LONG-TERM OUTCOMES OF TETRALOGY OF FALLOT FOLLOWING COMPLETE REPAIR

by

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ABSTRACT

Background: Tetralogy of Fallot (ToF) is the most common cyanotic heart defect, requiring not only early surgery in infancy, but usually one or more cardiac catheter interventions or open-heart operations into adulthood. Although ToF is 'completely repaired' at the initial surgery by closing the ventricular septal defect (VSD) and relieving the obstruction to pulmonary blood flow, it invariably leaves severe pulmonary valve regurgitation with volume loading of the right ventricle (RV). Over time, the RV dilates and will eventually fail without further intervention to implant a pulmonary valve prosthesis. We analysed early and late outcomes of ToF in one of the largest single-centre cohorts of both paediatric and adult congenital cardiac surgery in the UK, with a consistent approach to operative management over more than 30 years.

Methods: All patients who underwent complete repair of ToF over a 34-year period (1988-2022) in a single centre were included. Comparisons between morphological groups were undertaken using the Kruskal-Wallis tests for continuous variables, or Pearson's chi-squared test for categorical variables. Kaplan-Meier estimates were generated as all-cause mortality curves for the time-to- event analysis, and comparison between groups using the log-rank test. Event rates for reinterventions were estimated using cumulative incidence function with death as the competing risk.

Results: 821 patients were included in the final analysis with a median follow-up of 15.1 years over a study period of 34.3 years. 24% underwent a pre-repair intervention: either a systemic-to-pulmonary shunt or a right ventricular outflow tract stent. Median age at repair was 0.98 years with 95% of patients undergoing a trans-atrial approach to

the VSD closure. 74.4% required a transannular patch. Long-term survival was 92.5% at 30 years. Median interval from complete repair to pulmonary valve replacement (PVR) was 18.2 years. Incidence of PVR at 25 years was 39.1% with 50% of patients needing a PVR at 27 years. Following PVR, there was a decrease in the indexed right ventricular dimensions including end-diastolic volume (from 119ml/m^2 to 103ml/m^2) and end-systolic volume (84ml/m^2 to 52ml/m^2) with an associated increase in the right ventricular ejection fraction.

Conclusions: We demonstrate excellent long-term results for Tetralogy of Fallot over a 34-year study period with evidence of reverse remodelling following pulmonary valve replacement. This study provides a sound evidence-base to counsel parents about long-term outlook for children treated with Tetralogy of Fallot.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Mr. Nigel Drury, Associate Clinical Professor at the University of Birmingham, and Consultant in Paediatric Cardiac Surgery at Birmingham Children's Hospital, without whose support and guidance this project would not have been possible.

I would like to also thank Mr. John Stickley for providing invaluable advice and support with statistical analysis.

I would also like to thank the staff at the Department of Cardiac Surgery, Birmingham Children's Hospital who have not only maintained the invaluable clinical databases and helped with data collection, but also to those who have supported me during my year of research.

Last, but not the least, to my family, thank you for always being there.

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INTRODUCTION

Right ventricular anatomy and physiology

In the normal adult heart, the right ventricle (RV) is the pumping chamber connected in series after the systemic circulation, providing energy to the blood to reach the pulmonary circulation. It extends from the atrioventricular junction (attaching to the right atrium) to the ventriculoarterial junction (leading to the main pulmonary artery).

Broadly, the RV is described as having three components: inlet, apical trabecular and outlet. The tricuspid valvar apparatus and its attachments lie within the inlet. The outlet is the infundibulum, a muscular tube arising from the chamber leading to the pulmonary valve at the junction with the main pulmonary artery. The apical trabecular portion is the intervening chamber characterised by coarse trabeculae or muscle bundles.

The forces acting on the chamber may be broadly classified into two: the volume loading during diastole, and the pressure loading during systole. Being a muscle, the chamber undergoes remodelling in response to changes in its loading conditions to maintain adequate forward flow. For example, in utero, the right ventricle is subjected to pressure-loading at systemic pressures, such that both RV and LV have similar wall thickness. After birth, the RV remodels in response to the reduction in pulmonary resistance.

Adjoining the RV is the left ventricle, both chambers sharing a common mostly muscular wall – the interventricular septum. Adaptive structural changes to the RV can have an adverse impact on LV function.

Tetralogy of Fallot

Morphology

Originally described as the "blue disease", or "la maladie bleue", ToF was characterised by four common observations in the hearts of affected patients: an interventricular communication, biventricular origin of the aorta, right ventricular outflow obstruction and right ventricular hypertrophy. The first observations were published by Niels Stensen in the 1671 with other authors including Etienne-Louise Fallot making similar observations over the next 250 years. The term "Tetralogy of Fallot" was coined by Maude Abbott in 1924[1].

The hallmark feature is the antero-cephalad deviation of the outlet part of the interventricular septum[2]. This malalignment characteristically leads to a defect in the septum as well as a narrowing of the calibre of the RV outflow tract. The maldevelopment of this part of the ventricular outflow allows the otherwise normal aortic root to develop anteriorly into this space, thus "overriding" the defect towards the RV. The resulting gross overload in pressure (and volume) leads to RV hypertrophy.

It is important to note that the degree of mal-development lies on a spectrum of phenotypes, the extremes of which could be described as separate entities, e.g., double-outlet right ventricle, pulmonary atresia, pulmonary stenosis. The classic description of Tetralogy of Fallot lies within this spectrum, where obstruction of the right ventricular outflow tract may manifest itself as varying combinations of severity and/or location. Severity may vary from mild stenosis to complete atresia. The location may include one or more of the following areas: sub-valvar area (i.e., the muscular infundibulum), pulmonary valve, supravalvar area (main pulmonary artery) or the branch pulmonary arteries. In addition, it may occur in combination with other cardiac defects (e.g., aortopulmonary collaterals, patent arterial duct, atrioventricular septal defect) or normal variants of cardiac anatomy (e.g., right aortic arch, left anterior descending artery arising from the right coronary artery), that are important for the planning of any intervention.

Pathophysiology

Whereas in an isolated unrestrictive ventricular septal defect there is a large shunt from left to right during systole, in ToF, the fixed obstruction to RV outflow causes the blood to shunt from right to left through the VSD and into the systemic circulation. As the RV remodels to the large pressure load, the dynamic component to the obstruction worsens as the muscular outflow tract hypertrophies. In addition, “cyanotic spells” or episodes of profound desaturation may occur when the shunt worsens in response to catecholamine-induced muscular spasm of the outlet.

Natural history

Uncorrected, the life expectancy is severely curtailed, with most patients dying in the first few years of life. Though there are case reports of patients reaching their mid-to-later years, only 10% survive their third decade of life[3] in contrast to 94.5% 25-year survival in a contemporary cohort following surgical repair.[4] The severity of the obstruction to pulmonary blood flow is a major determinant of early mortality within the first year of life where risk is highest. Uncorrected patients suffer from the consequences of prolonged systemic hypoxaemia arising from right-to-left shunt including hypoxic spells, thromboembolic phenomena, and brain abscesses.

