-repeated interviews were planned to last 30 to 45 minutes and were all conducted online. These were done through the Zoom® platform and were recorded with an independent recorder that was securely stored in a key protected locker. The interviews were all conducted by me and followed the pre-planned topic guide. At the end of each answer from the participant, I gave them a brief verbal summary of the mentioned concepts to ensure a clear understanding of the participant's points and to give them opportunity to correct me or rephrase their answer. A few handwritten notes were taken during the interview to complement the recordings at the point of data analysis.

4.4.5 Participant recruitment and consent

The cancer care professionals interviewed at the four participating hospitals were chosen by the principal investigator at the site, as they were best placed to suggest a professional available and suitable to contribute. I did not give specific instructions on the criteria to choose the participants, leaving this decision entirely to the principal investigator. The only requirements were the ones dictated by the

purposive sampling (explained below). Although the purposive sampling required a range of different professionals, the same topic guide was used for all the interviews.

Upon being in contact with me, the participants had already been approached by the local principal investigator and agreed to take part in the study. The interviews were always preceded by a formal invitation by email from me, to which a short summary of the study goal and the informed consent form were attached. The informed consent was then signed ahead of the interview and kept by the local research team in the study files. The consent for the interview was confirmed verbally at the beginning of the interview following an opportunity for further questions about the study.

4.4.6 Sampling

Purposive sampling was used in this study, to capture the views of a range of professionals who have contact with colorectal cancer patients in different contexts. The goal was to include at least one oncology surgeon, one medical oncologist and one radiation oncologist from each centre, as adherence to the different types of cancer treatment was expected to be affected by distinct barriers. Besides this, the principal investigators were asked to try to recruit a stoma nurse (who would have regular contact with colorectal cancer patients and with whom patients could share additional struggles) and a professional at the hospital who would be responsible to explore funding options for cancer care with patients (this could be a social worker, a finance manager, or other appropriate

professional, who could give a complementary perspective on financial challenges which were expected to be frequent(47).

4.4.7 Data management and transcription

The interview recordings were transcribed by an external transcriber who had a track record and a service provider agreement with the University of Birmingham. This agreement included a method for confidentiality, in which the provider destroyed their copy of the recordings after the transcription was complete. All interviews were transcribed into clean verbatim by the same external provider (and the same person), with anonymisation of names and places.

4.4.8 Data analysis

The interviews started being analysed as they were transcribed. The first four interviews were double-coded by two researchers (myself and JC, an experienced qualitative researcher) to allow familiarisation with the data, coding practice and the development of an agreed codebook. All the interviews were then coded using this agreed codebook (including the first four), with an expansion of the codes whenever new themes or subthemes arose. The code tree included multiple levels of detail, from overarching to detailed codes. All the verbatim was coded even if not directly related to the research question, for completeness. NVivo V12 was used to code and manage all the data. A deductive approach was used to generate the codes and the themes from the

data, with an initial match to the topic guide and further code creation as new topics arose in the data.

The code tree was initially used to map and define themes and subthemes. The originating citations were revisited to explore repeating, overlapping and connected sub-themes. The subthemes were then reorganised into the themes, to reflect this second stage of data interpretation. The final organization and definition of themes was conducted in a pragmatic manner to facilitate closely related topics to be reported together.

4.4.9 Data reporting

The characteristics of the participants are described as per their sex, professional role, type of hospital where they worked and type of contact with colorectal cancer patients. The coding tree was presented up to the third level of codes. The themes and subthemes were reported together with their frequency in the dataset (overall references and number of participants referencing). The codes and original citations were reviewed at the time of results writing to ensure reliability of reporting from original data. Key messages from the original data were formulated to summarise the findings, being categorized as barriers or facilitators within each subtheme. Quotations were used to illustrate and provide a deeper understanding of the reported themes and subthemes, both embedded in the paragraphs and as isolated illustrative quotes.

4.4.9.1 Socio-ecological model

At the point of data analysis, it was clear that the factors influencing colorectal cancer treatment adherence were present at different levels of society. I have decided to report the results within a systemic approach, aiming to facilitate future action based on this study. The Socio-Ecological Model (SEM) is a public health tool that provides a multi-level perspective on factors influencing a particular health behaviour. The UNICEF's Socio-Ecological Model was used to report the factors influencing treatment adherence at five levels: individual, interpersonal, community, organisational and policy. This allowed a structured understanding of the contexts in which barriers emerge, how they interact, and how facilitating interventions can be designed. The following definitions were used for each level of the SEM(138, 139):

- Individual: individual traits, knowledge, behaviour, and practices that can influence treatment adherence.
- Interpersonal: social networks, interpersonal interactions and relationships that promote behaviours regarding treatment.
- Community: beliefs, norms, socio-economic conditions and community attitudes with an impact on treatment delivery.
- Organizational / system: institutional conditions, regulations, pathways and resources of the healthcare system that can affect patients' ability to adhere to treatment.
- Policy: Governance rules, laws and policies with a broad impact on the way cancer care is delivered, influencing treatment access and compliance.

4.4.10 Ground for reflexivity

The data collection and analysis were conducted by researchers based in the United Kingdom, whose healthcare pathways are necessarily very different from the ones in India, which could have influenced interview conduct and data coding. All the interviewees were professionals in India and although agreeing to take part in the study, the views expressed during interviews could contain some degree of social desirability bias based on the interviewee expectations of what I might want to hear.

My own assumptions and previous knowledge of how healthcare is organised and delivered in India might influence my interpretation of the findings. Coming from a background where cancer care tends to be almost free of cost, I assume that having to make high payments for treatment is incredibly distressing and I am therefore more likely to be sensitive to participant's views that corroborate this idea of mine. Imagining all the struggles that patients can face in India, that I probably do not see so much in HIC, might make me overvalue barriers over solutions. Other aspects of the observed dynamics during the interviews were reported and discussed.

4.5 Results

4.5.1 Participants

Fourteen healthcare professionals who routinely work with colorectal cancer patients participated: four oncology surgeons, four medical oncologists, four radiation oncologists, one stoma care nurse and one hospital finance manager. Although no one declined the invitation to participate, some principal investigators were unable to recruit nurses nor managers, due to logistic or time capacity issues. Most of the participants worked in charity/private hospitals (78.5% [11/14]), with the remainder working in a government funded setting. Eleven participants were male and three were female.

4.5.2 Coding tree

The following coding tree was developed from double coding of the first four interviews and further emerging codes in the remaining interviews. Table 24 shows the total number of references and the total number of interviewees mentioning each code, with aggregate totals for the different levels in the code tree.

Table 24: List of codes with total number of times that the code was referred to and number of interviewees mentioning each code.

List of codes	Total number of references	Number of interviewees referring (n=14)
BARRIERS	368	14
1. Socio-demographic and emotional	66	14
1.1. Demographic features	32	10
1.1.a) Gender related barriers	20	9
1.1.b) Elderly	8	5
1.1.c) Muslim population	4	3
1.2. Lack of social and family support	13	10
1.2.a) Lack of social support to accompany the patient	3	3
1.2.b) Family dynamic	2	2
1.2.c) Decrease in social support for patients during COVID	1	1
1.3. Social stigma and shame	9	6
1.4. Emotional	4	3
1.4.a) Patients would prefer to be treated by a doctor of the same religion or community	2	1
1.4.b) People can be keener on paying for treatment for their beloved ones than their own	1	1
1.5. Social status	4	4
1.6. Language barriers	3	2
2. Clinical events and staff	72	14
2.1. Clinical course	39	13
2.1.a) Treatment side effects	20	11
2.1.b) Palliative or progressive disease	9	6
2.1.c) Stoma related body image, social acceptability, and feasibility of keeping jobs	7	5
2.1.d) Unmet patients' expectations	3	3
2.2. Clinical staff	33	11
2.2.a) First line healthcare workers capacity and knowledge	22	8
2.2.b) Lack of qualified cancer care professionals	6	5
2.2.c) Insufficient knowledge and explanation of treatment options	5	2
3. Financial and professional	97	13
3.1. Economic status	53	13
3.1.a) Treatment is too expensive	35	13
3.1.b) Poor patients	9	4
3.1.c) Rich patients	8	3

3.1.d) Patients with less funds want the best for that budget whereas wealthier patients ask for the best overall	1	1
3.2. Access and use of funding schemes	33	8
3.2.a) Government schemes do not cover all costs	5	5
3.2.b) High burden of paperwork	6	5
3.2.c) Availability of schemes is not standardised across India	6	3
3.2.d) Funding schemes rules restrict treatment options	4	3
3.2.e) Hospital reimbursement is delayed and troublesome	4	3
3.2.f) Funding schemes take time to be approved	4	2
3.2.g) Government funds support benign disease easier than cancer treatment	1	1
3.2.h) Inappropriate allocation of funds	1	1
3.2.i) Patients are not aware of the available schemes	1	1
3.3. Professional barriers	7	4
3.3.a) Income loss	5	3
3.3.b) Unemployment (patient and relatives)	1	1
3.4. Access and use of private insurance	4	2
3.4.a) Agreements with insurance companies are not available everywhere	1	1
3.4.b) Insurance companies will not pay if there is a change in treatment delivery or plan	2	1
3.4.c) Private insurance is not reachable for everyone	1	1
4. Healthcare system and geography	84	13
4.1. Geographical	48	12
4.1.a) Distance to cancer centres	36	11
4.1.b) Rural areas	9	9
4.1.c) Urban areas	3	3
4.2. Insufficient capacity for high volume of patients	21	10
4.2.a) Bottlenecks and resource constraints in government hospitals	9	8
4.2.b) Long waiting times, particularly for RT machines	4	4
4.2.c) Insufficient capacity for follow-up	3	2
4.2.d) Insufficient capacity to do MRI and prompt neoadjuvant treatment for rectal cancers	1	1
4.2.e) Insufficient pathology reporting capacity	1	1
4.2.f) Investment in healthcare system is insufficient creating resource constraints and people to go to govt setup	1	1
4.2.g) Shorter waiting lists during COVID	1	1
4.3. Fragmentation of cancer care	10	5
4.3.a) Fragmented treatment plans	6	4
4.3.b) Multidisciplinary teams aren't always available	3	2
4.3.c) Disparity in treatment plans across sites	1	1

4.4. Patients prefer to be treated in branded cancer centres	5	2
5. Awareness and education	49	13
5.1. Lack of public awareness and education	16	9
5.1.a) Patients might think part of the treatment is enough to cure cancer e.g. surgery or symptom relief	3	3
5.1.b) Patients think all cancers are similar	2	2
5.1.c) Patient inability to understand the severity of the disease	1	1
5.1.d) Patients are more likely to take a treatment that is conveyed as curative even if that is not realistic	1	1
5.1.e) Patients are not aware that clinical opinions are based on evidence and are not personal	1	1
5.1.f) Patients are not aware that their symptoms could be cancer	1	1
5.2. Patient misconceptions and lay beliefs	25	8
5.2.a) Trust in traditional ineffective treatment	8	6
5.2.b) Nihilism	6	4
5.2.c) Distrust in English or allopathic medicine	5	2
5.2.d) Denial of the diagnosis	4	1
5.2.e) Misconception that surgery causes cancer spread	2	1
5.3. Distrust in healthcare professionals	8	5
5.3.a) Distrust in healthcare workers is more common in the East	2	2
5.3.b) Patients might follow their relatives opinions more than doctors' opinions	1	1
FACILITATORS	92	14
6. Financial and professional	17	10
6.1. Optimisation of funding schemes	9	6
6.1.a) Streamline patient eligibility and fund allocation	2	2
6.1.b) Anticipated approval of funding allows hospitals to provide faster treatment	1	1
6.1.c) Arranging free accommodation or food for patients near cancer centres	1	1
6.1.d) Create specific travelling funds for cancer patients	1	1
6.1.e) Improve organisation of funding allocation centrally	1	1
6.1.f) Streamlining the use of funding schemes for hospitals	1	1
6.2. Development of cost-effective treatment strategies	4	3
6.2.a) The cost of drugs needs to decrease	3	2
6.2.b) Development of biosimilars at lower cost	1	1
6.3. Increase job stability	1	1
6.4. More funding for palliative cancer	1	1
6.5. New solutions demand more funding	1	1
6.6. Temporary low premium insurances	1	1
7. Healthcare system	22	10

7.1. Expand capacity with additional or within current cancer centres	7	5
7.2. Improve links and referrals to cancer centres	8	4
7.2.a) Education exchange rural and cancer centres	2	1
7.2.b) Qualified professionals to deliver cancer care locally	2	1
7.2.c) Qualified professionals to handle chemotherapy side effects locally	1	1
7.3. Standardisation of MDTs to deliver integrated care	2	2
7.4. Definition of cancer goals at regional or national level	1	1
7.5. Evidence & research-based advocacy for CRC	3	1
7.5.a) Advocate for up prioritising of colorectal cancer treatment	2	1
7.6. Improvement of follow-up strategies	0	0
7.7. Research on quality of life during cancer treatment	1	1
8. Awareness and education	18	9
8.1. Awareness programmes for the public about CRC	13	6
8.1.a) Through ASHA workers network and in rural areas	2	2
8.1.b) Demystify stomas and their effects on peoples' social value	1	1
8.1.c) Mobile phone-based campaigns	1	1
8.2. Evidence based, public facing websites	3	1
8.1.a) Patient focused website created and maintained by impartial partners	1	1
8.1.b) Website content should include treatment options, survival expectancy and expected costs	1	1
8.3. Patients as advocates	1	1
9. Clinical staff	20	6
9.1. Better communication with patients	11	5
9.1.a) Clarify misconceptions, namely about stomas	2	2
9.1.b) Communicate various options and their rates of success letting patients choose	2	2
9.1.c) Communication of funding alternatives	2	2
9.1.d) Communication that is sensitive to patients' beliefs and lifestyle	1	1
9.1.a) Increase capacity to follow-up patients	1	1
9.2. Healthcare professionals' education and update	8	3
9.2.a) Awareness programmes for first line HCW	4	2
9.2.b) Clinical sessions compatible with clinical commitments	1	1
9.2.c) Education on multidisciplinary approach for all doctors involved (surgeons, oncologists, radiotherapists)	1	1
9.2.d) Mandatory periodic certification for doctors	1	1
9.2.e) Specific training on surgical oncology for surgeons	1	1
9.3. Adapt treatment plans as per patients needs and background	1	1
10. Socio-demographic and emotional	15	5

10.1. Patient support groups and sharing of experiences	9	4
10.1.a) Patient support groups need to be linked back to the healthcare system	1	1
10.2. Educating families to support patients	1	1
10.3. Social workers and patient advocates	5	2
10.3.a) Social workers to facilitate funding schemes application	1	1
10.3.b) Translation to local languages	1	1

The coding tree was then reviewed, together with the original raw data, to identify patterns and define the overall themes and subthemes. It was clear, at this stage, that although some topics had been coded under distinct branches of the coding tree, they connected or overlapped. The codes were therefore re-arranged into themes and subthemes, to integrate the connections between codes that benefitted from being interpreted together, while building a structured message that would be easy to understand for the reader. As an example: considerations made by participants about the distance to cancer centres were included in the "Geographical distribution of cancer care", under the theme "Healthcare system and capacity" but also in "Non-medical costs of treatment", under the theme "Financial and job protection". Supplementary Table 5 shows list of codes matching each theme and subtheme.

4.5.3 Themes, sub themes and key messages from the data

Five main themes were identified from the data after this re-arrangement: (1) social background and support, (2) awareness, education and beliefs, (3) healthcare system capacity and organisation, (4) clinical events and (5) financial and job protection. Barriers and facilitators within each theme are summarised below.

4.5.3.1 Social background and support

4.5.3.1.1 Social and family support

The majority of participants suggested that lack of social support was one of the barriers for patients to receive colorectal cancer treatment, particularly having someone to accompany the patient: "[it is] *very difficult to quit the work and accompany the patient for treatment, (...) that is another big factor, lack of social support*" (p13). This seemed to be aggravated during the pandemic, when "*many people will be hesitant to go to hospital"* (p10). Another common reference was how difficult it was for patients to find carers for dependents, for example *"if he brings his wife the children are alone, and he will need to find out who will look after the children"* (p1).

More broadly, participants suggested that barriers in the social context *"come from every corner (...) family members, society, friends circle" (*p11) and that family dynamics are an important determinant of patients' choices towards treatment: *"I think the family dynamics and whether it's a joint family or a nuclear family plays a very big role in how the patient treatment decisions are made"* (p8).

Some participants suggested that the setup of patient groups where experiences are shared, "*where patients can discuss with each other, can voice opinions, can mention their difficulties* (p5)" can mitigate against drop-outs, especially if these can be linked back to the healthcare system. These groups could potentially organise social support, lifting pressure from families and contributing to their

education on cancer and patient management: "*They could take care of the children while they are away for treatment, or they could look after their food while the main breadwinner is away"* (p1).

4.5.3.1.2 Elderly patients

Participants perceived that elderly patients are less likely to complete treatment, explaining that when a patient "*is very old, it is very difficult for them, so they quit treatment, that happens quite a lot*" (p13). A lower acceptance of the disease was mentioned in elderly patients "*They don't accept the fact that you should or can be treated*" (p4). Financial barriers in older patients were mentioned, namely the lack of "*good medical insurance*" (p8) and the fact that families often need to consider whether the health benefits are worth the monetary investment: *"Is it really worth [it], or should I just let her go? She has lived well so why bother for seven lakhs?"* (p4).