In patients with late correction, right ventricular muscle biopsies undertaken at the time of repair reveal hypertrophic and degenerative changes with endocardial thickening and interstitial fibrosis, progressing with age.[5]

Ventricular failure occurs when the chamber is unable to fulfil its function to maintain adequate forward flow despite remodelling.

Clinical interventions

The history of cardiac surgery is a history of the attempts to palliate or correct the lesions in Tetralogy of Fallot. Re-routing or 'shunting' blood from the subclavian artery to the pulmonary artery to increase pulmonary blood flow was the earliest successful surgical intervention carried out on a 3-month-old infant with ToF in 1944[6]. The first

intracardiac repairs to address the anatomic lesions would be carried out initially under cross-circulation in 1954[7] and later under cardiopulmonary bypass[8].

Pre-repair interventions

A staged approach to repair may be undertaken whereby an initial systemic-to-pulmonary artery shunt is surgically created or catheter-based stent may be placed in the RVOT. This approach is primarily reserved for high-risk, severely cyanotic patients with significant comorbidities, concomitant complex cardiac lesions, or neonate with small pulmonary arteries.

The systemic-to-pulmonary artery shunt commonly placed is the modified Blalock-Thomas-Taussig shunt which is an interposition polymer graft connecting the right subclavian artery to the right pulmonary artery. Its use has greatly decreased in ToF as results for early complete repair have improved[9]. Stenting of the RVOT is now the primary pre-repair intervention as it allows for a more stable circulation in comparison to the surgical shunt, as well as improved pulmonary artery growth[10].

Complete repair

Complete repair is a surgical procedure whereby the ventricular septal defect is closed and any obstruction to the RV outflow tract is relieved. This is performed through a sternotomy incision under general anaesthesia and with the support of a cardiopulmonary bypass machine, allowing the heart to be arrested using cardioplegia.

To close the VSD, the appropriate part of the ventricular septum must be visualised. This may be achieved by either a trans-atrial approach or a trans-ventricular approach, according to where the primary incision was undertaken. In a trans-atrial approach, the right atrium is incised and the tricuspid valve leaflets retracted to see the VSD. The main pulmonary artery is also incised, with the incision frequently extending across the valvar annulus into the infundibulum and a patch sutured to widen the RVOT.

In the transventricular approach, the primary incision is made in the RV free wall extended as necessary to visualise the VSD adequately. The resulting cardiotomy is usually larger than a corresponding repair through the RA, possibly also necessitating division of coronary artery branches. First reported in 1955, this technique has over time become less popular.[11]

The transatrial approach, though first reported in the 1960s[12,13] came into favour in the 1980s when the late morbidity associated with the ventriculotomy became evident.[11,14]

Remodelling after intervention

Assessment of remodelling may be undertaken in a variety of ways, including electrocardiography[15], echocardiography[16] and magnetic resonance imaging[17,18]. During complete repair, the dysplastic and diminutive pulmonary valve is usually incised and patched over to enlarge the RVOT, leading to pulmonary regurgitation. The RV dilates in response to the resultant volume loading, with associated increased risk

of arrhythmias, sudden cardiac death and exercise intolerance.[16] In addition to the volume loading due to PR, depending on the approach, the transannular patch or ventriculotomy can also create akinetic areas of RV that do not contribute to function.

Post-operatively, patients may also develop significant tricuspid regurgitation, the mechanism of which may be two-fold. It may be primary, relating to the surgical access to the VSD beneath the septal leaflet of the tricuspid valve and any ensuing repair attempts to maintain competency. It may be secondary, relating to the annular dilatation resulting from RV volume overload. Both create a substrate for progressive volume loading. A combination of the above factors can manifest as aberrant ventricular conduction in the form of late QRS prolongation (significant when more than 180ms), that in turn is associated with ventricular arrhythmias and sudden death[15]. Implanting a competent pulmonary valve appears to confer a lower risk of death or ventricular tachycardia[19].

Despite this, pulmonary regurgitation is well-tolerated even when the RV dilates and is subject to early systolic dysfunction[20]. It has been postulated that the low-resistance pulmonary vasculature branching into alveolar capillaries prevents reversal of flow back into the RV[21].

Magnetic Resonance Imaging

The crescentic shape of the right ventricle does not lend itself to precise volumetric analysis when using two-dimensional modality such as echocardiography. Cardiac MRI

is ideally suited for this purpose as it provides both highly reproducible and precise three-dimensional structural and functional evaluation, without using any ionising radiation[22].

Contouring the ventricular cavity at end-diastole and end-systole allows accurate quantification of ventricular volumes, and subsequent derivation of ejection fractions[23]. In addition, it allows assessment of functional data, including ventricular wall motions throughout the cardiac cycle, blood flow measurements including shunts and valvar regurgitation/stenosis measurements as well as fibrotic changes. MRI has become the gold standard for evaluating the RV after tetralogy of Fallot repair given its accuracy and reproducibility. In the current era, there are few contra-indications to MRI due to device implantation as more and more implantable devices are manufactured in a MR-compatible manner. The main barriers to follow-up scans usually are cost and availability. However, image quality can still be sub-optimal due to artefacts due to improper acquisition and gating, arrhythmias, patient compliance and implanted devices[24].

Reintervention after complete repair

The term “complete repair” does not take into account the necessary or accepted residual lesions such as pulmonary regurgitation that invariably necessitates future reintervention, especially in those with a transannular patch repair. To reduce the cumulative morbidity associated with these residual lesions, investigators have sought to define indicators for reintervention. These include markers that herald ventricular

decompensation such as RV dilatation, QRS duration, arrhythmogenic burden and exercise intolerance.

Implantation of a competent valve in the pulmonary position is therefore necessary to reduce the risk of ventricular failure, arrhythmias, and sudden death. The pulmonary valve may be implanted either by surgical approach, or a catheter-based delivery of a stented prosthetic valve. A surgical approach necessitates redo sternotomy, cardiopulmonary bypass and often cardioplegic arrest. Pulmonary valve replacement (PVR) produces significant and immediate reverse remodelling within a week of the procedure[25] with late mid-term and late benefits realised. However, the prosthetic valve is prone to structural valve deterioration over time and therefore PVR starts the clock ticking on the need for further valve replacement.

Objectives

We aim to describe the early and late outcomes of complete surgical repair including any re-interventions over a 34-year period. This will include how variations in morphology and surgical technique impact on outcomes including mortality, morbidity, cardiac function, and the need for late re-interventions.

METHODS

Ethics statement

The study was registered with the institution's Research & Development office and in accordance with the UK National Research Ethics Service guidance, neither individual informed consent nor formal research ethics committee review was required as the study was undertaken by the direct clinical care team using information previously collected in the course of routine care.

Patient population

The study population was identified from hospital databases at Birmingham Women's and Children's Hospital Foundation Trust and Queen Elizabeth Hospital Birmingham Foundation Trust. Using the search term in diagnostic codes, "tetralogy of fallot", all patients who underwent complete repair of ToF between 1988 and 2022 were retrieved. Other interventions on the patients before and after the complete repair were also retrieved. From the cohort, other lesions such as double-outlet-right ventricle, absent pulmonary valve syndrome, and associated cardiac lesions such atrioventricular septal defect were excluded. Any patient who underwent complete repair above the age of 16 years was also excluded. Those who underwent a right ventricle to pulmonary artery conduit implantation (for example, due to anomalous coronary arteries barring a right ventriculotomy) were also excluded from the analysis. These patients typically have several conduit changes to keep up with growth and

hence freedom from re-intervention will be substantially different re-intervention rates, difference in ventricular loading and re-modelling[26].

Operative technique

A preferred technique of transatrial repair was consistently used over the study period. After median sternotomy under general anaesthesia, the patient was placed on cardiopulmonary bypass under moderate hypothermia, the pulmonary arteries clearly delineated, and any residual arterial duct ligated. Under cold cardioplegic arrest, a right atriotomy was used to approach the ventricular septal defect through the tricuspid valve. The VSD was closed with a patch of double velour Dacron using interrupted pledgetted polypropylene or polyvinylidene fluoride sutures. Relief of the RVOT obstruction was undertaken by dividing or resecting the septo-parietal muscle bars that were carefully delineated. A longitudinal incision on the main pulmonary artery was created and any fused pulmonary valve leaflets separated with a valvotomy initially. If the pulmonary valve annulus was too small, and there were no significant aberrant coronary arteries that cross the infundibulum, a limited RVOT incision was made across the annulus, taking care not to extend beyond a virtual horizontal line from the level of the SVC-RA junction. This infundibular incision was limited to the extent it allows a dilator of adequate size (i.e., within a z-score of no smaller than -2). Any further RVOT obstruction was addressed by division of muscle bars. The transannular incision is patched with bovine pericardium where required. In select cases, a mono-cusp valve was sutured, usually fashioned from an aortic homograft.

Data collection and follow-up

The date of complete repair was taken as the initial timepoint for follow-up. Any records were interrogated to determine operative details including the specific type of intervention on the RVOT. The date of last follow-up was determined by date of clinic review by a cardiologist, or death. Cardiac magnetic resonance imaging was undertaken in follow-up to determine ventricular volumes, ejection fractions and degree of regurgitation. Survival status was determined from the patient records as well as from the UK Office for National Statistics for late deaths. Further information on the cause of death was obtained from hospital records.

Statistical analysis

Analysis was performed using R 4.3.0 (www.r-project.org). For continuous variables, median and interquartile ranges were presented, whereas frequencies and percentages were used for categorical variables. Non-parametric tests were used where appropriate. Cox proportional-hazards regression was used to investigate association between survival and several variables collected. Kaplan-Meier estimates of all-cause mortality were undertaken and comparisons between groups were made using the log-rank test. $p < 0.05$ was taken to be significant. Freedom from reintervention was plotted as a proportional hazards model with death as the competing risk.

RESULTS 1 – CLINICAL OUTCOMES

Overall cohort

836 patients who underwent ToF repair between 1988 and 2022 met the inclusion criteria in this study. From this population, 821 were included in the analysis after applying the exclusion criteria. Excluded patients were: 6 patients with missing data, 5 patients with primary repair at more than 16 years of age, and 4 patients who were identified as having other lesions such as atrioventricular septal defect, pulmonary atresia or absent pulmonary valve syndrome.

The median follow-up was 15.1 years (interquartile range 5.7,25.0) over a study period of 34.3 years. In sub-group analysis of patients who underwent pulmonary valve replacements, those with right ventricle-to-pulmonary artery conduits were excluded, leaving 776 patients in the follow-up analysis.

Pre-repair interventions

135 (16.4%) patients underwent a systemic-to-pulmonary artery shunt while 62 (7.6%) had implantation of a RVOT stent. Figure 1 illustrates trends in pre-repair interventions (i.e., none, systemic-to-pulmonary shunt, or RVOT stent). In the early part of the study, there were more patients who initially had shunts. In the last decade, a proportion of patients underwent RVOT stent implantation as the initial intervention prior to complete repair, with shunts being hardly used (Figure 1).

Age at repair

Apart from the early part of the study where there is a wide range of ages at which complete repair is undertaken, most patients are repaired early (Figure 2). Median age at complete repair was 0.98 years for the overall cohort. There was a significant decrease in the median age from the first to the third decile (Figure 3). In the last 10 years, the median age was 251 days. Repair in the neonatal period (<30d) was undertaken in only 5 patients, with only 3 surviving patients. 30 patients were operated in the first 3 months of life, with 24 survivors. 397 patients were operated in the first year with a mortality of 7.5%.

Operative techniques

311 (37.9%) were female with a median age of repair of 0.98 years (IQR 0.61, 1.54) at a median weight of 8.70kg (IQR 7.08, 12.1). In 624 patients (76.0%), a complete ToF repair was the first procedure with the remaining patients undergoing a pre-repair palliative procedure.

Surgical approach to VSD

Almost all patients, 780 (95.0%), underwent transatrial VSD closure, with very few patients (4.5%) undergoing a ventriculotomy to approach the VSD over the study period. A transventricular approach was used in 37 patients with 4 patients having missing information regarding the approach. (Figure 4)

611 (74.4%) required a transannular patch while 45 (5.5%) required placement of a RV-PA conduit. Of those undergoing a transannular patch, 150 (24.5%) had a monocusp valve implantation. Procedures had a median duration of 63 minutes (IQR 52, 76) and 88 minutes (IQR 73, 107) for aortic cross-clamp and cardiopulmonary bypass respectively.

RVOT intervention at complete repair

The majority of patients (611, 74.4%) required a transannular patch, of whom 150 (24.5%) patients had a monocusp. (Figure 5). A small proportion of patients (5.5%) required a separate conduit placement from the right ventricle to pulmonary artery (Table 2). There was no significant change in the cohort over time.

Long-term survival

Overall survival was 96% at 1 year, 95% at 2 years, 95% at 5 years, 94% at 10 years and 93% at 20 years and 92.5% at 30 years (Figure 6). Survival improved over time, with the most recent quartile of patients having greater compared to earlier cohorts (p=0.0062) (Figure 7). Only four patients in long-term follow-up had a cause of death available in the database – causes included road traffic collision, comorbidity from Duchenne muscular dystrophy and severe pulmonary hypertension.

The oldest quartile of patients has improved survival compared to the youngest quartile which includes those undergoing neonatal repair (p<0.001) (Figure 8).

There is no significant difference in long-term survival between the types of RVOT intervention :annulus-sparing, transannular patch, or RV-PA conduit ($p = 0.28$).

Results of Cox regression showed that age at repair had an early higher hazard ratio that decreased and plateaued by the end of the first year of life. Increased duration of cardiopulmonary bypass (beyond 100 minutes), and use of a RV-PA conduit also had a small adverse effect on long-term survival. There is a possibility of collinearity between the variables, that these variables demonstrated here may be associated with each other (e.g., type of intervention and cardiopulmonary bypass duration). (Figure 9)

RESULTS 2 – PULMONARY VALVE REPLACEMENT AND MAGNETIC RESONANCE IMAGING

Pulmonary valve replacement

A total of 135 patients in the whole cohort (135/821, 16.4%) underwent PVR in the study period. Most of these patients who underwent PVR were those who had a previous trans-annular patch (124/611, 20.3%). Only 11/165 patients (6.7%) who had annulus-sparing ToF repair needed a PVR in the study period.