4.5.3.1.3 Gender disparity

Some participants recognised that *"women with cancers tend to be neglected"* (p4), as their health can be devalued, they lack financial independence, and it can be unsafe to travel independently. "*None of the ladies would travel alone from a village to go into a city to get treatment, it's the culture plus the security is definitely a problem"* (p1). Women seemed more disadvantaged in rural settings "*It may not be true in cities, but in the rural India nobody cares for them, they are supposed to produce children*" (p1). Women from poor backgrounds were

particularly disadvantaged too: "*if they don't have money yes they will probably prioritise the gender*" (p3). However, four participants (3 men and 1 woman) did not perceive that gender would affect the treatment course: *"I don't see much of a gender bias"* (p7).

4.5.3.2 Awareness, education and beliefs

4.5.3.2.1 Lack of patient education and awareness

Most participants mentioned that lack of education and awareness can lead patients who *"are curable [to not] opting for treatment"* (p4), as they might be unable to understand *"the gravity of the disease"* (p9), with subsequent treatment drop-out, refusal or opting for alternative medicine: "*There are people who drop out, those who are not very educated, those who do not have the idea about how cancer spreads, how dangerous this disease is, who do not have this idea they may get, and they go for some alternative medicines like some Ayurveda"* (p10). Some professionals expressed that the a lack of education prevented patients from understanding that the treatment options and effects are evidence-driven: *"they don't understand that what I say is based on thousands of clinical trials, it's not my opinion"* (p5).

4.5.3.2.2 Distrust in conventional medicine

A level of patient distrust in conventional medicine and doctors was perceived by some of the cancer professionals. "*People feel that whatever treatment is given to them may not be the appropriate or the correct, they may be getting duped for*

this" (p8). Some participants also mentioned the common use of *"some* [form] *of alternative medicine before they come to us"* (p12), which can initially be more comfortable and cheaper, but is ineffective overall. Examples:

"You get steroids you will feel better for some time, so that is cheap, and at the end of the day that sells" (p4); *"They are more comfortable going to a nearby quack and getting treated because it saves them a lot of hassle, saves them the time of travelling, cost involved"* (p8).

Participants explained that some patients trust community members *"much more than what they hear from the doctor"* (p5), which can lead to treatment drop-outs: *"These patients are scared about chemotherapy because of the stories they hear"* (p3).

4.5.3.2.3 Community misconceptions and stigma

Some participants reported that misconceptions about cancer persist in communities, leading to diagnosis denial and nihilistic attitudes: "*the word cancer is the utmost word for the patient and their relatives, that they will die, they will not survive it*" (p11). It was also mentioned that shame about colorectal cancer symptoms and fear of social rejection can prevent patients from seeking or receiving prompt healthcare: "*People don't want to tell their doctor I am having some bleeding from the motion area (...) Sometimes people may just get treated secretly and they won't tell anybody*" (p8).

4.5.3.2.4 Awareness programmes

Community and individual level awareness programs about colorectal cancer symptoms, treatment options and demystification of stigmas were suggested to facilitate treatment access and compliance: *"they need to be aware that treatment is available, how quickly the patient can be diagnosed and access quality care. So if we can cut short that time period we can save many lives, rather than the patient revolving around everywhere and then landing up late to the hospitals"* (p2)

Various participants mentioned that these programs could be run through community workers (e.g., ASHA – Accredited Social Health Activist), mobile phone-based campaigns or evidence-based *"patient information websites"* (p6).

4.5.3.3 Healthcare system capacity and organisation

4.5.3.3.1 Geographical distribution of cancer care

The majority of participants mentioned that *"cancer centres in India are mostly concentrated in the metropolitan cities"* (p10), which can cause delays, drop-outs and lower adherence to lengthy treatments. It was perceived that for many patients living in rural settings, travelling is expensive and distressing, particularly during the COVID-19 pandemic when patients were "*paying double or nearly triple for travelling*" (p9). Example: "*some patients find it difficult to travel from far places like 200 or 250 kilometres, they are coming here every 15 days for chemotherapy (...) and he [patient] is a labourer, the accompanying person is a*

labourer, so it's very difficult to come or move to 50 kilometres away, then to quit his job, and then how he will be able to see his family, that is again a big question" (p13)

4.5.3.3.2 Hospital capacity and pathways

Many participants mentioned that there is insufficient capacity in the healthcare system to treat the current volume of patients, particularly in government hospitals where *"the long waiting list is the major issue"* (p12): *"It's humanly impossible to cater to such a high number of patients, and when the quantity goes up the quality comes down"* (p1). Participants explained that the "*manpower or time constraints" (p5)* result in a lack of capacity to offer all patients a multidisciplinary treatment plan and reliable follow-up appointments, meaning that patients can easily get lost in the care pathway: *"if one of my patients is not coming for treatment I don't even know, I will get to know three years down the line"* (p5). One participant mentioned that waiting times improved during the COVID-19 pandemic, as fewer patients were reaching hospitals, but another flagged that travel restrictions during *"lockdown have* [negatively] *affected the normal routine follow-up"* (p9).

Some participants made clear that expansion of capacity within existing or additional cancer centres is necessary to improve treatment delivery, particularly individual follow-up. It was also suggested that social workers or other professionals could support the integration of the care pathway, by acting as "*a*

patient navigator" (p7), translating documents and organising funding applications to increase patient retention.

4.5.3.3.3 Communication between cancer care professionals and patients

Most participants mentioned that an insufficient number of cancer care professionals means that they do not always deliver a comprehensive, evidence-based explanation of the treatment options: "*[Doctors] have busy outpatient clinics, we just say 'This is the prescription', and then she [the patient] will be wondering at home and there is nowhere she can come back and ask why, how, when*" (p5). The participants highlighted topics that should be covered when communicating to patients to improve treatment adherence, including the fact that a multimodal approach (including surgery, chemotherapy and radiotherapy) might be required to cure cancer, success rates of the treatment options as well as available funding opportunities: "*If they are poor, at the first appointment I start telling them about how funding can be applied for and how we can help them so that they don't run away*" (p1). Some participants suggested that communication strategies that are sensitive to patients' lifestyle, fears, beliefs and misconceptions can improve the acceptability of treatment: "*When you present facts you should not scare them, and we should take measures to erase the existing myths*" (p1); "*If he has a mobile job [and] you do a very low anterior section but at the end of the day if he has to go about in a diaper, it creates a problem. So I think that talking and understanding what environment they will go back to is very important*" (p8); "*We tell them about long course radiation, they get*

scared (...) Then they get the surgery done and go home and then they recur, and why did that happen? Because I didn't give him a second choice" (p5).

4.5.3.3.4 Capabilities of first line healthcare workers

Participants explained how first-line healthcare workers lack updated knowledge and resources to diagnose cancer: "*A [doctor in a] primary healthcare centre, does not have everything which is available to me, or may not have that kind of training to pick up things"* (p8). Therefore, they might prescribe ineffective treatment causing delays in presentation, potentially restricting treatment options and chances of cure: "*They get treatment for haemorrhoids without a proper imaging or clinical examination, and after two or three months there is a rectal cancer, but the disease has advanced*" (p10). It was mentioned that *"local healthcare drains them not only mentally, but physically and financially*" (p2) and the creation of low-premium insurance was suggested as a way of supporting initial investigations and treatments. Clinical sessions targeting first-line healthcare practitioners and adoption of mandatory periodic learning with "*renewal of certification to practice*" (p1) were suggested to improve cancer knowledge, with particular emphasis on colorectal symptoms: "*if bleeding persists then we need to do imaging or a colonoscopy*" (p10).

4.5.3.3.5 Integration of cancer care

Participants mentioned that "*there is no proper referral system*" (p14) for cancer patients in India and suggested that the expansion of whole-system capacity

requires the creation of better links between tertiary care and district or community doctors: "*Smaller hospitals in rural areas can be connected to larger hospitals, who can then provide training to medical professionals in those rural areas and setup basic cancer care facilities*" (p2).

4.5.3.4 Clinical events

4.5.3.4.1 Disease and treatment burden

Some participants mentioned that patients who have progressive or palliative disease "*are less likely to stick with you*" (p4) and that they "*may refuse treatments which are high cost*" (p6). It was also mentioned that some patients can't cope with the general burden of the treatment: "*some patients don't have the willpower to carry the treatment for one year, one and a half years*" (p11). Side effects of chemo and radiotherapy were identified as a common reason for treatment drop-out: "*Whenever they develop some treatment related toxicity there is a tendency to dropout*" (p12). Participants explained that patients can refuse treatment due to the fear of toxicity and complications: *"They are a bit scared about systemic chemotherapy because of the toxicity"* (p9); *"Some are very afraid of surgery, they don't want to get operated"* (p13). In line with integration of treatment pathways, it was suggested that doctors at local practices could help manage side effects of treatment to support patient retention.

4.5.3.4.2 Stoma acceptance

Some participants flagged that patients to whom a stoma is proposed raise social acceptability concerns, particularly if they come from small villages or Muslim communities: *"If the patient comes from a small village or a town, you imagine you're walking around in the streets and you are having this bag over there (...) occupationally once they start imagining how I can do my job with this bag*" (p7); "*They can't go to the Mosque and pray because they are considered unclean"* (p6).

It was said that a mindset shift would facilitate treatment delivery *"That barrier needs to be broken"* (p8) and it was suggested that a *"stoma nurse has a very important role [in explaining that] you will have a reasonably good quality of life with this stoma, so don't avoid treatment because of the stoma bag"* (p10).

4.5.3.5 Financial and job protection

4.5.3.5.1 Medical costs of treatment

Almost all participants recognised that *"the majority* [of the patients] *have financial issues*" (p12), with an impact on treatment dropouts: "*It is difficult for a family that is earning 10,000 a month to pay for treatment that is worth 20,000 a month, they can't afford. So that patient will get lost in the system, they will get lost for sure*" (p4).

Participants explained that this happens in private, but also in government hospitals: "*[In private hospitals] some people take the [treatment] plan and go away, find it too expensive*" (p5); "*[In public hospitals] although the treatment is not very costly, some people are very poor so they find it very difficult to arrange the medicines*" (p13).

It was flagged that expenses are particularly problematic when treatment is multimodal or complicated by adverse events: "*They had neoadjuvant chemotherapy or chemoradiotherapy, and by the time they come for surgery they don't have money*" (p6).

4.5.3.5.2 Non-medical costs of treatment

Another source of over-expenditure raised by participants was long distance transportation to tertiary hospitals, accommodation costs and income loss: "*They have to find some accommodation, arrange their food, take care of daily necessities, these expenses are not factored in any of our bills (...) and because of these expenses they might not continue the treatment*" (p14); "*Loss of working, general labour days or the opportunity to earn also is a fearful thing*" (p3).

Directed funding to support travel and accommodation expenses was suggested as a way to improve treatment adherence, as well as investment in job stability strategies: *"I feel like we need a support system for these patients, [to give] some kind of free accommodation (...) or arrange for food for patients who stay here so*

the financial constraint might be reduced" (p12); "*If we can do something to ensure job stability (...) it's not that if you are sick you lose your job*" (p1).

4.5.3.5.3 Cancer funding schemes

Challenges regarding government or state funding schemes for cancer care were frequently mentioned, such as (1) irregular availability "*Application or implementation of these policies are sporadic*" (p3), (2) burdensome application processes with "*lots of paperwork, you have to run to the ministers of the state or the country to get that certificate signed*" (p9), (3) delays in approvals: *"It takes time, so in the meantime your disease may progress, your treatment gets delayed"* (p10) and (4) deferred reimbursements "*It takes about two years to get one patient's money. So hospitals are also not forthcoming for accepting these schemes*" (p1). It was also flagged that these funding schemes can restrict treatment options. "*They may get capecitabine instead of oxaliplatin, maybe we do open surgery rather than laparoscopy because that's cheaper. So there is an element of people completing treatment but with a slightly modified plan*" (p6).

Streamlining eligibility, application processes, individual fund allocation and hospital reimbursement for sponsored treatments were mentioned as important facilitators by some participants: "*First priority is at the bureaucratic levels, every patient should get enrolled in the state or centre sponsored scheme [by default]"* (p13); *"If they can go home to home, create awareness there and do that*

verification rather than doing it at the time of [hospital] registration, which actually just drains the patient" (p2).

4.5.3.6 Policy and research

Some participants mentioned that an increase in national health expenditure is necessary to improve treatment delivery for all cancers and that patients and professionals should lobby and advocate for goal-based cancer policies*: "Right now we have guidelines from the scientific bodies, but I will say from the policy point of view if your country there might be [the need for] goals"* (p7). Research was recognised as way to improve care and the identified priorities included: (1) treatment cost-effectiveness *"Multimodality treatment which is affordable and cost effective"* (p4), (2) biosimilar drugs that come at lower cost *"There should be some provision for these costly molecules so they are within the reach of every common man"* (p13) and (3) patient quality-of-life, as *"most patients dropout because they are just not feeling good on the treatment"* (p5).

4.5.3.7 Key messages from the interviews

The main messages and points raised by the interviewees are shown in Table 25, within the themes and sub-themes that they were grouped into.

Table 25: List of themes, subthemes and key messages from the data within each theme and subtheme, categorised into identified barriers and facilitators for colorectal cancer treatment adherence.

Theme	Subtheme	B/F	Key messages from the data
Social support and background	**Social and family support**	B	Lack of emot ona support from fam y and fr ends
			Fam y dynam cs has an mpact on dec s ons for treatment
			D ff cu ty n f nd ng compan ons for pat ents
			Lack of support to care for dependents
			COVID-19 made soc a support even more d ff cu t
		F	Set up of pat ent support groups to share exper ences
			Organ sed support for to take care of dependents
	Elderly patients	B	D sease has a h gher burden n o der pat ents
			O der pat ents have ower acceptance of cancer
			Management of f nanc a nvestment and short fe expectancy
			O der pat ents are ess ke y to have good nsurance
	Gender disparity	B	Women s hea th s deva ued
			It s more d ff cu t for women to trave to get treated
			Women are more neg ected n rura areas and poor backgrounds
			Gender d spar ty s not a ways present
Awareness, education and beliefs	**Lack of patient education and awareness**	B	Non acceptance of d sease and treatment
			Inab ty to understand the d sease sever ty and behav our
			Inab ty to understand the pr nc p es of treatment and ev dence-based med c ne
	Distrust in conventional medicine	B	Pat ents don t trust convent ona doctors
			Pat ents trust the r c osest ones more than doctors
			Pat ents often use a ternat ve med c ne opt ons
			A ternat ve treatments can de ay appropr ate treatment
			It can seem eas er or more comfortab e to access a ternat ve med c ne
	Community misconceptions and stigma	B	N h st c att tudes towards cancer
			Shame and st gma towards co orecta cancer symptoms
	Awareness programmes	F	Commun ty and nd v dua awareness programmes
			Use of commun ty workers, phone based campa gns or ev dence-based webpages to ncrease awareness
Healthcare system capacity and organisation	**Geographical distribution of cancer care**	B	Cancer centres are concentrated n urban areas
			Trave ng s expens ve and d stress ng
			COVID-19 has made trave ng more d ff cu t

	Hospital capacity and pathways	B	Insuff c ent capac ty of the hea thcare system to cope w th demand
			Long wa t ng sts
			Lack of capac ty to fo ow-up cancer pat ents
			Lack of capac ty to offer mu t d sc p nary dec s ons for a pat ents
			COVID-19 has added cha enges to rout ne fo ow-up
		F	Expans on of capac ty and / or number of cancer centres
			Hosp ta nav gat on support for pat ents can mprove retent on
	Communication with cancer care professionals	B	Lack of comprehens ve exp anat on of the treatment p an
			Lack of focus on the benef ts of mu t moda treatment approach
		F	Exp anat on of treatment opt ons and success rates
			Upfront commun cat on of fund ng opportun t es
			Commun cat on strategy that s sens t ve to pat ents fears, be efs and m sconcept ons
			Cons derat on of pat ent s festy e n treatment d scuss ons
	Capabilities of frontline healthcare workers	B	Lack of updated know edge and resources n f rst ne hea thcare
			Inadequate management n f rst ne hea thcare can cause de ays and ncrease expend ture
		F	Low prem um nsurances to ensure affordab e nvest gat ons and f rst ne care
			Cont nued med ca earn ng and per od c cert f cat on for a doctors
	Integration of cancer care	B	Lack of eff c ent referra pathways
		F	Improvement of nks and know edge exchange between tert ary, d str ct and commun ty doctors
Clinical events	**Disease and treatment burden**	B	Treatment s de-effects and comp cat ons
			Progress ve and pa at ve d sease
			Genera burden of undergo ng treatment
		F	Management of s de effect at oca pract ces
	Stoma acceptance	B	Low nd v dua and soc a acceptab ty of stomas
			St gma s h gher n rura and Mus m commun t es
		F	M ndset sh ft about stomas n commun t es s needed
			Stoma nurses p ay an mportant ro e s demyst f cat on
Financial and job protection	**Medical costs of treatment**	B	Treatment s expens ve and most pat ents strugg e to pay
			Treatment expenses are part cu ar y prob emat c n mu t moda treatment or when there are comp cat ons
			Pat ents m ght sh ft to government hosp ta s due to h gh costs but bott enecks ex st
			Unaffordab e treatment s a prob em n both pr vate and government hosp ta s