PVR was undertaken at a median interval of 18.2 years (IQR 14.9, 21.0) after ToF repair. Incidence of PVR (excluding those with RV-PA conduit) for any type of RVOT intervention was 0.2% at 5 years, 0.8% at 10 years, 2.3% at 15 years, 18.5% at 20 years, 39.1% at 25 years and 82.5% at 30 years. (Figure 10)

50% of patients were free from pulmonary valve replacement or death at 27 years. PVR is rare before the mid-teens but there is a rapid increase such that 50% of patients undergo PVR by 27 years. PVR was rare in those patients with annulus-sparing repairs - incidence of PVR in this group was 12.5% at 25 years. (Figure 11)

For patients who underwent PVR, survival was 99.3% at 1 year, 98.5% at 5 years, 98.5% at 10 years and 98.5% at 20 years. (Figure 12) Freedom from death or re-do pulmonary valve replacement (including percutaneous valve implantation) after pulmonary valve replacement is shown in Figure 13.

Magnetic Resonance Imaging

270 patients underwent cardiac-gated magnetic resonance imaging following ToF repair but before PVR. Median RVEDVi before PVR was 114ml/m^2 (IQR 90,138). There were too few MRI scans (9) undertaken in the first 12 months following PVR to be able to undertake meaningful comparison, though within these small group of patients, the RVEDVi decreased to 88ml/m^2 (IQR 81.5, 102.5) within 1 year of PVR.

68 patients had an MRI after 12 months following PVR. In this group, paired MRI showed that RVEDVi significantly dropped from a mean of 119 ml/m^2 to 103 ml/m^2 ($p<0.001$). (Figure 14). RVESVi significantly reduced from a mean of 84ml/m^2 to 52ml/m^2 ($p<0.001$). (Figure 17) RV ejection fraction increased from a mean of 46.7% to 49.8% ($p<0.05$). (Figure 15)

Results - Tables

Table 1 - Demographics

Total cohort	821
Sex	
Male	510 (62.1)
Female	311 (37.9)
Median age at repair, years [IQR]	0.98 [0.61, 1.54]
Median height, cm [IQR]	71 [63.0, 81.0]
Median weight, kg [IQR]	8.7 [7.1, 12.1]
Pre-repair intervention	
Primary repair	624 (76.0)
Systemic-to-pulmonary shunt	135 (7.6)
RVOT stent	62 (7.6)

RVOT – right ventricular outflow tract; IQR – interquartile range

Table 2 – Operative data

Operative details	n (%)
Approach to VSD	
Transatrial	780 (95.0)
Transventricular	37 (4.5)
Missing	4 (0.5)
RVOT intervention at repair	
Transannular patch	611 (74.4)
RV-PA conduit	45 (5.5)
Annulus-sparing	165 (20.1)
Aortic cross-clamp duration (minutes)	63 (52, 76)
Cardiopulmonary bypass duration (minutes)	88 (73, 107)

VSD – ventricular septal defect; RVOT – right ventricular outflow tract; RV-PA – right ventricle to pulmonary artery.

Results - Figures

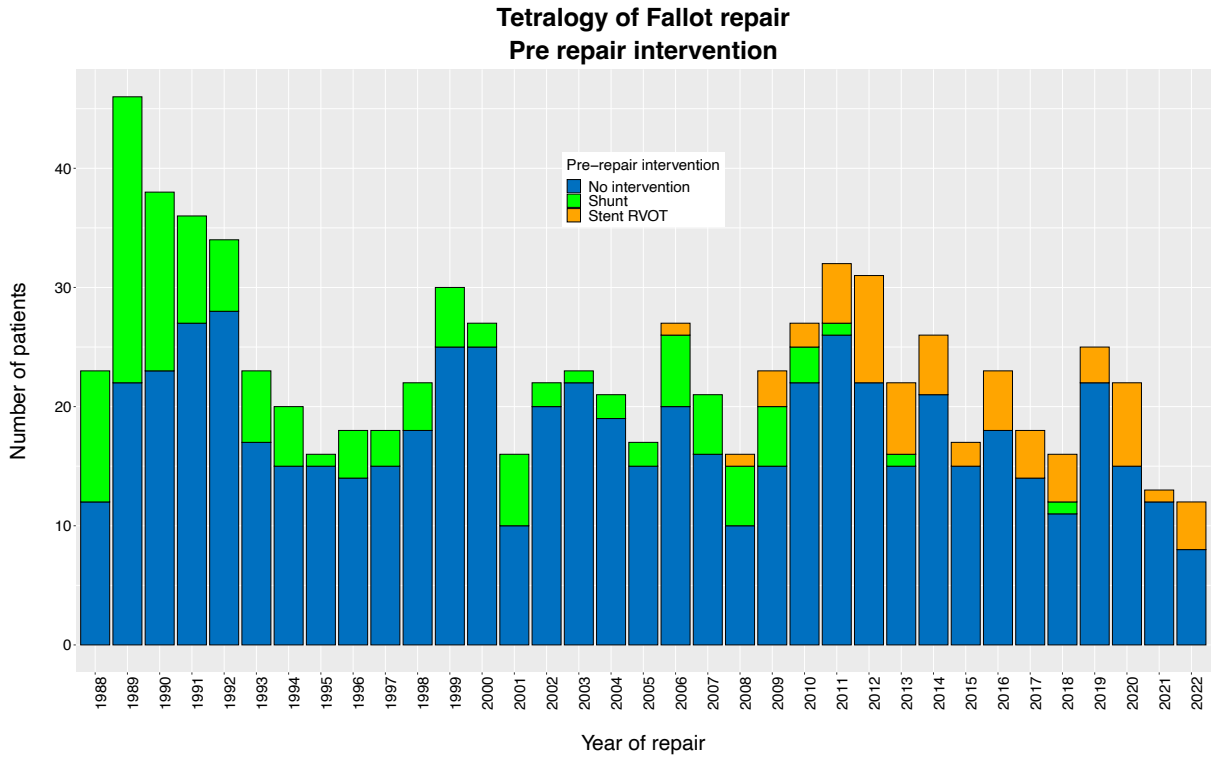

Figure 1 Histogram showing the number of Tetralogy of Fallot repairs by year of repair, and sub-divided into groups based on whether they had no previous intervention (blue), systemic-to-pulmonary artery shunt (green) or a stent in the RVOT (orange)