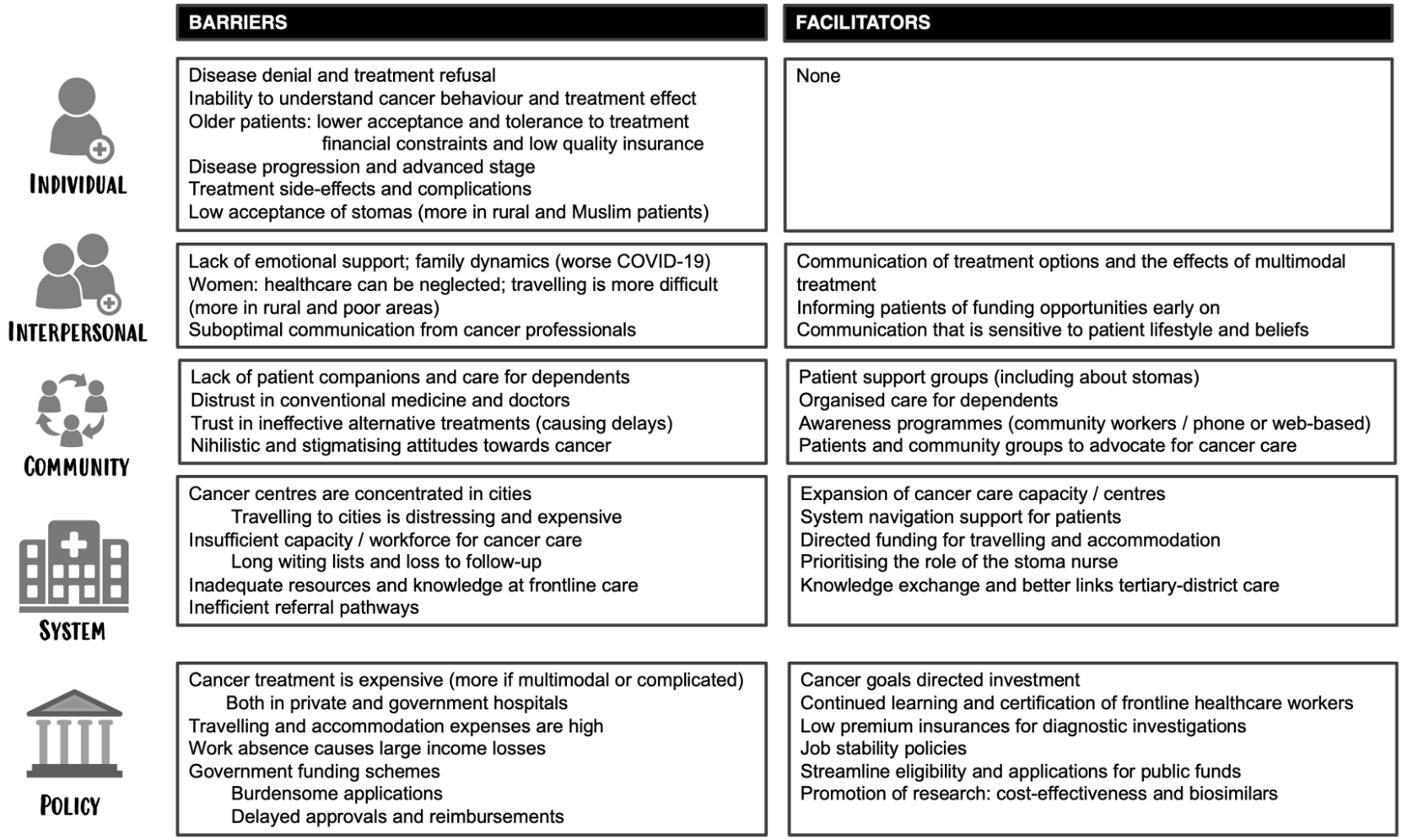
	Non-medical costs of treatment	B	Trave ng and accommodat on costs for pat ents who ve far from the hosp ta
			S gn f cant ncome oss due to work absence
		F	Fund ng support d rected to trave and accommodat on expenses
			Job stab ty strateg es
	Cancer funding schemes	B	Government subs d sed fund ng s not a ways ava ab e
			Burdensome app cat on processes
			Restr ct on of treatment opt ons f pat ents are funded by a scheme
			De ays n fund ng approva s can de ay treatment
			De ayed re mbursement of hosp ta s that engage n these schemes
		F	Stream n ng app cat on processes, fund a ocat on and re mbursements
			E g b ty checks ahead of cancer d agnos s and hosp ta reg strat on to avo d de ays
	Policy and research	F	Estab shment of nat ona and reg ona cancer care goa s
			Increase of nat ona and reg ona tota hea th expend ture for cancer care prov s on
			Research on cost-effect veness to mprove affordab e care
			Investment n drug research and b os m ars to prov de best care to a pat ents
			Pat ent and profess ona groups to obby w th the government and advocate for cancer care

The table shows the themes and subthemes in which each code was incorporated, after theme derivation was complete. In this table, *not included n=1* reflects codes that were only mentioned by one or two interviewees and were not related to any other mentioned topic, hence considered to be outside the general pattern of the data. B= barriers; F= facilitators.

4.5.4 Barriers and facilitators categorised according to Socio-Ecological Model

The key messages from the data, within each theme, were reviewed and mapped to the Socio-Ecological Model, depending on the level of society where they best fit (see Figure 37). Whereas barriers were identified across all themes, facilitators were mainly raised at system and policy levels.

Figure 37: Summary of the key messages from the data, mapped to the five levels of the Socio-Ecological Model.



4.6 Discussion

4.6.1 Main findings

This study identified a range of barriers influencing colorectal cancer treatment adherence and provided potential targets for the improvement of cancer care delivery in India. These data shows that barriers for treatment adherence are multifactorial and exist at all societal levels. They also show that solutions are likely to require combined policy, healthcare system or community interventions. Although some factors might not be modifiable (e.g. clinical events), patient retention in treatment can be improved by: increasing the capacity and efficiency of the healthcare system, ensuring timely funding and job stability for cancer patients, conducting programs to improve patient education and enhancing social support.

Although, to my knowledge, no data studies exist on the factors influencing colorectal cancer adherence in India, some of the findings are consistent with previous studies on other types of cancer. One of the most common factors associated with poor cancer treatment compliance in the literature is the distance that patients have to travel to get treated(140-143). This was found to lead to more advanced stages of cancer at presentation, inappropriate treatment (e.g., lower breast conserving surgery rates in breast cancer), worse prognosis and lower quality of life(141). As it was highlighted by the participating cancer professionals in this study, a longer distance to the hospital is linked to

transportation and lodging costs that can impair treatment compliance on their own (144), but also to stress and discomfort for cancer patients, including safety concerns for women.

Low education levels are also often mentioned in the literature as a predictive factor in cancer treatment drop-out (144-146), which can be linked to a lower purchasing power and difficulties accessing care but also the inability to fully understand the disease and the treatment plan. Health illiteracy is a factor that can delay effective treatment at any stage, since it prevents early recognition of symptoms, impairs patients' ability to reach the appropriate facilities and has a negative impact on the ability to understand the natural history of the disease, as well as the treatment options(132, 147-149).

Financial hardship and a low income have also been identified as major barriers for cancer treatment completion, in which financial protection strategies play an important role(144, 146). Few studies have looked at the barriers to access funding for cancer care in India, and only two have associated the access to government health schemes with treatment completion (143, 146). This study exposed the challenges that clinicians observe in their patients' pathways while accessing these funds, namely burdensome applications, delayed approvals and inconstant availability. These should guide future decision making on the management of these government funds, in order to improve financial protection in India.

Social support has been one of the main themes raised by the participants as preventing patients from complying with their treatment plan, which had been identified as a barrier to seek cancer care in India (132). This study adds depth to previous knowledge as it explains how logistic support (e.g. care for dependents) but also emotional support from communities are important drives of treatment completion and optimal oncological outcomes. The participants reinforced the idea that behaviours resulting from stigma, shame and nihilism in the community can reduce patient retention in their treatment course (144), which seemed to be related to education levels to a degree but also to spiritual beliefs.

Alternative medicines (e.g., Ayurveda) have an important effect on patient's willingness to receive adequate cancer treatment (144), as some might quit conventional medicine to receive the former. Distrust in conventional medicine can be driven by community beliefs but is perpetuated by low education levels, which limits patients in their ability to question traditional/non-conventional treatments. A recent study in South Asia that did not include India, found that patients often used complementary non-conventional medicine during their cancer treatment and that those patients were more likely to suffer catastrophic expenditure (133). The authors suggested that complementary medicine should be funded as part of cancer treatment. The participants of this study did not share this view however, as they seemed to prioritise population education on effective treatments, to prevent treatment course detours and unnecessary costs.

From the study findings and the review of the literature, it is evident that some of the identified barriers for colorectal treatment completion are similar to those faced by patients with other types of cancer. Although the findings should not be directly generalised, these data can provide insights into what can be changed to improve the delivery of cancer care more broadly. However, specific challenges faced by colorectal patients were described. Bowel cancer symptoms can be associated with shame and there is low symptom awareness among communities. Stomas can also trigger shame, interfere with religious beliefs and the availability of stoma devices can be limited specially in rural areas. Finally, the need for multimodal treatment, although not exclusive of colorectal cancer, is common and treatment drop-out can be related to patient's inability to understand the synergistic effect of e.g., chemotherapy and surgery.

This study also highlights barriers that are specific to the various treatment modalities. Adherence to chemo and radiotherapy seems to be particularly affected by the fear of side effects, symptoms of actual toxicity and regular travelling to the site where they are administered. This is aligned with previous findings in treatment for other types of cancer that revealed that Indian patients who suffer the side effects of chemotherapy are more likely to drop out, as well as patients who face logistic and transportation barriers(144, 150, 151). Additionally, low socio-economic and education status have been associated with difficulties in adhering to radiotherapy courses (152). In this study, the reasons for patients

opting out of colorectal cancer surgery were more related to the formation of a stoma as well as the fear of complications.

4.6.2 Reflexivity and sources of bias

Being a researcher from a high-income country, questions about struggles that patients face in India, a lower-middle income country, can prompt feelings in the interviewee that influence their answers. Although the interviews were conducted using open, non-judgemental questions, aiming to be accepting of any perspectives, the fact that I am not from India and do not work there as a clinician could have influenced the degree of transparency in the answers given during the interviews. Some interviewees were visibly hesitant to mention barriers for colorectal cancer delivery, especially at the beginning of the interview. Conversely, the fact that I was external to their working environment might have allow participants to more freely share their thoughts, without fear of repercussions (e.g., the lack of multidisciplinary decision making can be a reflection of conflicts in clinical teams as well as a fault of the system).

Some of the interviewees were keen on demonstrating knowledge on the topic of cancer care in India, mentioning percentages and detailed information, almost in a performative manner. This can reflect a form of power dynamic through which some interviewees might have felt they should demonstrate knowledge and abilities, rather than perspectives and experiences, which I tried to work around during the interviews. This was particularly evident when I interviewed one

interviewee, who seemed concerned about conveying the good performance of the department where they worked, perhaps thinking that any mention of barriers could be perceived as a weakness.

I had met some of the interviewees in my visit to India in February 2020 and those interviews ran smoother with these, usually with more content, likely due to an increased level of trust. All interviews were conducted online and some interviewees might have felt apprehensive about sharing their views though digital means, with someone they had never met. Finally, the interviewees were chosen by the principal investigators at each site, which could have been a source of bias in itself, out of my control.

My own point of view, specifically my presumption that cancer care in India would be expensive and difficult to access, could have influenced the way I designed the topic guide and analysed the data. Being a woman and knowing that women are disadvantaged in many societal settings (historically and globally) could have influenced not only my interpretation of gender related barriers, or even the way that the participants conveyed them to me. Finally, my knowledge of the day-to-day life of people in India is extremely limited and my ideas on how living standards interact with the ability to thrive in a treatment pathway could have influenced my interpretation of the findings.

4.6.3 Key strengths

This body of work included interviews with colorectal cancer professionals, which ostensibly cover a broader range of experiences than interviews with individual patients would do. The range of different professionals participating allowed a multi-perspective study exploring barriers in patients undergoing chemotherapy, radiotherapy, surgery and a combination of those. The study included four hospitals in four different states of India, reflecting a number of different settings within such a diverse country. Within the mentioned limitations, this study set out to detect not only barriers about also areas for improvement in the delivery of colorectal cancer in India, aiming to contribute to future decision making. Many of the identified themes are identical to those found in the treatment of other cancer types and can potentially be used to intervene on adherence to treatment of other neoplasms.

Although some of the identified barriers had previously identified in studies focusing on other types of cancer in India, new topics were raised in this study. The suggestions for improvement of treatment adherence constitute a novel contribution to this area of research. And in addition, this study contributed to the literature into why older and female patients might struggle to complete their treatment, how hospital pathways and communication with cancer professionals can impact adherence, the key role of primary healthcare workers to improve whole-system capacity, research and policy priorities and also on specific challenges for colorectal patients.

4.6.4 Key limitations

I acknowledge a number of limitations in this study. Although the professionals might be able to convey a multiplicity of patient experiences, they do not have lived experience of receiving cancer treatment and therefore this study might have missed struggles faced by patients of which professionals are not aware. Furthermore, professionals might not be entirely aware of the barriers for patients who drop out of colorectal cancer treatment and never return to the tertiary care centre.

A higher number of barriers have been identified, compared to facilitators, from the qualitative interviews. This could be related to the topic guide including more prompt questions about the former, but it could also be. because of some difficulty in identifying solutions to current problems. Although the interviews included specific questions on treatment adherence, it might have been difficult for some professionals to distinguish between barriers to access, and barriers to receive cancer colorectal cancer treatment. All barriers were presented, as a degree of overlap is expected.

Three of the four included hospitals are charity/privately funded, with only one government hospital, meaning that the barriers and facilitators in patients receiving publicly funded care may be underrepresented. While this was a multicentre study, India is a large country with varied social, cultural and

economic contexts of which this study might not be fully illustrative. One should reflect on the fact that an online format was used for all the interviews due to COVID-19 travel restrictions. However, previous studies identified no difference in the number of topics raised in online versus face-to-face interviews (136).

4.6.5 Implications for policy

From the data gathered in this study, I conclude that future interventions to improve the delivery of colorectal cancer treatment in India demand larger public investment in cancer care to strengthen the whole healthcare system, with a specific focus on expanding the abilities of frontline healthcare workers, while also supporting an increase in the capacity of tertiary hospitals to deal with for the high volume of cases.

Government investment in cancer care would allow better resourcing of government hospitals, expanding their capacity to provide good quality free care, decreasing waiting lists and increasing capacity for follow-up. An increase in public spending towards cancer care could also improve the patient/professional ratio, improving the communication of treatment options and minimising drop-outs. Out-of-pocket payments for cancer care would be likely to decrease if the government contribution increased, reducing treatment attrition due to financial burden, especially if this investment is done in public facilities where treatment charges can be easily regulated (68). If conventional medicine is affordable and

of good quality, patients might be less inclined to seek out alternative medicine which is likely to be ineffective and has proven to be expensive(133).

The improvement of frontline healthcare could increase the rate of early symptom recognition and diagnosis, leading to better survival outcomes and potentially less expensive treatments. Better support to patients from trustworthy frontline healthcare workers is likely to improve symptom recognition and prompt referrals, avoiding delays in presentation and high expenditure in inappropriate immediate management. Trained frontline workers can function as promoters of health literacy, addressing patient's questions before and during treatment, informing them about funding options, with fewer language or cultural barriers than patients would encounter at tertiary care. As part of an investment in local healthcare workers, specific training on how to manage side effects of cancer therapy, deliver stoma care or even deliver parts of cancer treatment (e.g., chemotherapy or palliative drugs), could improve whole system capacity and reduce the number of drop-outs.

4.6.6 Future research

The participants in this study indicated some areas where research is needed, namely evaluations of cost-effectiveness evaluations to identify which treatment options are the best investments in India and quality-of-life assessments to explore patient acceptability and optimise retention. The participants advocated

for research into biosimilar drugs aiming to make the best and newest treatment technologies available to all patients.

In addition, this study identified modifiable factors that can influence treatment adherence, which can be the target of future quality improvement interventions or clinical trials, to increase treatment adherence and optimise oncological outcomes. This study identified a wider range of barriers than facilitators, and future studies might chose to focus more on the drivers to continue treatment. Finally, I reiterate the relevance of a study capturing patients' perspectives on treatment adherence, which was not feasible in this study.

5 Final discussion and conclusions

5.1 Summary

This final chapter summarises my thesis aims and main findings. I explore how the findings of the different chapters can be interpreted together, as implications of this work are drawn. For each aim, I outline the implications for policy making and future research. At the end, I rediscuss the key limitations of the whole thesis, finishing with an overall conclusion.

5.2 Aim 1

To describe out-of-pocket payments for cancer surgery across income country groups. This aim was explored in Chapter 2.

5.2.1 Key findings:

i) OOPP to pay for the majority of the cost of cancer surgery are high in L&MIC, increasing from high to low-income groups.

ii) OOPP for cancer surgery were independently associated with low country income groups, male sex and elective surgery.

5.2.2 Interpretation and integration within the thesis

My first chapter provided original knowledge and a global perspective on out-of-pocket payments for cancer surgery. Rates of OOPP in surgical care were higher in L&MIC, a pattern that has been seen in other areas of global healthcare(31). This is powerful knowledge, as it allows evidence-based advocacy for the prioritisation of surgery in cancer policy. The benefit of investing in cancer surgery is that it usually provides cure for curative cases and significant improvements in quality of life for palliative patients, mitigating patient suffering at the end of life. When performed in a timely manner, surgery can prevent death and disability both for cancer and benign conditions, allowing societies to stay healthy and productive. Public investment in surgical services is therefore justified and might help narrow the gap between cancer incidence and mortality in L&MIC.