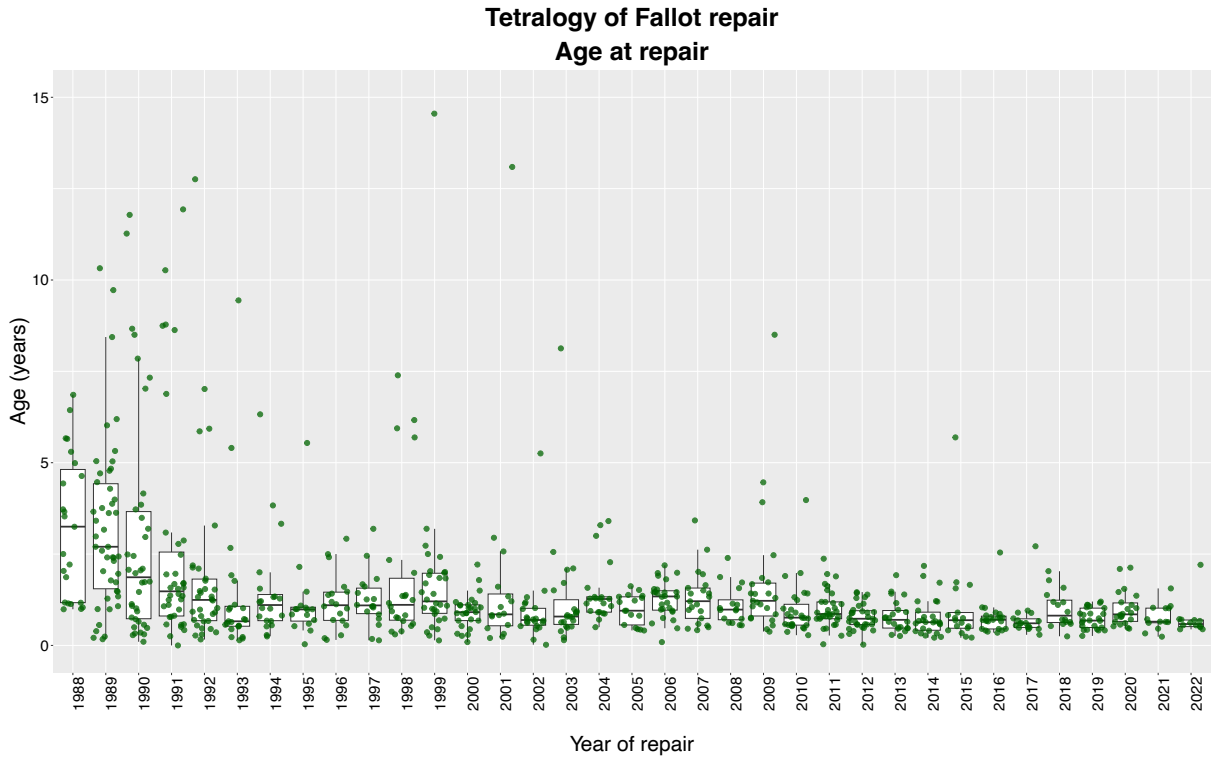

Figure 2 Box plot showing median age of repair at each year of the study.

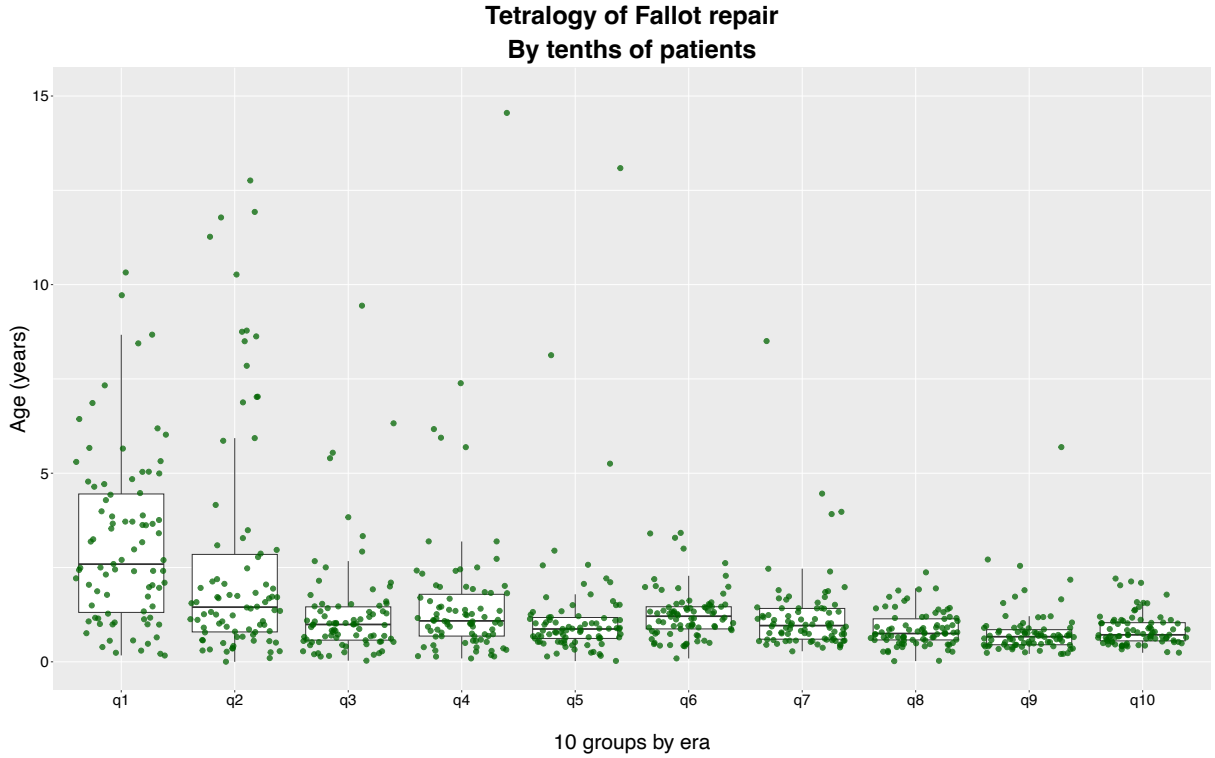

Figure 3 Box plot showing median age at time of Tetralogy of Fallot repair by each decile of the study period.