It is expected that the need for surgery increases over the next few decades and urgent investment in capacity to deliver surgery at global level is needed. The Lancet Oncology Commission on Global Cancer Surgery has previously pointed out some solutions to the problem, including better regulated public systems, international partnerships, super-centralisation of surgical services, novel surgical clinical trials, and new approaches to improve quality and scale up cancer surgical systems through education and training(19). Strategies to increase the surgical capacity worldwide will probably need global guidance but also a degree of adaptation across settings. My qualitative chapter explores some of the factors influencing patient's decisions regarding cancer treatment in general and surgery in particular. In the context of colorectal cancer, patient's views on stomas and complications of surgery e.g. need to be addressed when cancer policies are designed to tackle the surgical delivery in India. Acceptability by the population and adherence is crucial for any successful policy, and qualitative work is the ideal method to understand patients' views that can eventually impact the effectiveness of policy change. The quantitative data in Chapter 3 pointed in the same direction, with some patients declining specific components of the treatment, but the low numbers and the absence of depth in the quantitative data prevent firm conclusions.

5.2.3 Implications for policy

Two main implications of these findings can inform future cancer policy:

i) There is a need for better financial protection of patients undergoing cancer surgery at global level, particularly in low- and middle-income countries. Surgery should be prioritised in cancer policy programmes and in cancer funding plans.

ii) Although emergency surgery must be a priority due to its life-saving nature, patients undergoing elective cancer surgery seem to be particularly exposed to financial risk. Cancer financing plans should account for the high OOPP in elective surgery.

5.2.4 Implications for future research

A few research questions arose when I reflected on the findings of Chapter 2:

a) What are the consequences of OOPP for cancer surgery on household financial stability? This question couldn't be addressed in my thesis, as the household's capacity to pay wasn't collected in Chapter 2, but this was explored at a smaller scale in Chapter 3. This question is equally relevant for surgical conditions as a whole, provided that, to date, only a modelling study exists estimating global catastrophic expenditure rates in surgery (83). There is a need for a real-world assessment of OOPP and catastrophic expenditure in surgery.

b) What components of surgical care are patients paying for out of their pocket? Some components of surgical care might be financed through government funds and acquired for free, whereas others might tend to be supported by patients. Having a better understanding of the latter could inform funding plans to reduce the financial burden on patients and could facilitate advocacy for policies that promote global equality in accessibility and affordability of surgery.

c) What is the benefit of investing in surgery? More cost effectiveness studies are needed in surgery and cancer surgery, to justify the increase in public investment. While it seems intuitive that most surgeries will provide cancer cure and save lives, surgery is usually an expensive item at the time of service provision. Evidence of individual and societal benefits of larger public spending on surgical care are likely to help its up-prioritisation by governments in L&MIC.

5.3 Aim 2

To determine costs, catastrophic expenditure and treatment adherence rates in a cohort of patients with a treatment plan for colorectal cancer. This aim was explored in Chapter 3.

5.3.1 Key findings

i) Patients undergoing treatment for colorectal cancer treatment at tertiary care in India spend on average close to 400,000 INR out-of-pocket (around 5000 USD), for their cancer care. This is much higher than the costs reported for other types of cancer in India (25,000 to 100,000 INR for mixed cancers and 295,679 for pancreatic cancer) (47).

ii) Catastrophic expenditure for colorectal cancer treatment in India was found to be very common in tertiary care. Low levels of education and male sex were associated with higher odds of financial catastrophe. Some features of treatment showed to be associated with catastrophic expenditure too, such as surgical resection, advanced disease stage, rectal cancer and treatment in private hospitals.

iii) Government schemes are still failing to protect patients from catastrophic expenditure within six months of a treatment decision for cancer.

iv) A low number of patients experienced treatment attrition, most of them due to declining treatment. Patients with treatment attrition made less OOPP than the ones who complied with their treatment plan.

5.3.2 Interpretation and integration within the thesis

Although colorectal cancer is currently not a major focus of health policies in India, its increasing incidence without specific control programmes, places this type of cancer as a threat for the Indian population in the near future. My Chapter 3 showed that this is simultaneously a health threat, as most patients who presented to tertiary care with advanced disease and palliative treatment plans were common, but also a financial threat, as catastrophic expenditure rates were found to be very high. The study limitations, with patient and hospital selection as well as short follow-up in the context of a cancer, can contribute to an overestimation of cost and catastrophic expenditure but the direction of findings is expected to remain the same.

Colorectal cancer needs attention and investment that takes the complexity of the treatment pathways into consideration. Previous authors have criticised the central government of India for including cancer in broader programmes to control non-communicable diseases (68). Although a National Cancer Control Programme does exist and efforts have been made to improve access to cancer care, these are still insufficient to meet the population's needs. My Chapter 4

provided suggestions from professionals working with colorectal patients on what could be done at multiple societal levels to improve treatment completeness, tackling financial barriers that patients face but also other challenges that can increase the success of cancer control programmes.

5.3.3 Implications for policy

i) Colorectal cancer should be up-prioritised in cancer control programmes in India, as the incidence is expected to increase and out-of-pocket payments are high.

ii) The funding of cancer care in India needs to account for the complexity of the disease. In order to protect colorectal cancer patients from financial toxicity, an average of 400,000 INR would need to be made available per patient. If categories are to be established for colorectal cancer funding, patients eligible for surgical resection, who present with rectal or advanced cancer might need more funding than the remainder.

iii) Government funding schemes need to be expanded or other risk pooling strategies need to be created, to improve financial protection of cancer patients in India.

iii) Further efforts within the healthcare systems must tackle the reasons why patients drop out of treatment, exploring preferences and patients' decisions, promoting a fully evidence-driven decision by patients.

5.3.4 Implications for future research

i) What are the costs of colorectal cancer at a larger scale, in India and internationally? The small sample in this study does not allow wide generalisability and a larger scale research is needed.

ii) What are the costs and treatment attrition of colorectal cancer at other levels of care in India? Tertiary care is usually where colorectal cancer is treated, but many patients might not reach it and might be paying for other therapeutic options elsewhere, or simply not receiving the adequate treatment. The major challenge of delivering a study to capture colorectal cancer patients at multiple levels of care would be their identification and recruitment. Additionally, the undiagnosed or untreated patients might represent the most vulnerable group, but a study designed to detect them and their outcomes would be extremely difficult to deliver.

5.4 Aim 3

To assess the feasibility of the International Wealth Index (IWI) and the Gapminder tool as indirect measures of household income, comparing them to self-reported income. This was a secondary aim of Chapter 3.

5.4.1 Key findings

Almost all patients could complete the IWI and the Gapminder questionnaires, meaning it is feasible to use them as patient facing tools. The IWI showed better agreement with self-reported income than the Gapminder, and both showed

better agreement for low earning households. Their use resulted in different catastrophic expenditure rates, when compared to self-reported income.

5.4.2 Interpretation and integration within the thesis

Although this was quite a contained section of my thesis, defined as a secondary aim of one of the chapters, I believe it is still relevant for the interpretation of the whole work. The use of the IWI and Gapminder tools ties in particularly well with two topics raised in the qualitative chapter. One of them is that financial capacity is a common concern in patients diagnosed with cancer. One can understand that, as raised in the interviews, being diagnosed with cancer is enough of a burden and having to deal with financial issues at the same time must be difficult. Alternative, non-monetary, ways to assess patients' ability to pay for treatment could potentially mitigate against the overall burden seeking funds at the time of diagnosis. Secondly, it was also mentioned during the interviews how difficult it is for patients to navigate hospital systems. Patients might then be cautious about revealing their income, given that hospital pathways can seem overwhelming, breaking patient's trust in the system. The use of the indirect ways of assessing household income could eventually improve cancer patients' experience, when finance departments at the hospital seek this information to check eligibility for external funding.

5.4.3 Implications for policy

i) It is feasible to use alternative methods to assess household income, and this should be considered in future household assessments, as a way to avoid the biases related to self-reported income. If this is possible and generalisable, these tools could be used to monitor global rates of catastrophic expenditure.

ii) If alternative tools become available and are accurate, these could potentially be part of the assessment made in many hospitals in India to decide which funding support patients are eligible to.

5.4.4 Implications for future research

i) How can the IWI and the Gapminder be refined so their accuracy is higher and the estimated income is more similar to the real one? This would probably involve the assessment of a large number of households using these tools, to refine their prediction power. Regarding the IWI, a few other items could also be added to increase the precision of the total score. From the Gapminder's One Dollar Street project, many house pictures are available and a study could be done to determine which ones are better correlated with household income.

ii) Can the IWI and Gapminder mitigate against the biases observed with self-reported income. An assessment of patient experience completing the IWI and Gapminder tool would be needed, with qualitative work to explore biases arising from these tools.

5.5 Aim 4

To assess the views and perspectives of colorectal cancer professionals on barriers and facilitators for colorectal cancer care adherence. This was explored in my Chapter 4.

5.5.1 Key findings

i) Treatment attrition is low at tertiary care but barriers exist at multiple levels of the healthcare system and the society. Interventions at community, healthcare system and policy can potentially improve patient retention and improve cancer outcomes.

ii) Barriers and facilitators for colorectal cancer treatment adherence were identified within five main themes: (1) social background and support, (2) awareness, education and beliefs, (3) healthcare system capacity and organisation, (4) clinical events and (5) financial and job protection.

5.5.2 Interpretation and integration

There was a convergence of the findings of chapter 3 and 4 regarding colorectal cancer treatment adherence. In my chapter 3, following up a cohort of patients with a treatment plan for colorectal cancer allowed me to capture a group of patients who dropped-out of treatment and try to understand their motives. The limitations inherent to the small sample and the inclusion of tertiary hospitals only

certainly influenced the findings. Chapter 3 complemented this knowledge in three key areas:

a) Treatment attrition rates in patients with an established cancer care plan is not frequent, as illustrated in this quote from one of my interviews "*In colorectal cancer, the dropout rates are very low. Once you have started treatment I would say almost 98%/99% of patients comply (...) So it is all again the public healthcare system"* (p7). It was suggested that the struggles to complete cancer treatment are present at other levels of the healthcare system, including patients who never reach tertiary care or who were, for some reason, not captured in the study (e.g. patients who consult tertiary care for a second opinion but don't initiate a treatment course there).

b) The cost of colorectal cancer treatment is a major burden for most patients. Funding schemes are available heterogeneously and fail to fully provide financial protection, eventually because applications and reimbursements are burdensome and delayed. Insurance seems to protect patients better but it is only within reach of a small group of patients.

c) Multiple factors can influence a patient's decision to take up and complete treatment, and a whole system approach with multilevel interventions is needed to improve cancer outcomes in India. Some patients from the cohort study declined treatment, which can be explained by social, community, education and

financial factors raised in the qualitative interviews. A number of suggestions were made to improve the delivery of cancer care from primary care to tertiary hospitals, requiring individual and community interventions to policy making at government level.

Together with suggestions from professionals in the field, published policy making approaches and examples from other countries might be useful in India. The investment framework approach was successful in AIDS control and refers to an approach where a monetary investment is made now with the hope of achieving substantially greater benefits in the future, within a defined timeframe. This is very suitable to cancer policy, as the benefits of cancer control are likely to bring wider population benefits(19). India needs to identify the best strategy to achieve universal health coverage and widely available cancer care, as different workframes are likely to succeed or fail depending on the context, e.g. universal health coverage programmes were financed through tax-based models for Thailand and social insurance models for Mexico through a pro-poor approach, with increasingly successful outcomes in both cases(19). The Lancet Commission on Global Health 2035 endorsed two pro-poor pathways to achieving UHC, the first being a publicly financed insurance, to cover essential health-care interventions (poor populations disproportionately affected, hence benefiting more). A second pathway was endorsed, providing a larger benefit package, funded through a range of financing mechanisms, with poor people exempted from payments(90). Other policy considerations are active or passive financing of cancer care, with the first consisting of healthcare being provided in

public facilities and the second involving performance or outcome-based funding of care(19). A deep understanding of the current healthcare pathways, patients' and professionals' decisions influencing outcomes is needed to inform these decisions and, although further research is needed, I believe my work has contributed to that knowledge.

5.5.3 Implications for policy

i) An improvement of education levels in India seems crucial to retain patients in treatment and promote adherence to the most effective treatments. Better access to education would also promote financial equality, and currently vulnerable groups (e.g. women, elder) could eventually be more independent to decide about their treatment courses.

ii) National policy in India should be clear on the cancer goals to be achieved, allocating more public funds to cancer care provision. This includes increasing the scale of government funding schemes but also direct investment on the healthcare system infrastructure and staff. These changes could improve the capacity to deliver treatment and follow-up and might allow for better communication strategies with patients, contributing for their treatment compliance.

iii) The processes to apply for funding schemes should be simplified, made accessible to all patients and widely available in the country. Patient and hospital reimbursements should be prompt to increase the use of these schemes by those at most need for them. Non-medical expenses should be accounted for in cancer

funding, as they can be a source of high costs for patients, especially in remote areas of the country.

iv) At the community level, awareness programmes and patient empowerment are needed to inform and support patients in their treatment journey, enabling better adherence. Patient groups to share experience and organise social support seem to be a valuable tool, fighting patient isolation and erasing misconceptions.

5.5.4 Implications for future research

Some research topics were identified by the interviewees, including the need for cost-effectiveness studies to identify treatments that are worth the public investment, promoting affordability of care to individual patients. Research into biosimilars was also raised as a priority, aiming at a decrease in the cost of cancer drugs, making them more widely available.

Further research questions arose from interpreting the results of this qualitative work:

i) What is the patient lived experience of receiving cancer treatment and what can be done, from a patient's perspective, to improve retention in treatment? A qualitative or mixed-methods assessment of barriers and facilitators from a patient perspective is needed.

ii) Would community, awareness and educational programmes increase patient ability to access and comply with cancer treatment? The impact of these

programmes on population's knowledge and, ideally, on rates of early cancer detection should be assessed.

iii) Can communication skills of cancer care professionals influence patient retention in treatment? The impact of specific communication strategies would need to be determined, by understanding their impact on patients understanding of the disease and the treatment, as well as treatment retention rates.

5.6 Key limitations

As with any research project, it is crucial to highlight the limitations at the point of interpretation of findings. Overall, the key limitation of my thesis is selection bias, which is present in all chapters. In the first chapter, although a large and diverse group of patients was analysed, the inclusion criteria was patients undergoing surgery, leaving out patients without access to surgery or for whom OOPP would make surgery unaffordable. In the second chapter, I tried to address the previous limitation by including all patients with a treatment plan rather than a complete treatment, allowing me to detect treatment attrition and the reasons for it. However, the small sample and the fact that only tertiary hospitals were included, does not allow generalisability of the findings to all Indian patients with colorectal cancer patients, as they could have never reached tertiary care. The socio-economic characteristics of the population of India can also influence the type of patients accessing tertiary care, specifically hospitals with expertise in colorectal cancer, and my findings can be influenced by that selection bias. Although I tried to tackle this in the third chapter and give a more holistic and deep view of which barriers patients can face at all societal levels, I acknowledge that the depth of

qualitative data sacrifices breath. In a country as large as India, it is possible that the views collected in fourteen interviews have missed various perspectives.

While my first chapter captured a wide range of surgical settings, with low level of detail, the second chapter provided granular information from a much smaller group of cancer patients. A trade-off between depth and breath is needed in all research studies, and my decisions on that balance for each chapter were based on the research question and the feasibility within the timeline of my PhD.

Regarding the qualitative work, the other key limitation is the absence of patient interviews that prevented the findings from being informed by lived experience. Although professionals are able to convey the experiences of multiple patients, the value of self-reported experiences is high and should be included in future qualitative work in this area.

5.7 Conclusion

From my thesis, I can conclude that patients accessing cancer and surgical care in L&MIC need better financial protection. Financial and non-financial challenges might prevent a wider population of cancer patients from entering a treatment pathway, with a negative impact on their clinical outcomes. The lack of protective financial mechanisms together with insufficient cancer care availability can result in unstable societies, impairing their productivity and human development. Future policy should focus on improving accessibility and affordability of cancer care.

I can. I want. I will.

End of story.

7 References

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APPENDIX

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Supplementary Table 1: List of excluded procedures (SurgWeek study, chapter 2).

Specialty	Excluded procedures
Abdominal surgery	Ascitic drain (drainage of peritoneal cavity)
	Endoscopic ultrasound
	Laparoscopic ultrasound
Breast surgery	Breast biopsy
Cardiac surgery	Insertion of cardiac pacemaker
	Percutaneous coronary intervention
	Transluminal balloon angioplasty of coronary artery
Colorectal surgery	Colonoscopy (diagnostic or therapeutic)
	Flexible sigmoidoscopy (diagnostic or therapeutic)
	Proctoscopy (diagnostic or therapeutic)
Dental procedures	Implantation of tooth
	Insertion of dental prosthesis
	Orthodontic operations
	Restoration of tooth
	Extraction of tooth
Gynaecology	Cervical biopsy
	Colposcopy (diagnostic or therapeutic)
Obstetrics	Any vaginal delivery (normal delivery, breech delivery, forceps delivery, vacuum delivery)
	Surgical termination of pregnancy
Ophthalmology	Removal of foreign body from cornea
Orthopaedics	Bone biopsy
	Injection in to joint
	Muscle biopsy
Otolaryngology	Laryngoscopy (diagnostic or therapeutic)
	Nasendoscopy (diagnostic)
	Packing of cavity of nose
Thoracic surgery	Bronchoscopy (diagnostic)
	Insertion of chest drain
Upper gastrointestinal surgery	Endoscopic retrograde cholangiopancreatography (diagnostic or therapeutic)
	Liver biopsy
	Oesophago-gastro-duodenoscopy (diagnostic or therapeutic)
Urology*	Bladder biopsy
	Extracorporeal shock-wave lithotripsy
	Flexible cystoscopy (diagnostic)
	Percutaneous nephrostomy
Vascular surgery	Endovenous laser treatment for varicose veins

	Insertion or removal of dialysis catheter
	injection into varicose vein of leg
	Transluminal (endovascular) procedures on arteries (diagnostic or therapeutic), including with open cut down to the artery
	Transluminal (endovascular) procedures on veins (diagnostic or therapeutic)
	Insertion or removal of Hickmann line
Other	Insertion of central venous catheter/ line
	Insertion of chest drain
	Lumbar (spinal) puncture
	Percutaneous tracheostomy
	Skin biopsy (including shave biopsy of skin)
	Therapeutic epidural injection
	Vacuum dressing

*Transurethral resection of the prostate, transurethral resection of bladder tumour, rigid cystoscopy under general anaesthesia, and insertion of ureteric stent should be included.