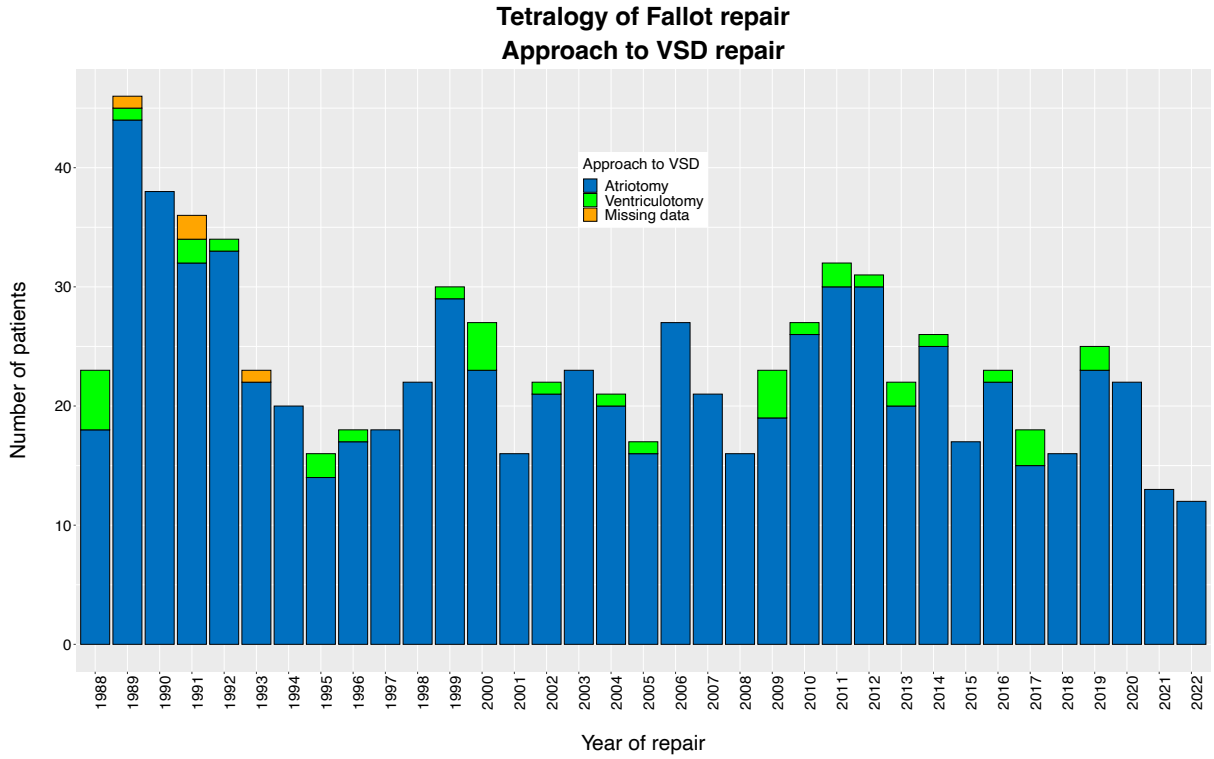

Figure 4 Histogram showing number of Tetralogy of Fallot repairs per year stratified by surgical approach to the VSD: right atriotomy (blue), right ventriculotomy (green), missing data (orange).

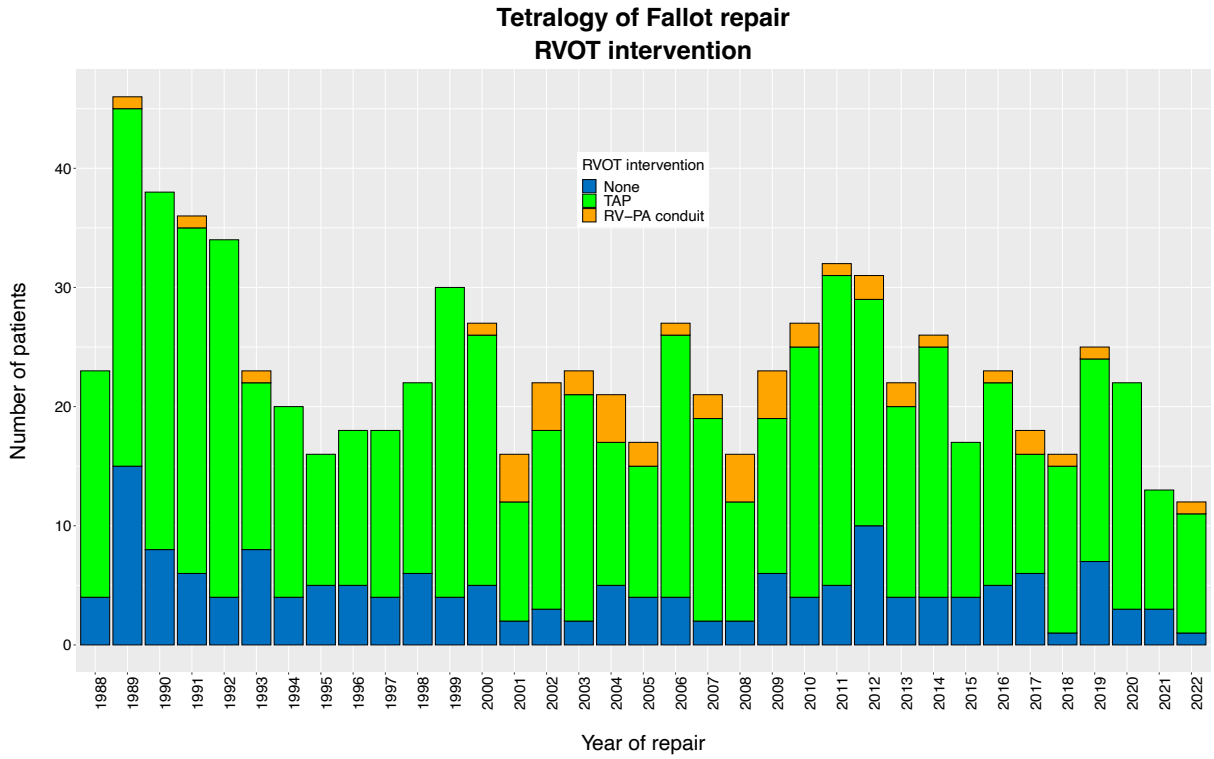

Figure 5 Histogram showing number of Tetralogy of Fallot repairs per year stratified by type of intervention on the right ventricular outflow tract (RVOT): annulus-sparing (blue), trans-annular patch (green), right ventricle to pulmonary artery conduit (orange).

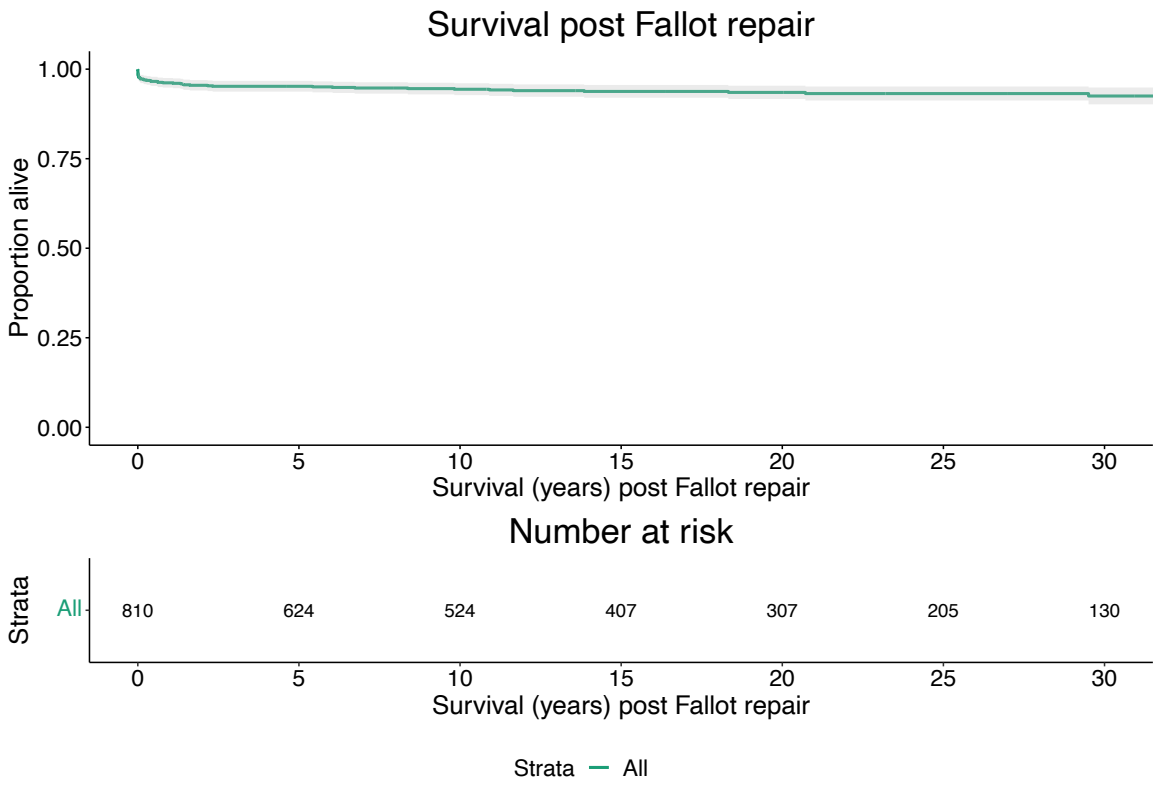

Figure 6 Kaplan-Meier plot showing survival of entire cohort.

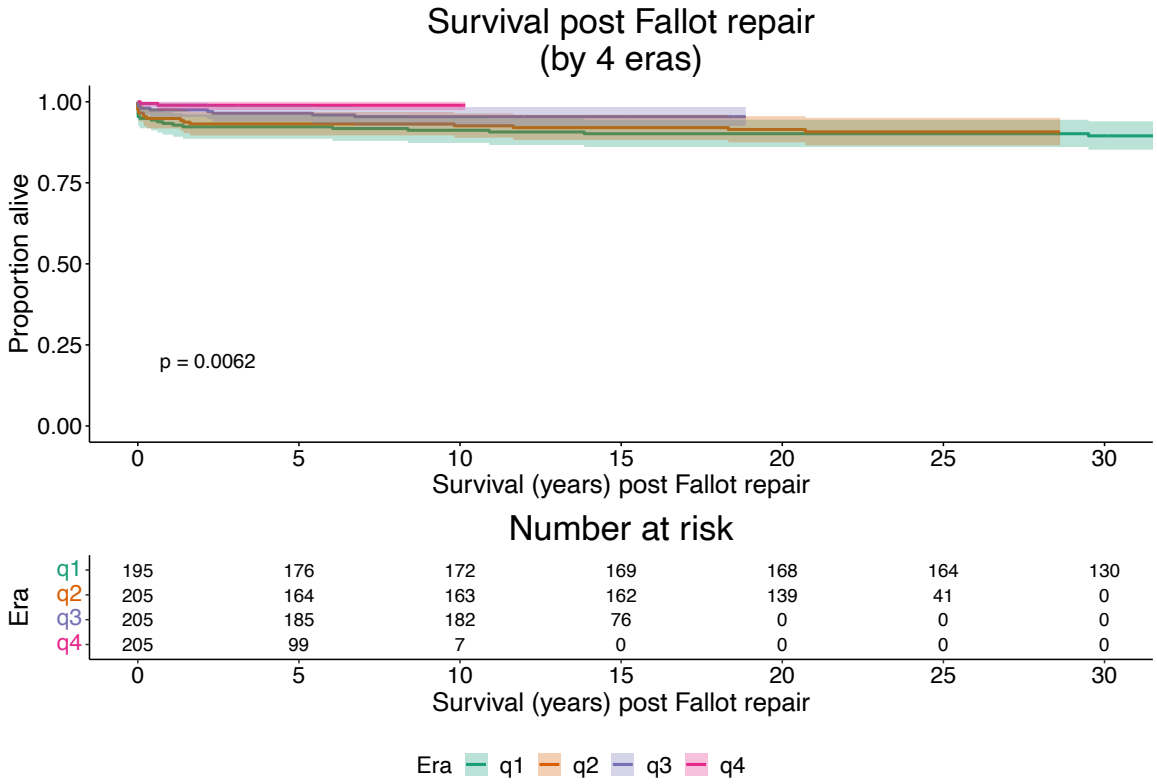

Figure 7 Kaplan-Meier plot showing survival of patients operated in each quartile of the study period from early to late (q1 1988-1996, q2 1996-2005, q3 2005-2013, q4 2013-2022).

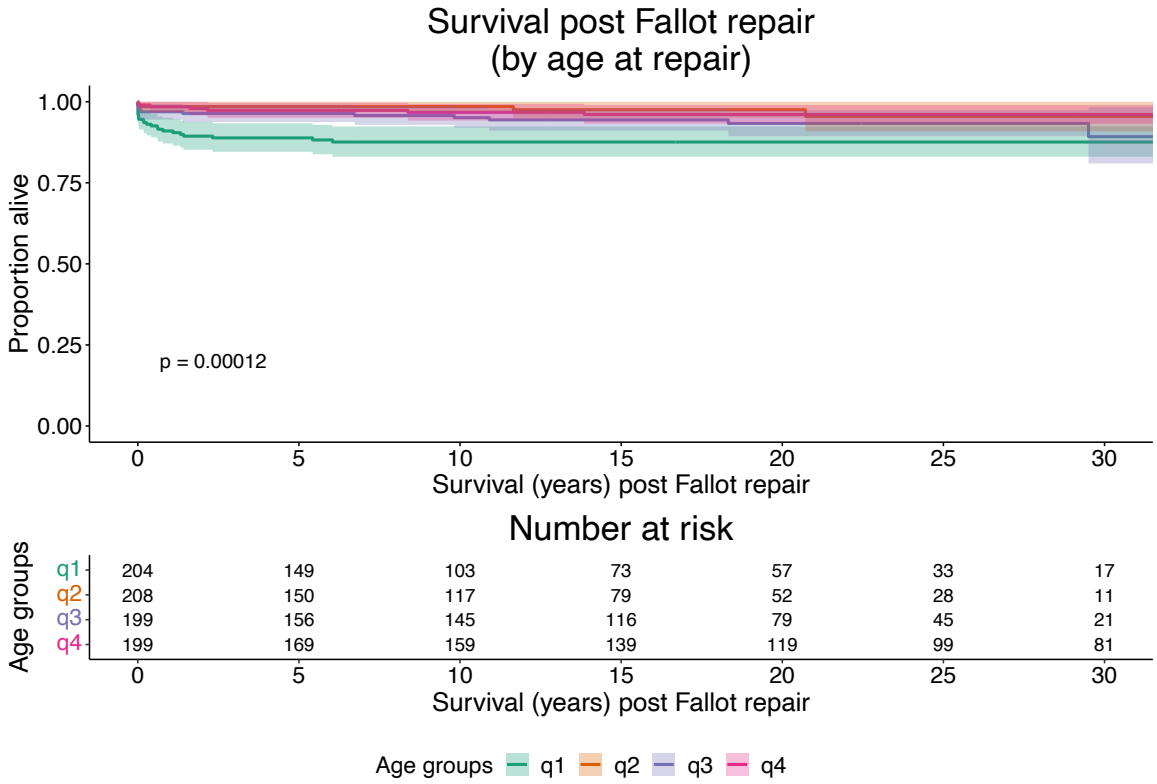

Figure 8 Kaplan-Meier plot showing survival of patients stratified into quartiles by age of repair (q1 <0.61y, q2 <0.98y, q3 <1.54y, q4 <14.6y)