Supplementary Table 2: Full list of surgical procedures and number of patients who underwent each procedure.

SURGICAL ONCOLOGY DISCIPLINE - procedure (alphabetical order)	**Number of patients n(%)**
BRAIN & SKULL - any other procedures not listed	25 (0.1)
BRAIN & SKULL - brain - any operation on the meninges	32 (0.1)
BRAIN & SKULL - brain - any operation on ventricles of brain	20 (0.1)
BRAIN & SKULL - brain - biopsy of lesion of tissue of brain	129 (0.5)
BRAIN & SKULL - brain - clipping of intracranial aneurysm	1 (0.0)
BRAIN & SKULL - brain - drainage of lesion of tissue of brain	30 (0.1)
BRAIN & SKULL - brain - excision of tissue of brain	356 (1.5)
BRAIN & SKULL - brain - intracranial pressure	3 (0.0)
BRAIN & SKULL - insertion of ventriculoperitoneal shunt	36 (0.1)
BRAIN & SKULL - skull - craniectomy	15 (0.1)
BRAIN & SKULL - skull - craniotomy	172 (0.7)
BRAIN & SKULL - skull - drainage of extradural space	1 (0.0)
BRAIN & SKULL - skull - drainage of subdural space (subdural haemorrh age; SDH)	1 (0.0)
BRAIN & SKULL - skull - repair of dura	2 (0.0)
BREAST - .any other procedures not listed	78 (0.3)
BREAST - augmentation or reduction	25 (0.1)
BREAST - axilla - axillary clearence (lymphadenectomy)	160 (0.7)
BREAST - axilla - sentinal node biopsy	116 (0.5)
BREAST - immediate reconstruction - implant/ LD/ DIEP	154 (0.6)
BREAST - incision and drainage of breast abscess	11 (0.0)
BREAST - lumpectomy/ wide local excision +/- wire	1391 (5.7)
BREAST - mastectomy	1844 (7.5)
BREAST - oncoplasty/ mammoplasty	215 (0.9)
COLON & RECTUM - .any other procedures not listed	65 (0.3)
COLON & RECTUM - abdominoperineal resection (APR; APE)	262 (1.1)
COLON & RECTUM - anterior resection (LAR)	810 (3.3)
COLON & RECTUM - any operation for prolapse of rectum	4 (0.0)
COLON & RECTUM - completion proctectomy	25 (0.1)
COLON & RECTUM - formation of colostomy (stoma)	346 (1.4)
COLON & RECTUM - left hemicolectomy (excision of left hemicolon)	381 (1.6)
COLON & RECTUM - panproctocolectomy (total excision of colon and re ctum)	26 (0.1)
COLON & RECTUM - proctology - any other proctology (pilonidal sinus; fi stula-in-ano)	41 (0.2)
COLON & RECTUM - proctology - excision of lesion of anus	62 (0.3)
COLON & RECTUM - proctology - haemorrhoidopexy (hemorrhoidopexy)	1 (0.0)
COLON & RECTUM - refashioning or resiting of colostomy (stoma)	27 (0.1)

COLON & RECTUM - reversal of colostomy (colostomy closure; stoma)	76 (0.3)
COLON & RECTUM - right hemicolectomy (excision of right hemicolon)	1170 (4.8)
COLON & RECTUM - sigmoid colectomy (Hartmanns procedure; excisio n of sigmoid colon)	401 (1.6)
COLON & RECTUM - subtotal colectomy	89 (0.4)
COLON & RECTUM - total colectomy (total excision of colon)	50 (0.2)
COLON & RECTUM - transanal endoscopic microsurgery (TEMS)	56 (0.2)
COLON & RECTUM - transanal total mesorectal excision (taTME)	36 (0.1)
COLON & RECTUM - transverse colectomy (excision of transverse colon)	46 (0.2)
DENTAL - .any other dental procedure not separately listed (note non-surgical extraction of teeth excluded)	2 (0.0)
DENTAL - excision of dental lesion of jaw	2 (0.0)
EMERGENCY SURGERY - abdominal packing	5 (0.0)
EMERGENCY SURGERY - any other procedures not listed	7 (0.0)
EMERGENCY SURGERY - drainage of haematoma	4 (0.0)
EMERGENCY SURGERY - peri-anal/ pilonidal abscess drainage (incision and drainage; I&D)	5 (0.0)
EMERGENCY SURGERY - superficial abscess drainage - non-anorectal (incision and drainage; I&D)	8 (0.0)
EMERGENCY SURGERY - trauma laparotomy	3 (0.0)
EMERGENCY SURGERY - wound exploration & washout (debridement)	25 (0.1)
ENDOCRINE - adrenals - .any other procedures not listed	5 (0.0)
ENDOCRINE - adrenals - adrenalectomy (excision of adrenal gland)	71 (0.3)
ENDOCRINE - parathyroid - parathyroidectomy (excision of parathyroid g land)	24 (0.1)
ENDOCRINE - pituitary - excision of pituitary gland	3 (0.0)
ENDOCRINE - thymus - excision of thymus gland	14 (0.1)
ENDOCRINE - thyroid - .any other procedures not listed	40 (0.2)
ENDOCRINE - thyroid - thyroidectomy (excision of thyroid gland)	874 (3.6)
EYES - .any other procedure not separately listed	36 (0.1)
EYES - correction of deformity of eyelid	7 (0.0)
EYES - excision of lesion of eyelid	35 (0.1)
EYES - operations on retina	13 (0.1)
EYES - operations on vitreous body	5 (0.0)
FEMALE REPRODUCTIVE ORGANS - abdominal hysterectomy and bila teral salpingoophrectomy (TAH-BSO)	110 (0.4)
FEMALE REPRODUCTIVE ORGANS - ablation or excision of intraabdo minal endometriosis	7 (0.0)
FEMALE REPRODUCTIVE ORGANS - any other operation not listed	67 (0.3)
FEMALE REPRODUCTIVE ORGANS - dilatation and curettage	22 (0.1)
FEMALE REPRODUCTIVE ORGANS - evacuation of retained products o f pregnancy	3 (0.0)
FEMALE REPRODUCTIVE ORGANS - fallopian tubes - salpingectomy (excision of fallopian tube; ectopic)	13 (0.1)
FEMALE REPRODUCTIVE ORGANS - hysteroscopy + insertion / remov al of contraceptive implant	3 (0.0)

FEMALE REPRODUCTIVE ORGANS - hysteroscopy + intervention	18 (0.1)
FEMALE REPRODUCTIVE ORGANS - hysteroscopy + polypectomy / biopsy	23 (0.1)
FEMALE REPRODUCTIVE ORGANS - laparoscopic procedures for ovarian cysts other than oophorectomy	46 (0.2)
FEMALE REPRODUCTIVE ORGANS - oophorectomy - unilateral/ bilateral (excision of ovary/ ovaries)	83 (0.3)
FEMALE REPRODUCTIVE ORGANS - open procedures for ovarian cysts other than oophorectomy	1 (0.0)
FEMALE REPRODUCTIVE ORGANS - ovarian cystectomy	3 (0.0)
FEMALE REPRODUCTIVE ORGANS - ovaries - other	5 (0.0)
FEMALE REPRODUCTIVE ORGANS - perineum - any procedures on female perineum	12 (0.0)
FEMALE REPRODUCTIVE ORGANS - salpingo-oophorectomy - unilateral/ bilateral (excision of ovary/ ovaries and fallopian tubes)	111 (0.5)
FEMALE REPRODUCTIVE ORGANS - uterus - abdominal hysterectomy (excision of uterus)	846 (3.5)
FEMALE REPRODUCTIVE ORGANS - uterus - any other procedures not listed	34 (0.1)
FEMALE REPRODUCTIVE ORGANS - uterus - excision of uterus (trachelectomy; cervicectomy)	114 (0.5)
FEMALE REPRODUCTIVE ORGANS - uterus - partial excision of uterus (including myomectomy)	14 (0.1)
FEMALE REPRODUCTIVE ORGANS - uterus - repair of uterus	4 (0.0)
FEMALE REPRODUCTIVE ORGANS - uterus - vaginal hysterectomy (excision of uterus)	72 (0.3)
FEMALE REPRODUCTIVE ORGANS - vagina - .any other procedures not listed	41 (0.2)
FEMALE REPRODUCTIVE ORGANS - vagina - excision of vagina	13 (0.1)
FEMALE REPRODUCTIVE ORGANS - vagina - repair of vaginal prolapse	2 (0.0)
FEMALE REPRODUCTIVE ORGANS - vulva - excision of vulva	88 (0.4)
GALLBLADDER & BILIARY TREE - .any other procedure not seperately listed	37 (0.2)
GALLBLADDER & BILIARY TREE - bilio-intestinal diversion	32 (0.1)
GALLBLADDER & BILIARY TREE - cholecystectomy	55 (0.2)
GENERAL SURGERY - appendicectomy (appendectomy; excision of appendix)	28 (0.1)
GENERAL SURGERY - diagnostic laparoscopy +/- washout or drainage	338 (1.4)
GENERAL SURGERY - diagnostic laparotomy +/- washout or drainage	215 (0.9)
GENERAL SURGERY - laparoscopic adhesiolysis	7 (0.0)
GENERAL SURGERY - laparotomy + adhesiolysis	64 (0.3)
HEAD & NECK - any other procedures not listed	98 (0.4)
HEAD & NECK - ear - drainage of middle ear	2 (0.0)
HEAD & NECK - ear - exenteration of mastoid air cells	4 (0.0)
HEAD & NECK - ear - procedures on inner ear	1 (0.0)
HEAD & NECK - ear - procedures on middle ear	1 (0.0)
HEAD & NECK - ear - procedures on the external ear	23 (0.1)

HEAD & NECK - excision of adenoids	4 (0.0)
HEAD & NECK - larynx - .any MAJOR procedures not seperately listed	56 (0.2)
HEAD & NECK - larynx - .any MINOR procedures not seperately listed	154 (0.6)
HEAD & NECK - larynx - excision of larynx (laryngectomy)	83 (0.3)
HEAD & NECK - lip - any procedures on the lips	35 (0.1)
HEAD & NECK - mandible - any other procedure	87 (0.4)
HEAD & NECK - mandible - reduction and/or fixation of mandible	5 (0.0)
HEAD & NECK - maxilla - partial excision of bone of face	62 (0.3)
HEAD & NECK - microlaryngoscopy	9 (0.0)
HEAD & NECK - mouth - any other procedures on the mouth	47 (0.2)
HEAD & NECK - mouth - any procedures on the palate	17 (0.1)
HEAD & NECK - mouth - reconstruction of mouth	18 (0.1)
HEAD & NECK - mouth - removal of lesion of mouth	108 (0.4)
HEAD & NECK - nasendoscopy + intervention	17 (0.1)
HEAD & NECK - neck - radical neck dissection	98 (0.4)
HEAD & NECK - neck - selective neck dissection	203 (0.8)
HEAD & NECK - nose - any other procedure on nose	86 (0.4)
HEAD & NECK - nose - endoscopic sinus surgery	14 (0.1)
HEAD & NECK - nose - operations on septum of nose	5 (0.0)
HEAD & NECK - nose - other endoscopic surgery	7 (0.0)
HEAD & NECK - orbit - exploration +/- repair	8 (0.0)
HEAD & NECK - pharynx - any procedures other than excision	44 (0.2)
HEAD & NECK - pharynx - excision of pharynx (pharyngectomy)	22 (0.1)
HEAD & NECK - repair soft tissue of head and neck	12 (0.0)
HEAD & NECK - salivary gland/ duct - any other procedure on the salivar y gland or duct	5 (0.0)
HEAD & NECK - salivary gland/ duct - excision of parotid gland	101 (0.4)
HEAD & NECK - salivary gland/ duct - excision of submandibular/subling ual gland	16 (0.1)
HEAD & NECK - skin - excisional of lesion of skin of head or neck	166 (0.7)
HEAD & NECK - submental mandibulectomy	27 (0.1)
HEAD & NECK - surgical tracheostomy (note: percutaneous tracheostom y excluded)	75 (0.3)
HEAD & NECK - tongue - .any other procedures on the tongue	41 (0.2)
HEAD & NECK - tongue - partial glossectomy	132 (0.5)
HEAD & NECK - tonsils - operation on tonsils ther than tonsillectomy	3 (0.0)
HEAD & NECK - tonsils - tonsillectomy (excision of tonsil)	32 (0.1)
HEART (CARDIAC) - any other procedures not listed	8 (0.0)
HEART (CARDIAC) - aortic valve surgery (AVR; valvular)	7 (0.0)
HEART (CARDIAC) - coronary artery bypass graft (CABG)	7 (0.0)
HEART (CARDIAC) - insertion of pacemaker	1 (0.0)
HERNIA - abdominal wall reconstruction (component separation)	9 (0.0)
HERNIA - femoral hernia repair (herniorrhaphy; hernioplasty)	1 (0.0)

HERNIA - incisional hernia repair (herniorrhaphy; hernioplasty)	4 (0.0)
HERNIA - ventral / Spigelian / epigastric hernia repair (herniorrhaphy; her nioplasty)	2 (0.0)
KIDNEY - any other procedures not listed	15 (0.1)
KIDNEY - nephrectomy (excision of kidney)	555 (2.3)
KIDNEY - percutaneous nephrolithotomy (PCNL; stone; calculus)	5 (0.0)
KIDNEY - pyeloplasty	8 (0.0)
KIDNEY - transplantation of kidney	5 (0.0)
LIMB - any operation on bursa (joint)	1 (0.0)
LIMB - excision of ganglion	10 (0.0)
LIMB - lower limb	30 (0.1)
LIMB - lower limb - .any other procedure repair not seperately listed (key waords: orthopaedics)	39 (0.2)
LIMB - lower limb - amputation of leg	30 (0.1)
LIMB - lower limb - amputation of toe	7 (0.0)
LIMB - lower limb - any other operation on toe	3 (0.0)
LIMB - lower limb - arthroscopy of knee - therapeutic (keywords: othopae dic; orthopedic)	1 (0.0)
LIMB - lower limb - knee replacement (keywords: othopaedic; orthopedic)	7 (0.0)
LIMB - lower limb - osteotomy and fixation (scarf osteotomy)	1 (0.0)
LIMB - lower limb - reconstruction of wound (including skin graft, local, re gional or free flap)	22 (0.1)
LIMB - lower limb - removal of implant	4 (0.0)
LIMB - lower limb - revision of total hip replacement	1 (0.0)
LIMB - lower limb - total hip replacement	7 (0.0)
LIMB - lower limb - wound debridement	7 (0.0)
LIMB - lower limb fracture - closed reduction and external fixation	2 (0.0)
LIMB - lower limb fracture - closed reduction and internal fixation	5 (0.0)
LIMB - lower limb fracture - FEMUR - open reduction and intramedullary f ixation	26 (0.1)
LIMB - lower limb fracture - partial hip replacement (hemiarthroplasty)	9 (0.0)
LIMB - lower limb fracture - TIBIA - open reduction and intramedullary fix ation	2 (0.0)
LIMB - muscle - any other procedure on muscle	2 (0.0)
LIMB - muscle - muscle excision	29 (0.1)
LIMB - upper limb - amputation of hand	6 (0.0)
LIMB - upper limb - .any other procedure repair not seperately listed	22 (0.1)
LIMB - upper limb - amputation of arm	6 (0.0)
LIMB - upper limb - amputation of finger	6 (0.0)
LIMB - upper limb - debridement and irrigation of joint	2 (0.0)
LIMB - upper limb - elbow replacement	1 (0.0)
LIMB - upper limb - open reduction, wire fixation (k-wire; wire)	3 (0.0)
LIMB - upper limb - osteotomy and fixation	4 (0.0)
LIMB - upper limb - repair of ligament	1 (0.0)

LIMB - upper limb - repair of nerve	1 (0.0)
LIMB - upper limb - shoulder replacement	3 (0.0)
LIMB - upper limb - washout and closure of wound	1 (0.0)
LIMB - upper limb fracture - closed reduction and internal fixation	1 (0.0)
LIMB - upper limb fracture - open reduction and intramedullary fixation	6 (0.0)
LIMB - upper limb fracture - open reduction, no fixation	1 (0.0)
LIVER - anatomical liver resection (hepatic resection)	240 (1.0)
LIVER - any other procedures not listed	77 (0.3)
LIVER - non-anatomical liver resection (hepatic resection)	197 (0.8)
LIVER - partial hepatectomy	179 (0.7)
LIVER - transplantation of liver	20 (0.1)
LUNG & AIRWAYS - anatomical/non-anatomical lung resection (excision of a lung lobe)	829 (3.4)
LUNG & AIRWAYS - any other procedures not listed	165 (0.7)
LUNG & AIRWAYS - bronchoscopy, therapeutic	37 (0.2)
LUNG & AIRWAYS - chest exploration for trauma	6 (0.0)
LUNG & AIRWAYS - mediastinal mass resection	54 (0.2)
LUNG & AIRWAYS - mediastinoscopy	79 (0.3)
LUNG & AIRWAYS - operations on bronchus	5 (0.0)
LUNG & AIRWAYS - pneumonectomy (excision of whole lung)	27 (0.1)
LUNG & AIRWAYS - radical surgery for pleural mesothelioma	6 (0.0)
LUNG & AIRWAYS - resection of chest wall tumour +/- lung resection	84 (0.3)
MALE REPRODUCTIVE ORGANS - prostate - prostatectomy	494 (2.0)
MALE REPRODUCTIVE ORGANS - prostate biopsy	42 (0.2)
MALE REPRODUCTIVE ORGANS - testis - orchidectomy (excision of testis)	136 (0.6)
OBSTETRICS - any other procedures not listed	2 (0.0)
OBSTETRICS - evacuation of contents of uterus / manual removal of placenta (MROP)	1 (0.0)
OESOPHAGUS & STOMACH - oesophagus - any other procedure	14 (0.1)
OESOPHAGUS & STOMACH - oesophagus - oesophagectomy	166 (0.7)
OESOPHAGUS & STOMACH - oesophagus - oesophagogastrectomy (excision of oesophagus and stomach)	51 (0.2)
OESOPHAGUS & STOMACH - stomach - any other procedure	34 (0.1)
OESOPHAGUS & STOMACH - stomach - feeding gastrostomy	74 (0.3)
OESOPHAGUS & STOMACH - stomach - gastrectomy (excision of stomach)	547 (2.2)
OESOPHAGUS & STOMACH - stomach - gastric band insertion (obesity surgery)	1 (0.0)
OESOPHAGUS & STOMACH - stomach - gastric bypass, roux en y / sin gle anastomosis gastric bypass (obesity surgey)	27 (0.1)
OESOPHAGUS & STOMACH - stomach - repair of perforated peptic ulcer (gastric)	4 (0.0)
OTHER - block dissection of lymph nodes	130 (0.5)
OTHER - Excision of lipoma	15 (0.1)

OTHER - hyperthermic intraperitoneal chemotherapy (HIPEC)	83 (0.3)
OTHER - lymph node biopsy	344 (1.4)
OTHER - multiorgan resection (sarcoma; including pelvic exenteration)	144 (0.6)
OTHER - Operation on Germ cell tumour	2 (0.0)
OTHER - skin - suture of skin of head or neck	10 (0.0)
OTHER - skin - suture of skin other than head or neck	2 (0.0)
PANCREAS - any other procedure not separately listed	32 (0.1)
PANCREAS - distal pancreatectomy (excision of pancreas)	137 (0.6)
PANCREAS - pancreaticoduodenectomy (Whipple)	445 (1.8)
PANCREAS - total pancreatectomy (excision of pancreas)	35 (0.1)
PLASTICS - abdominoplasty	3 (0.0)
PLASTICS - any other procedure not separately listed	33 (0.1)
PLASTICS - burns - debridement, excision or dressing	7 (0.0)
PLASTICS - local flap	6 (0.0)
PLASTICS - paediatric - any operation	2 (0.0)
PLASTICS - regional lymphadenectomy for skin cancer	44 (0.2)
PLASTICS - sentinel lymph node biopsy for skin cancer	66 (0.3)
PLASTICS - Skin - excision of benign skin lesion	14 (0.1)
PLASTICS - Skin - excision of malignant skin cancer	650 (2.7)
PLASTICS - Skin - excision of malignant skin cancer and reconstruction (any type)	313 (1.3)
PLASTICS - Skin - excision of scar	19 (0.1)
PLASTICS - skin graft	9 (0.0)
SARCOMA - Excision of lesion of extremity (major)	59 (0.2)
SARCOMA - Excision of lesion of extremity (minor/intermediate)	79 (0.3)
SARCOMA - Excision of lesion of posterior peritoneum	78 (0.3)
SMALL BOWEL - .any other procedure not seperately listed	14 (0.1)
SMALL BOWEL - feeding jejunostomy	81 (0.3)
SMALL BOWEL - formation of ileostomy (stoma)	118 (0.5)
SMALL BOWEL - ileocaecal resection (excision of ileum)	38 (0.2)
SMALL BOWEL - refashioning or resiting of ileostomy (stoma)	10 (0.0)
SMALL BOWEL - reversal of ileostomy (ileostomy closure; stoma)	93 (0.4)
SMALL BOWEL - small bowel bypass (including gastrojejunostomy)	96 (0.4)
SMALL BOWEL - small bowel resection	146 (0.6)
SPINE & NERVOUS SYSTEM - any operation on cranial nerves	2 (0.0)
SPINE & NERVOUS SYSTEM - any operation on peripheral nerve	5 (0.0)
SPINE & NERVOUS SYSTEM - any operation on spinal cord	52 (0.2)
SPINE & NERVOUS SYSTEM - any other operation on vertebrae	96 (0.4)
SPINE & NERVOUS SYSTEM - decompression or excision of intervebral disc	26 (0.1)
SPLEEN - .any other procedure not separately listed	2 (0.0)
SPLEEN - splenectomy	27 (0.1)
URINARY TRACT - bladder - .any other procedure not seperately listed	78 (0.3)

URINARY TRACT - bladder - cystectomy (excision of urinary bladder)	155 (0.6)
URINARY TRACT - bladder - transurethral resection of bladder tumour (TURBT)	1073 (4.4)
URINARY TRACT - bladder - transurethral resection of the prostate (TURP)	88 (0.4)
URINARY TRACT - female incontinence surgery	3 (0.0)
URINARY TRACT - flexible cystoscopy + intervention	69 (0.3)
URINARY TRACT - lithotripsy	5 (0.0)
URINARY TRACT - rigid cystoscopy	53 (0.2)
URINARY TRACT - ureter - replantation of ureter	8 (0.0)
URINARY TRACT - ureter - uretectomy (excision of ureter)	8 (0.0)
URINARY TRACT - ureter - ureteric stent insertion	129 (0.5)
URINARY TRACT - ureteroscopy (therapeutic)	56 (0.2)
URINARY TRACT - urethra - any procedure	27 (0.1)
VASCULAR - .any other procedure not seperately listed (artery; vein)	45 (0.2)
VASCULAR - embolectomy / thrombectomy	3 (0.0)
VASCULAR - varicose vein - ligation and stripping	1 (0.0)
BRAIN & SKULL - skull - repair of cranium	2 (0.0)
DENTAL - any procedure on gingiva (gum)	1 (0.0)
DENTAL - orthodontic procedures (tooth; teeth)	1 (0.0)
EMERGENCY SURGERY - neck wound exploration	1 (0.0)
ENDOCRINE - parathyroid - .any other procedures not listed	1 (0.0)
EYES - corneal surgery	1 (0.0)
EYES - phacoemulsification (cataract surgery)	1 (0.0)
HEAD & NECK - ear - other procedures on mastoid	3 (0.0)
HEAD & NECK - ear - procedures on the external auditory canal	1 (0.0)
HEAD & NECK - mandible - orthognathic surgery (jaw)	2 (0.0)
HEAD & NECK - mouth - drainage extra-oral abscess	1 (0.0)
HEAD & NECK - mouth - drainage intra-oral abscess	6 (0.0)
HEART (CARDIAC) - mitral valve surgery (valvular)	3 (0.0)
HEART (CARDIAC) - ventricular septal defect repair (VSD)	3 (0.0)
HERNIA - any hernia repair not separately listed (herniorrhaphy; herniopl asty)	1 (0.0)
HERNIA - inguinal hernia repair (herniorrhaphy; hernioplasty)	4 (0.0)
LIMB - any operation on nerve	2 (0.0)
LIMB - any operation on tendon	1 (0.0)
LIMB - lower limb - amputation of foot	4 (0.0)
LIMB - lower limb - arthroscopy of joint other than knee - therapeutic (key words: othopaedic; orthopedic)	1 (0.0)
LIMB - lower limb - closed reduction, wire fixation	1 (0.0)
LIMB - lower limb - debridement and irrigation of joint	1 (0.0)
LIMB - lower limb - joint fusion	2 (0.0)
LIMB - Lower limb fracture - cannulated screws for proximal femoral fract ure	2 (0.0)

LIMB - lower limb fracture - dynamic hip screw (DHS)	2 (0.0)
LIMB - upper limb - Dupuytren's disease / trigger finger surgery	1 (0.0)
LIMB - upper limb - manipulation of hand fracture	1 (0.0)
MALE REPRODUCTIVE ORGANS - any operation on epididymis	3 (0.0)
MALE REPRODUCTIVE ORGANS - any other procedures not listed	27 (0.1)
MALE REPRODUCTIVE ORGANS - any procedure on scrotum	4 (0.0)
MALE REPRODUCTIVE ORGANS - circumcision	2 (0.0)
MALE REPRODUCTIVE ORGANS - penis - any operation on penis	21 (0.1)
MALE REPRODUCTIVE ORGANS - penis - any operations on the penis	21 (0.1)
MALE REPRODUCTIVE ORGANS - scrotal / testicular exploration	1 (0.0)
MALE REPRODUCTIVE ORGANS - testis - any procedure other than orc hidectomy	7 (0.0)
MALE REPRODUCTIVE ORGANS - testis - orchiopexy	1 (0.0)
OESOPHAGUS & STOMACH - nissens fundoplication (anti-reflux surgery)	1 (0.0)
OESOPHAGUS & STOMACH - stomach - pyloroplasty	1 (0.0)
OESOPHAGUS & STOMACH - stomach - sleeve gastrectomy (obesity s urgery)	1 (0.0)
OTHER - Extraction of foreign body	1 (0.0)
PLASTICS - burns - reconstruction	2 (0.0)
PLASTICS - free flap	3 (0.0)
SMALL BOWEL - repair of perforated duodenal ulcer (PUD)	1 (0.0)
VASCULAR - bypass of femoral artery	1 (0.0)
VASCULAR - femoral artery endarterectomy	2 (0.0)
VASCULAR - lower limb - amputation of leg	1 (0.0)
VASCULAR - lower limb - amputation of toe	1 (0.0)
VASCULAR - repair of abdominal aorta aneurysm (AAA)	1 (0.0)
VASCULAR - repair of iliac artery aneurysm	2 (0.0)

Supplementary Table 3: STROBE checklist (Chapter 2).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	100
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	101
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	102/3
Objectives	3	State specific objectives, including any prespecified hypotheses	104
Methods			
Study design	4	Present key elements of study design early in the paper	105
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	111
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	114
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	115-124
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	125
Bias	9	Describe any efforts to address potential sources of bias	115-124
Study size	10	Explain how the study size was arrived at	112
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	127
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	128/9
		(*b*) Describe any methods used to examine subgroups and interactions	128/9
		(*c*) Explain how missing data were addressed	128/9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	128/9
		(*e*) Describe any sensitivity analyses	NA
Results			**Page**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	130-134
		(b) Give reasons for non-participation at each stage	130-134
		(c) Consider use of a flow diagram	133
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	136-139
		(b) Indicate number of participants with missing data for each variable of interest	All tables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	125
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*140-145*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	146
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	150-166
Discussion			
Key results	18	Summarise key results with reference to study objectives	167
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	176-178
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	167-175
Generalisability	21	Discuss the generalisability (external validity) of the study results	178
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	vii

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary Table 4: Interview topic guide.

1. Introduction and thanking
Thanking the participant for taking the time to share their perspectives
Brief introduction of the interviewer and interviewee
Brief introduction of the study topic: aiming to explore what prevents and facilitates that patients receive appropriate care after they've been diagnosed with colorectal cancer
Verbal consent for interview and recording (written consent previously obtained via email), with information on withdrawal and ability to not answer any questions that the participant wouldn't feel comfortable with
Make the participant comfortable to talk about any other issues they might want to raise during the interview
2. Questions about the patient treatment pathway, to bring the participant into the scope of the interview:
In which setting do you usually see colorectal cancer patients?
(prompt) Which types of cancer treatment are you involved in?
Tell me about how easy you think it is for patient to access cancer care?
(prompt) What can be the main barriers and facilitators?
3. Questions to openly explore the main barriers to receive and complete treatment pathways in colorectal cancer patients:

When you propose a cancer treatment to a patient, what are their main concerns regarding taking the treatment?
(prompt) Do you have patients for whom you have proposed a treatment but have never started it? What were the reasons?
After patients start their treatment with you, are there some who stop half way?
(prompt) What are the reasons for patients to do that?
4. Questions to explore previously identified factors influencing access to cancer care:
4.1: Economic factors
How do your patients find paying for their treatment? Which funding schemes might be available for them?
Do they have difficulties applying or accessing those funds?
What do you think could be improved to make it easier for patients to apply?
4.2: Social and cultural factors
Do you think you are any social groups for whom it's more difficult to receive care?
Do you think cultural habits or beliefs can prevent some people from receiving or continuing treatment?
Do you think it is more difficult for women or men to get cancer treatment? Is there a difference?

5. Question on other barriers that the interview would like to explore: From what you know, do you think there are other issues stopping patients in India from having their cancer treatment done?
6. Question exploring participant's views on facilitators, apart from the ones related to the specific factors explored previously: What do you think that could be done to make it easier to patients to receive cancer care?
7. Final question to leave an open space for the participant to talk about anything else they wish: Is there anything else you would like to tell me?
8. Thanking again and closing up.

Supplementary Table 5: Themes and subthemes in which each code was included.

List of codes	Subtheme	Theme
BARRIERS		
1. Socio-demographic and emotional		
1.1. Demographic features		
1.1.a) Gender related barriers	Gender d spar ty	Soc a support and background
1.1.b) Elderly	E der y pat ents	Soc a support and background
1.1.c) Muslim population	Stoma acceptance	C n ca Events
1.2. Lack of social and family support		
1.2.a) Lack of social support to accompany the patient	Soc a and fam y support	Soc a support and background
1.2.b) Family dynamic		
1.2.c) Decrease in social support for patients during COVID		
1.3. Social stigma and shame	Commun ty m sconcept ons and st gma	Awareness, educat on and be efs
1.4. Emotional		
1.4.a) Patients would prefer to be treated by a doctor of the same religion or community	*Not included n=1**	*Not included n=1**
1.4.b) People can be more keen on paying for treatment for their beloved ones than their own		
1.5. Social status	Med ca costs of treatment + Soc a and fam y support	F nanc a and ob protect on + Soc a support and background
1.6. Language barriers	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
2. Clinical events and staff		
2.1. Clinical course		
2.1.a) Treatment side effects	D sease and treatment burden	C n ca events
2.1.b) Palliative or progressive disease		
2.1.c) Stoma related body image, social acceptability, and feasibility of keeping jobs	Stoma acceptance	C n ca events
2.1.d) Unmet patients' expectations	D sease and treatment burden	C n ca events
2.2. Clinical staff		
2.2.a) First line healthcare workers capacity and knowledge	Capab t es of f rst ne hea thcare workers	Hea thcare system capac ty and organ sat on
2.2.b) Lack of qualified cancer care professionals	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
2.2.c) Insufficient knowledge and explanation of treatment options	Capab t es of f rst ne hea thcare workers	Hea thcare system capac ty and organ sat on
3. Financial and professional		
3.1. Economical status		
3.1.a) Treatment is too expensive	Med ca costs of treatment	F nanc a and job protect on
3.1.b) Poor patients		
3.1.c) Rich patients		
3.1.d) Patients with less funds want the best for that budget whereas wealthier patients ask for the best overall	*Not included n=1**	*Not included n=1**
3.2. Access and use of funding schemes		

3.2.a) Government schemes do not cover all costs	Cancer fund ng schemes	F nanc a and job protect on
3.2.b) High burden of paperwork		
3.2.c) Availability of schemes is not standardised across India		
3.2.d) Funding schemes rules restrict treatment options		
3.2.e) Hospital reimbursement is delayed and troublesome		
3.2.f) Funding schemes take time to be approved		
3.2.g) Government funds support benign disease easier than cancer treatment	*Not included n=1**	*Not included n=1**
3.2.h) Inappropriate allocation of funds		
3.2.i) Patients are not aware of the available schemes	Cancer fund ng schemes	F nanc a and job protect on
3.3. Professional barriers		
3.3.a) Income loss	Non-med ca costs of treatment	F nanc a and job protect on
3.3.b) Unemployment (patient and relatives)	Non-med ca costs of treatment + Soc a and fam y support	F nanc a and job protect on + Soc a support and background
3.4. Access and use of private insurance		
3.4.a) Agreements with insurance companies are not available everywhere	*Not included n=1**	*Not included n=1**
3.4.b) Insurance companies will not pay if there is a change in treatment delivery or plan		
3.4.c) Private insurance is not reachable for everyone	E der y pat ents	Soc a support and background
4. Healthcare system and geography		
4.1. Geographical		
4.1.a) Distance to cancer centres	Geograph ca d str but on of cancer care + Non-med ca costs of treatment	Hea thcare system capac ty and organ sat on + F nanc a and job protect on
4.1.b) Rural areas		
4.1.c) Urban areas		
4.2. Insufficient capacity for high volume of patients		
4.2.a) Bottlenecks and resource constraints in government hospitals	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
4.2.b) Long waiting times, particularly for RT machines		
4.2.c) Insufficient capacity for follow-up		
4.2.d) Insufficient capacity to do MRI and prompt neoadjuvant treatment for rectal cancers	*Not included n=1**	*Not included n=1**
4.2.e) Insufficient pathology reporting capacity		
4.2.f) Investment in healthcare system is insufficient creating resource constraints and people to go to govt setup	Med ca costs of treatment	F nanc a and job protect on
4.2.g) Shorter waiting lists during COVID	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
4.3. Fragmentation of cancer care		
4.3.a) Fragmented treatment plans	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
4.3.b) Multidisciplinary teams aren't always available		
4.3.c) Disparity in treatment plans across sites	*Not included n=1**	*Not included n=1**
4.4. Patients prefer to be treated in branded cancer centres		
5. Awareness and education		
5.1. Lack of public awareness and education		

5.1.a) Patients might think part of the treatment is enough to cure cancer e.g. surgery or symptom relief	Lack of pat ent educat on and awareness	Awareness, educat on and be efs
5.1.b) Patients think all cancers are similar		
5.1.c) Patient inability to understand the severity of the disease		
5.1.d) Patients are more likely to take a treatment that is conveyed as curative even if that is not realistic	*Not included n=1**	*Not included n=1**
5.1.e) Patients are not aware that clinical opinions are based on evidence and are not personal	Lack of pat ent educat on and awareness + Commun cat on w th cancer care profess ona s	Awareness, educat on and be efs + Hea thcare system capac ty and organ sat on
5.1.f) Patients are not aware that their symptoms could be cancer	Lack of pat ent educat on and awareness	Awareness, educat on and be efs
5.2. Patient misconceptions and lay beliefs		
5.2.a) Trust in traditional ineffective treatment	D strust n convent ona med c ne	Awareness, educat on and be efs
5.2.b) Nihilism	Commun ty m sconcept ons and st gma	
5.2.c) Distrust in English or allopatic medicine	D strust n convent ona med c ne	
5.2.d) Denial of the diagnosis	Commun ty m sconcept ons and st gma	
5.2.e) Misconception that surgery causes cancer spread	*Not included n=1**	*Not included n=1**
5.3. Distrust in healthcare professionals		
5.3.a) Distrust in healthcare workers is more common in the East	*Not included n=1**	*Not included n=1**
5.3.ab Patients might follow their relatives opinions more than doctors' opinions	D strust n convent ona med c ne	Awareness, educat on and be efs
FACILITATORS		
6. Financial and professional		
6.1. Optimisation of funding schemes		
6.1.a) Streamline patient eligibility and fund allocation	Cancer fund ng schemes	F nanc a and job protect on
6.1.b) Anticipated approval of funding allows hospitals to provide faster treatment		
6.1.c) Arranging free accommodation or food for patients near cancer centres	Non-med ca costs of treatment	F nanc a and job protect on
6.1.d) Create specific travelling funds for cancer patients		
6.1.e) Improve organisation of funding allocation centrally	Cancer fund ng schemes	F nanc a and job protect on
6.1.f) Streamlining the use of funding schemes for hospitals		
6.2. Development of cost-effective treatment strategies		
6.2.a) The cost of drugs needs to decrease	Po cy and research	F nanc a and job protect on
6.2.b) Development of biosimilars at lower cost		
6.3. Increase job stability	Po cy and research	F nanc a and job protect on
6.4. More funding for palliative cancer	*Not included n=1**	*Not included n=1**
6.5. New solutions demand more funding	Po cy and research	F nanc a and ob protect on

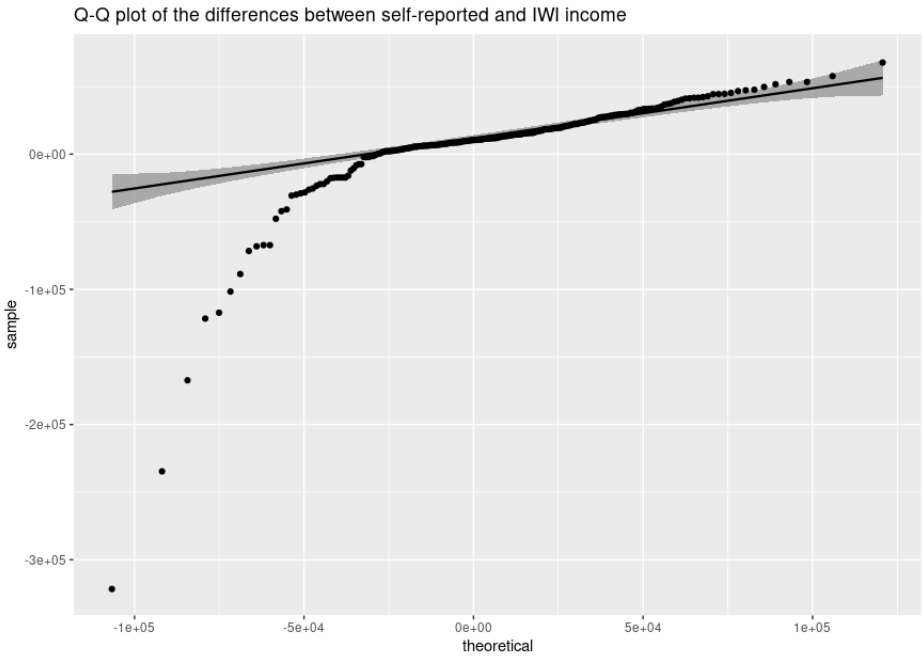
6.6. Temporary low premium insurances	Capab t es of f rst ne hea thcare workers	Hea thcare system capac ty and organ sat on
7. Healthcare system		
7.1. Expand capacity with additional or within current cancer centres	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
7.2. Improve links and referrals to cancer centres		
7.2.a) Education exchange rural and cancer centres	Integrat on of cancer care	Hea thcare system capac ty and organ sat on
7.2.b) Qualified professionals to deliver cancer care locally	*Not included n=1**	*Not included n=1**
7.2.c) Qualified professionals to handle chemotherapy side effects locally	D sease and treatment burden	C n ca events
7.3. Standardisation of MDTs to deliver integrated care	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
7.4. Definition of cancer goals at regional or national level	Po cy and research	F nanc a and ob protect on
7.5. Evidence & research-based advocacy for CRC		
7.5.a) Advocate for up prioritising of colorectal cancer treatment	Po cy and research	F nanc a and job protect on
7.6. Improvement of follow-up strategies	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
7.7. Research on quality of life during cancer treatment	*Not included n=1**	*Not included n=1**
8. Awareness and education		
8.1. Awareness programmes for the public about CRC		
8.1.a) Through ASHA workers network and in rural areas	Awareness programmes	Awareness, educat on and be efs
8.1.b) Demystify stomas and their effects on peoples' social value	Stoma acceptance	C n ca events
8.1.c) Mobile phone-based campaigns	Awareness programmes	Awareness, educat on and be efs
8.2. Evidence based, public facing websites		
8.1.a) Patient focused website created and maintained by impartial partners	Awareness programmes	Awareness, educat on and be efs
8.1.b) Website content should include treatment options, survival expectancy and expected costs	Awareness programmes + Commun cat on w th cancer care profess ona s	Awareness, educat on and be efs + Hea thcare system capac ty and organ sat on
8.3. Patients as advocates	Po cy and research	F nanc a and job protect on
9. Clinical staff		
9.1. Better communication with patients		
9.1.a) Clarify misconceptions, namely about stomas	Stoma acceptance	C n ca events
9.1.b) Communicate various options and their rates of success letting patients choose	Commun cat on w th cancer care profess ona s	Hea thcare system capac ty and organ sat on
9.1.c) Communication of funding alternatives		
9.1.d) Communication that is sensitive to patients' beliefs and lifestyle		
9.1.a) Increase capacity to follow-up patients	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
9.2. Healthcare professionals' education and update		

9.2.a) Awareness programmes for first line HCW	Capab t es of f rst ne hea thcare workers	Hea thcare system capac ty and organ sat on
9.2.b) Clinical sessions compatible with clinical commitments		
9.2.c) Education on multidisciplinary approach for all doctors involved (surgeons, oncologists, radiotherapists)	*Not included n=1**	*Not included n=1**
9.2.d) Mandatory periodic certification for doctors	Capab t es of f rst ne hea thcare workers	Hea thcare system capac ty and organ sat on
9.2.e) Specific training on surgical oncology for surgeons	*Not included n=1**	*Not included n=1**
9.3. Adapt treatment plans as per patients needs and background	Commun cat on w th cancer care profess ona s	Hea thcare system capac ty and organ sat on
10. Socio-demographic and emotional		
10.1. Patient support groups and sharing of experiences		
10.1.a) Patient support groups need to be linked back to the healthcare system	Po cy and research	F nanc a and job protect on
10.2. Educating families to support patients	Soc a and fam y support	Soc a support and background
10.3. Social workers and patient advocates		
10.3.a) Social workers to facilitate funding schemes application	Hosp ta capac ty and pathways	Hea thcare system capac ty and organ sat on
10.3.b) Translation to local languages		

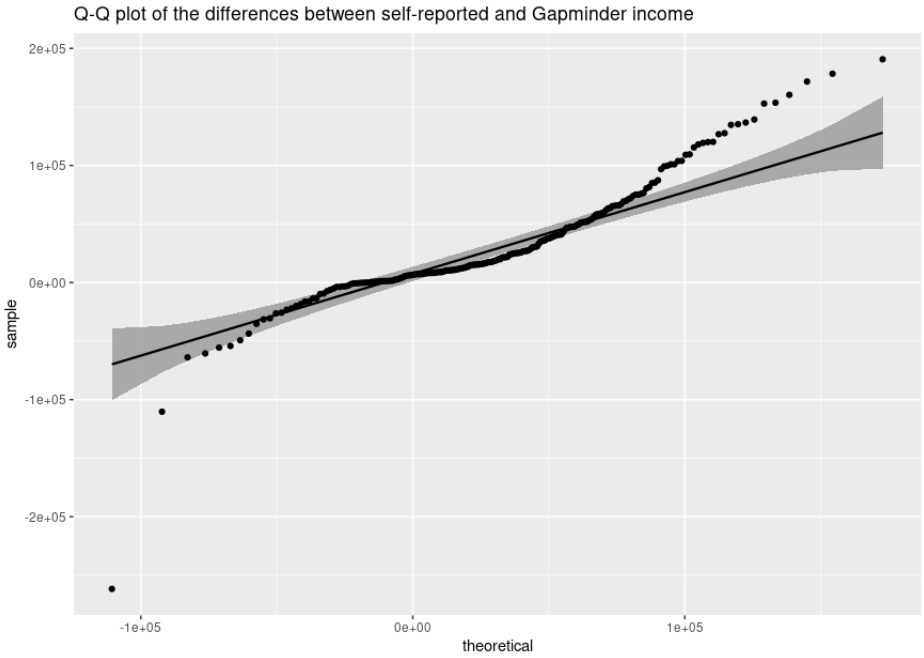
*Not included n=1** reflects codes that were only mentioned by one interviewee and were not related to any other mentioned topic, hence considered to be outside the data pattern.

Supplementary Figure 1: Q-Q plots of the differences between income assessments.

(A) Q-Q plot of the difference between the IWI and the self-reported income

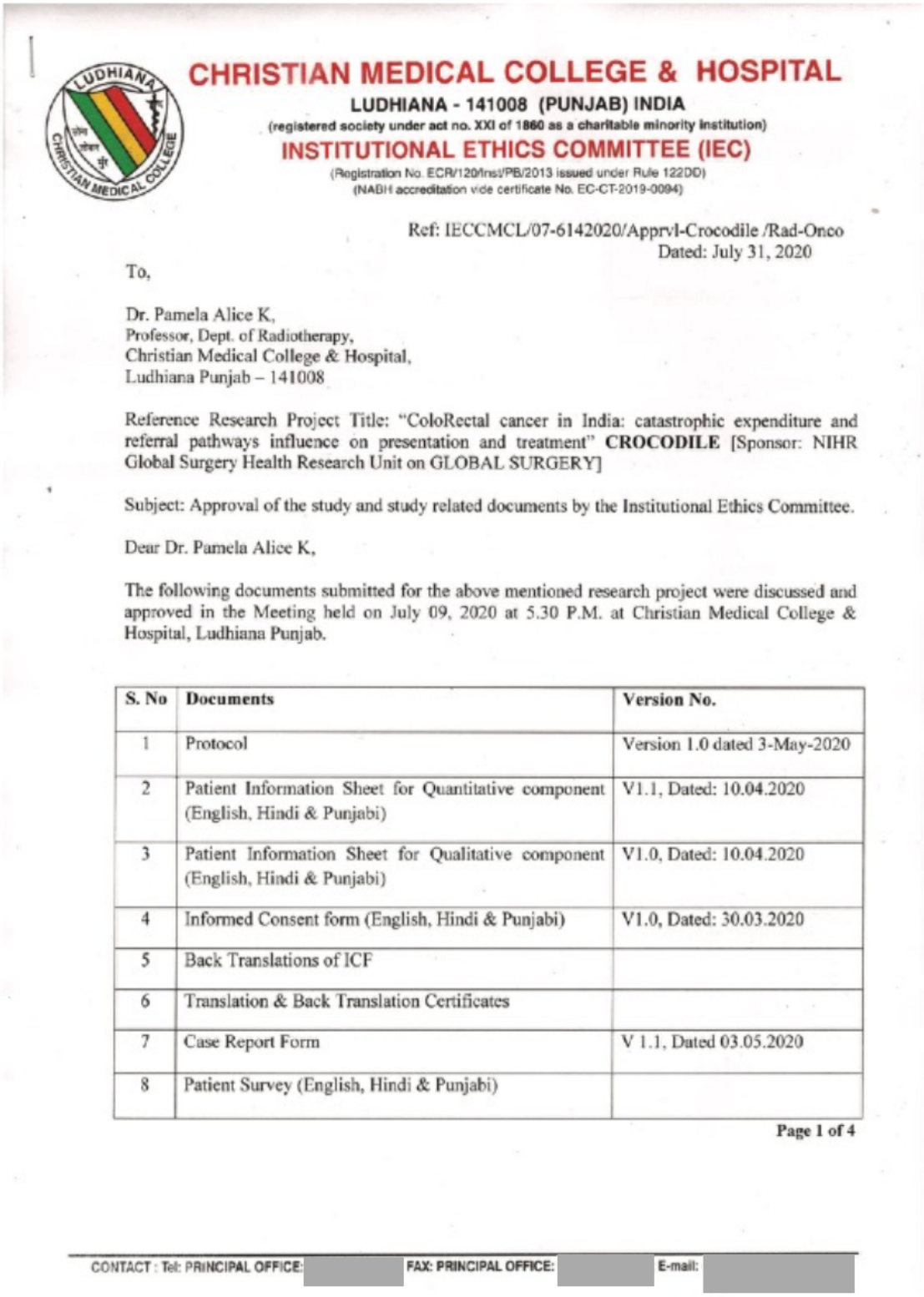


(B) Q-Q plot of the difference between the Gapminder and the self-reported income



Supplementary Figure 2: Approval letters at all participating hospitals (CROCODILE study).

(A) Approval from Christian Medical College and Hospital, Ludhiana.



CHRISTIAN MEDICAL COLLEGE & HOSPITAL

LUDHIANA - 141008 (PUNJAB) INDIA

(registered society under act no. XXI of 1860 as a charitable minority institution)

INSTITUTIONAL ETHICS COMMITTEE (IEC)

(Registration No. ECR/129/Inst/PB/2013 issued under Rule 122DD)
(NABH accreditation vide certificate No. EC-CT-2019-0094)

Ref: IECCMCL/07-6142020/Apprvl-Crocodile /Rad-Onco
Dated: July 31, 2020

To,

Dr. Pamela Alice K,
Professor, Dept. of Radiotherapy,
Christian Medical College & Hospital,
Ludhiana Punjab – 141008

Reference Research Project Title: "ColoRectal cancer in India: catastrophic expenditure and referral pathways influence on presentation and treatment" **CROCODILE** [Sponsor: NIHR Global Surgery Health Research Unit on GLOBAL SURGERY]

Subject: Approval of the study and study related documents by the Institutional Ethics Committee.

Dear Dr. Pamela Alice K,

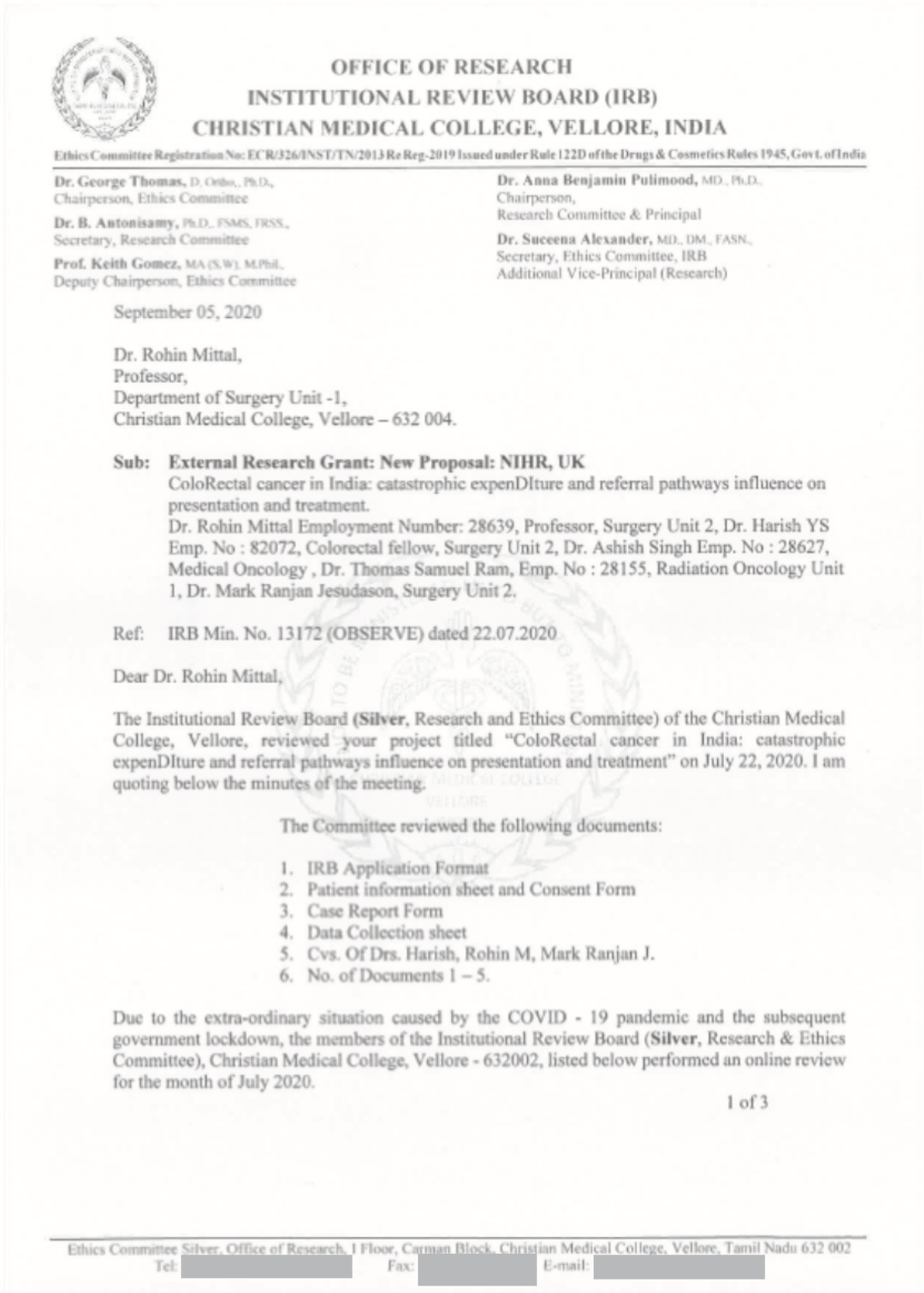
The following documents submitted for the above mentioned research project were discussed and approved in the Meeting held on July 09, 2020 at 5.30 P.M. at Christian Medical College & Hospital, Ludhiana Punjab.

S. No	Documents	Version No.
1	Protocol	Version 1.0 dated 3-May-2020
2	Patient Information Sheet for Quantitative component (English, Hindi & Punjabi)	V1.1, Dated: 10.04.2020
3	Patient Information Sheet for Qualitative component (English, Hindi & Punjabi)	V1.0, Dated: 10.04.2020
4	Informed Consent form (English, Hindi & Punjabi)	V1.0, Dated: 30.03.2020
5	Back Translations of ICF	
6	Translation & Back Translation Certificates	
7	Case Report Form	V 1.1, Dated 03.05.2020
8	Patient Survey (English, Hindi & Punjabi)	

Page 1 of 4

CONTACT : Tel: PRINCIPAL OFFICE: FAX: PRINCIPAL OFFICE: E-mail:

(B) Approval from Christian Medical College and Hospital, Vellore.



OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 Re Reg-2019 Issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

September 05, 2020

Dr. Rohin Mittal,
Professor,
Department of Surgery Unit -1,
Christian Medical College, Vellore – 632 004.

Sub: External Research Grant: New Proposal: NIHR, UK
ColoRectal cancer in India: catastrophic expenDIture and referral pathways influence on presentation and treatment.
Dr. Rohin Mittal Employment Number: 28639, Professor, Surgery Unit 2, Dr. Harish YS Emp. No : 82072, Colorectal fellow, Surgery Unit 2, Dr. Ashish Singh Emp. No : 28627, Medical Oncology , Dr. Thomas Samuel Ram, Emp. No : 28155, Radiation Oncology Unit 1, Dr. Mark Ranjan Jesudason, Surgery Unit 2.

Ref: IRB Min. No. 13172 (OBSERVE) dated 22.07.2020

Dear Dr. Rohin Mittal,

The Institutional Review Board (**Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed your project titled "ColoRectal cancer in India: catastrophic expenDIture and referral pathways influence on presentation and treatment" on July 22, 2020. I am quoting below the minutes of the meeting.

The Committee reviewed the following documents:

1. IRB Application Format
2. Patient information sheet and Consent Form
3. Case Report Form
4. Data Collection sheet
5. Cvs. Of Drs. Harish, Rohin M, Mark Ranjan J.
6. No. of Documents 1 – 5.

Due to the extra-ordinary situation caused by the COVID - 19 pandemic and the subsequent government lockdown, the members of the Institutional Review Board (**Silver**, Research & Ethics Committee), Christian Medical College, Vellore - 632002, listed below performed an online review for the month of July 2020.

1 of 3

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: [redacted] Fax: [redacted] E-mail: [redacted]

(C) Approval from Tata Medical Centre, Kolkata.

Tata Medical Center-Institutional Review Board
(TMC-IRB)
14, Major Arterial Road (EW)
New Town, Rajarhat
Kolkata – 700 160
email :

October 10, 2020
Ref. No. : 2020/Govt/34/IRB50

Dr. Amrit Pipara
Consultant
Department of GI-HBP
Tata Medical Center
Kolkata

Dear Principal Investigator,

Ref: ColoRectal cancer in India: catastrophic expenDIture and referral pathways influence on presentation and treatment – (CROCODILE)

Sub: Ethics Committee approval for the documents and conduct of the referenced study at Tata Medical Center, 14 Major Arterial Road (EW), New Town, Rajarhat, Kolkata-700160, West Bengal, India

This refers to your Submission Letter to the Chairperson, which was submitted along with the following documents:

- Summary of Protocol, Version No.1.0, Dated:03.05.2020
- Protocol Version No.1.0, Dated: 03.05.2020
- Undertaking by the Investigator, Version No: 9.1 Dated: 08.02.2018.
- Inform Consent Form, Version No.1.0, Dated: 30.03.2020.
- SOP 4,Version No:V8.3,Dated:01.06.2020
- Updated CV and GCP.

The Member Secretary reviewed the documents and found the documents appropriate. The other Members of the Group also approved the documents.

The TMC-IRB approved the Study.

(D) Approval from All India Institute Medical Sciences, Rishikesh.

All India Institute of Medical Sciences, Rishikesh
अखिल भारतीय आयुर्विज्ञान संस्थान, ऋषिकेश
Institutional Ethics Committee
संस्थागत नीति समिति

DHR Reg. No.: EC/NEW/Inst/2020/1046
CDSCO Reg. No.: ECR/736/Inst/UK/2015/RR-18

Chairman

Prof Sunil Saini
Clinician

Members

Prof Shalinee Rao
Basic Medical Scientist

Dr Sujata Kadam
Basic Medical Scientist

Dr Manisha Bisht
Basic Medical Scientist
& Pharmacologist

Prof Yogesh K. Chawla
Clinician

Dr Kalyani Shridharan
Clinician

Dr Meenakshi Khapre
Clinician

Mr Pradeep Pandey
Legal Expert

Swami Dayadhipananda
Theologian & Social
Scientist

Dr S K Kaakran
Scientific Member

Dr Sadhana Dimri
Philosopher

Mrs Seema Shukla
Lay Person

Member Secretary

Dr Ashish R. Bhute
Basic Medical Scientist

Letter No- AIIMS/IEC/20/769 **Date:** 21/11/2020

To

Dr Rajkumar Kottayasamy Seenivasagam
Associate Professor
Department of Surgical Oncology
AIIMS, Rishikesh

Sub: Research Proposal titled **"Colorectal Cancer in India: Catastrophic Expendlture and Referral Pathways Influence on Presentation and Treatment (CROCODILE Trial)"** submitted to Institutional Ethics Committee (IEC), AIIMS, Rishikesh.

Dear Dr Rajkumar Kottayasamy Seenivasagam

This is in reference to (No. 704/IEC/EM/2020) your research proposal titled **"Colorectal Cancer in India: Catastrophic Expendlture and Referral Pathways Influence on Presentation and Treatment (CROCODILE Trial)".** Institutional Ethics Committee, All India Institute of Medical Sciences, Rishikesh has **approved** this Research Proposal in its present form.

All clinical trials as well as biomedical and health research should be registered with Clinical Trial Registry of India (CTRI) and seek approvals as per relevant guidelines and applicable regulations.

This approval is valid until duration of project mentioned from date of approval. In case of extension in research period, a written request for extension is to be sent to Institutional Ethics Committee forwarded through Research Cell.

It is mandatory for you to report any adverse event in relation to this research, and number of subjects dropping out from this research, or any changes in study protocol and patient information sheet/informed consent form, if applicable to Institutional Ethics Committee.

You are advised to be familiar with ICMR guidelines on Biomedical Research in Human beings and also to adhere to principles of Good Clinical Practice. You are required to submit completion report of your research within 6 months of scheduled completion date of IEC, AIIMS, Rishikesh.

Yours Sincerely

[redacted]

Dr Ashish R. Bhute
Member Secretary
Institutional Ethics Committee
AIIMS, Rishikesh 249203

(E) Approval from Tata Memorial Hospital, Mumbai.

TATA MEMORIAL CENTRE
टाटा स्मारक केन्द्र
TATA MEMORIAL HOSPITAL
टाटा स्मारक अस्पताल
भा.प.अ.वि. भारत सरकार का एक स्वायत्तता अनुदान प्राप्त संस्थान
A GRANT-IN-AID INSTITUTION UNDER DEPARTMENT OF ATOMIC ENERGY, GOVT. OF INDIA

INSTITUTIONAL ETHICS COMMITTEE
DCGI Reg. No. :
IEC I :- ECR/170/Inst/MH/2013/RR-19
IEC II :- ECR/414/Inst/MH/2013/RR-19

OIEC/3735/2021/00002

July 22, 2021

To,
Dr. Avanish Saklani,
Principal Investigator,
Department of Surgical Oncology,
Tata Memorial Centre.

Ref: Final Approval - 3735

Dear Dr. Saklani,

Institutional Ethics Committee reviewed and discussed your application dated **12/04/2021** to conduct the research study entitled "**ColoRectal cancer in India: catastrOphiC expenDIture and referral pathways infLuencE on presentation and treatment (CROCODILE study)**" during the Institutional Ethics Committee-II meeting held via **video-conferencing (Zoom meeting) on 12/05/2021** at 1.00 p.m. in the **IRB Meeting Room, Main bldg., 3rd Floor, Tata Memorial Hospital.**

At the IEC-II meeting held on **12/05/2021**, the Committee, after due consideration had raised certain queries and IEC query letter dated **24/05/2021** was issued.

We received query responses on **26/06/2021, 12/07/2021 and 14/07/2021** the supporting documents which were reviewed and approved on **22/07/2021.**

The following documents were reviewed and approved

1. Project Submission Form
2. Study protocol version 2.0 dated 18/06/2021
3. Lay summary 1.0 version dated 03.05.2020
4. Case Record Form version 1.4.2 dated 03.05.2020
5. Participant information sheet and informed consent form for qualitative component of TMH in English version 2.1 dated 06/07/2021
6. Participant information sheet and informed consent form for qualitative component of TMH in Hindi and Marathi version 2.0 dated 18/06/2021
7. Participant information sheet and informed consent form for quantitative component of TMH in English version 2.1 dated 06/07/2021
8. Participant information sheet and informed consent form for quantitative component of TMH in Hindi and Marathi version 2.0 dated 18/06/2021
9. Verbal informed consent form for healthcare professional version 1.2 dated 13/07/2021 in English, Hindi and Marathi
10. Draft Data sharing Agreement by Christian Medical college & Hospital Ludhiana with Tata Memorial Centre, Parel, Mumbai, Christian Medical College, Vellore, All India Institute of Medical Sciences, Rishikesh, and Tata Memorial Centre, Kolkata submitted on 12.07.2021
11. CTRI Registration no. CTRI/2020/09/027896 dated 18.09.2020
12. Email dated 05.11.2020 for HMSC approval for CMC, Vellore and CMC, Ludhiana
13. Response letters dated 18/06/2021, 12/072021 & 13/07/2021
14. IEC form for re-review of research proposals dated 25/06/2021
15. CVs, GCP & MRC certificates of Principal investigator and Co-investigators

IEC Office
Dr. E. Borges Marg, Parel,
Mumbai - 400 012. India
Phone : [redacted]
Fax : [redacted]

आय ई सी ऑफिस
डॉ. ई. बोर्जेस मार्ग, परेल,
मुंबई - ४०० ०१२. भारत
दूरभाष : [redacted]
फैक्स : [redacted]

Cancer is curable, if detected early

जल्द इलाज होने पर कैंसर ठीक हो सकता है।

E-mail : [redacted]
Website : [redacted]

Consent form

NIHR Global Health Research Unit on Global Surgery

Catastrophic expenditure and referral pathways influence in clinical presentation of colorectal cancer in India

Consent Form

Christian Medical College & Hospital, Ludhiana

Version 1.0 30-March-2020

#	Statement (please read)	Participant *(initial or thumb print each box)*
1	I have read/ had read to me of the Patient Information Sheet for the above study (dated DD/MM/YYYY, version ____) and have had the opportunity to consider the information and ask questions.	
2	I understand that my participation in this study is voluntary and that I may withdraw at any time, without giving a reason. This will not affect my medical care or legal rights.	
3	I understand that a copy of my consent form and information about me will be supplied in confidence to study coordinators at _____.	
4	I have been informed that information about me related to the study will be stored on password protected computer systems at my local centre and also at the University of Birmingham in England.	
5	I chose TO / NOT TO (please mark as appropriate) provide my e-mail address in order to receive information about the results of the mentioned study. (If you chose to share your e-mail address, the research team will keep it in as isolated and secure document, circulating information to you only about the study results and no other issues).	

Name of participant	**Name of researcher taking consent**
Signature (or thumbprint) of participant	**Signature of researcher**
Name of Witness:	**Signature of Witness:**
Date form signed (or thumb printed) by participant DD / MM / YYYY	**Date form signed by researcher** DD / MM / YYYY

Catastrophic expenditure and referral pathways influence in clinical presentation of colorectal cancer in India (quantitative component)

Patient information sheet for data collection (clinical, expenses and income)

Version 1.1 10-April-2020

Background:
Previous studies show that colorectal cancer (CRC) patients in India present with more advanced disease compared to western patients. The main goals of this project are to explore barriers in access to cancer treatment in India, particularly affordability of care.

What this study entails:

To do this, we need to collect data about your disease and the treatment you received, including how much it cost for you. You were enrolled in this study because you have a CRC diagnosis and you will undergo treatment. Participation in this study will have no impact on your treatment. No changes to your treatment will be made whether you decide to participate or not.

Time commitment:

The time commitment for you is very low (about 20 minutes). Whilst you are in hospital we will invite you to answer the survey and we will support you in any questions you have about it.At6 weeks, 3 months and 6 months after this in-person contact, we will make a telephone call to confirm the total cost of cancer treatment with you. After this, your participation will be over and nothing further will need to be done.

Information to be collected:

We will collect data about your disease and the treatment you were or will be given. Data about your treatment cost will be collected from hospital records.You will be asked to fill a survey with some details about your incomeand the assets you own. Besides that, you will be asked to identify 5 pictures of house goods that look like your own. The questionnaire also covers transport, food and accommodation expenses. If any questions make you uncomfortable, you do not have to answer them.

Confidentiality:

Information about you will be kept confidential.Your telephone contact will be used only for the study purpose and will be kept in a locked secure place in the hospital. You will be given the choice to share your email in case you want to get feedback about the study results. If you don't wish to share it or don't hold an e-mail account, you can always ask the local research partners (NIHR Global Surgery India Hub) for this information, if you are interested. The least possible information about you that is needed for the research will be sent to the University of Birmingham which is coordinating this study. It will be stored for 05 years but will then be destroyed. We will keep the data as safely and less detailed as possible; no records of your name e-mail or telephone will be kept in the study central files.

Consent:
It is up to you to decide to join the study. If you agree to take part, we will ask you to sign (or fingerprint) a consent form. You are free to leave the study, without giving a reason. If requested, we can remove your information from the study. Withdrawing from the study will not affect the care you receive.

Catastrophic expenditure and referral pathways influence in clinical presentation of colorectal cancer in India (qualitative component)

Patient information sheet for participant interview: Pathways to receive cancer care

Version 1.1 10.04.2020

Background:

Colorectal cancer is the 4th most incident cancer in India according to World Health Organization and its incidence is increasing. Previous studies show that colorectal cancer patients in India are usually younger than in the West and have more advanced disease. This study aims to explore patient and healthcare professional's perspectives on how patients access treatment care in India.

What this study entails:

Participation in this study will have no impact on patient treatment. You were enrolled in this study because you are either a patient with a CRC diagnosis or a healthcare professional in charge of CRC patients (diagnosis or treatment). A researcher will ask you about the steps involved in receiving cancer treatment, difficulties in that process and your views on what should be done differently to facilitate access to cancer care.

Time commitment:

The time commitment for you is very low (about 1 hour). Once this interview is completed, your participation will be over and nothing further will need to be done.

Information to be collected:

Only basic information will be collected. This will include information about you, your illness, how did you seek health care and your ideas about how to improve access to cancer care. During the interview the researcher may make some notes. The researcher will ask for permission to audiotape their interview with you (this is optional). If any questions make you uncomfortable, you do not have to answer them.

Confidentiality:

Information about you will be kept confidential. You will be given the choice to share your email in case you want to get feedback about the study results. If you don't wish to share it or don't hold an e-mail account, you can always ask the local research partners (NIHR Global Surgery India Hub) for this information, if you are interested. The least possible information about you that is needed for the research will be sent to the University of Birmingham which is coordinating this study. This information will be stored for 05 years but will then be destroyed. We will keep the data as safely and less detailed as possible; no records of your name or e-mail will be kept in the study central files.

Consent:

It is up to you to decide to join the study. If you agree to take part, we will ask you to sign (or fingerprint) a consent form. You are free to leave the study, without giving a reason. If requested, we can remove your information from the study up to 30 days after your interview. Withdrawing from the study will not affect the care you receive.