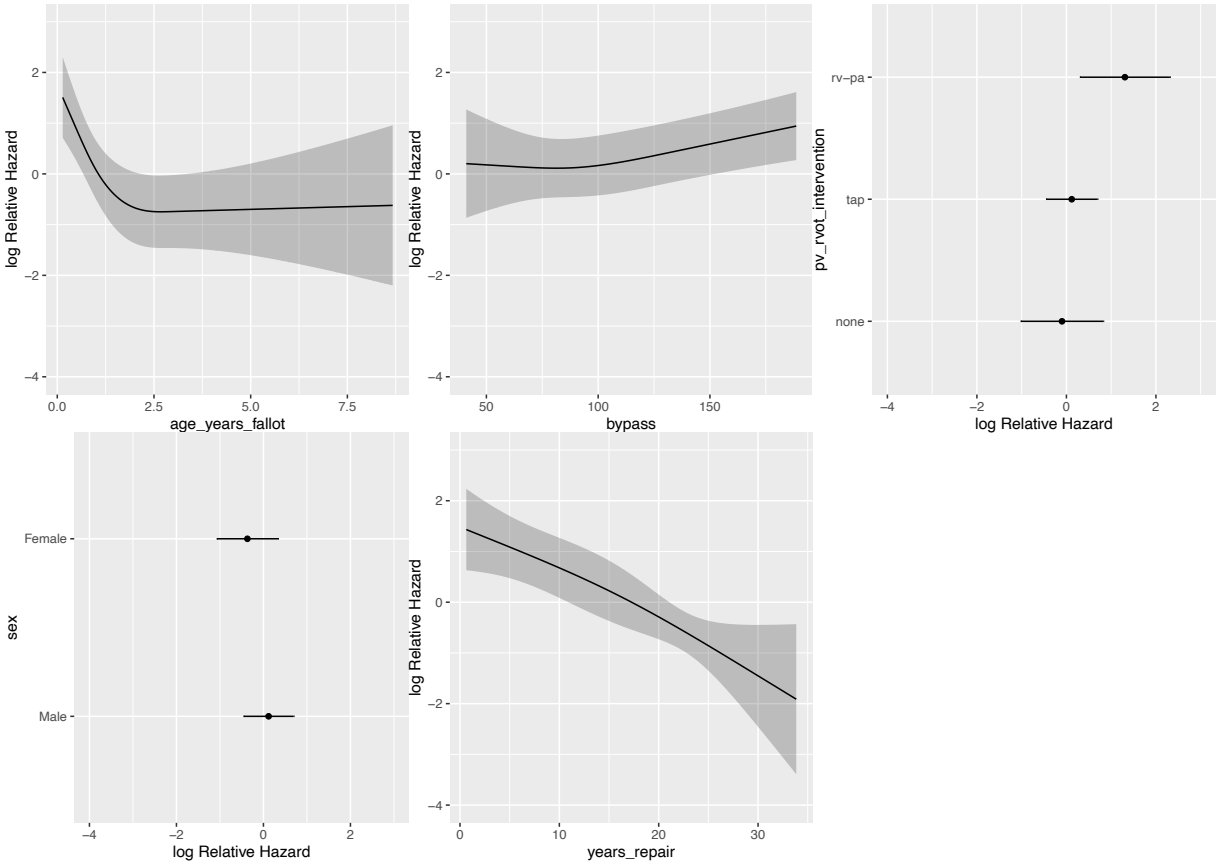

Figure 9 Cox-regresison analysis showing non-linear splines of the relative log hazard ratios of each variable (age at repair, cardiopulmonary bypass duration, type of intervention (RV-PA conduit, transannular patch, annulus-sparing), sex, years since repair)

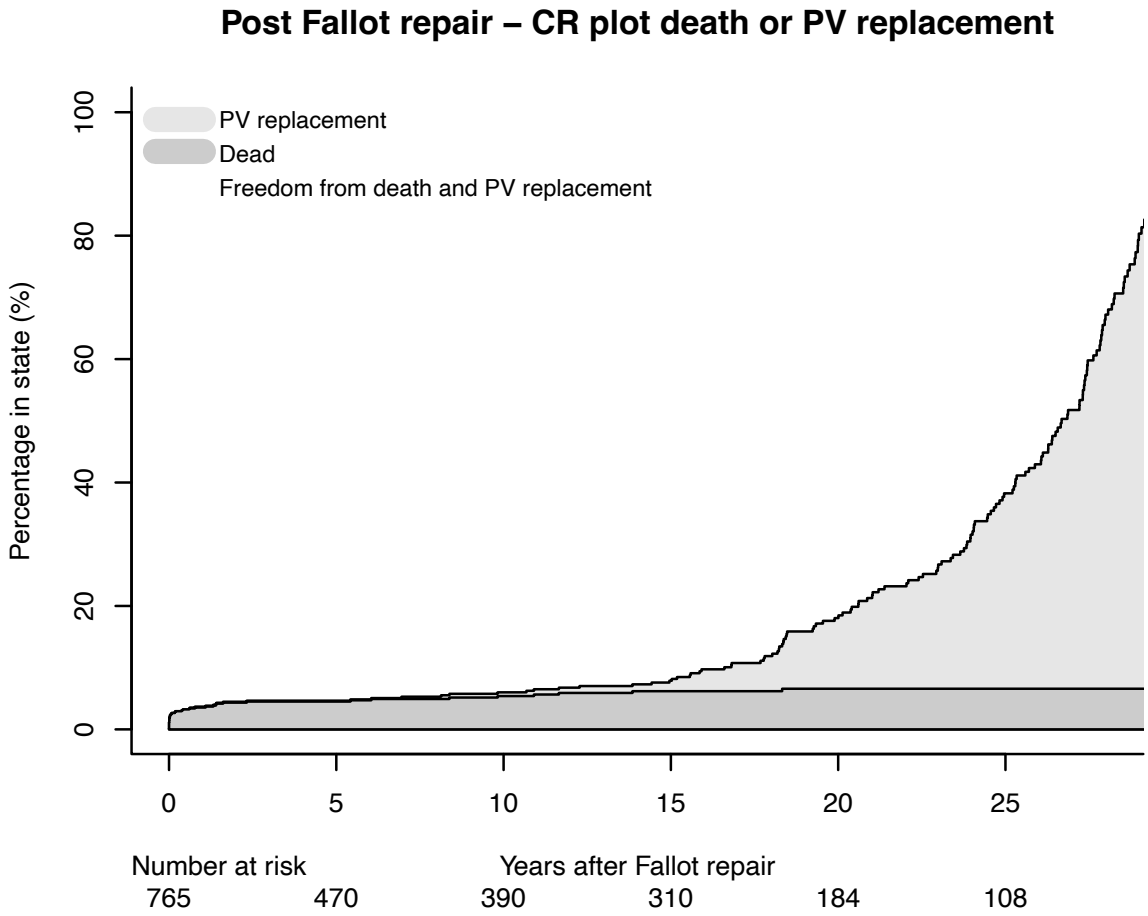

Figure 10 Stacked cumulative incidence curve of competing risk: death or pulmonary valve replacement after Tetralogy of Fallot repair

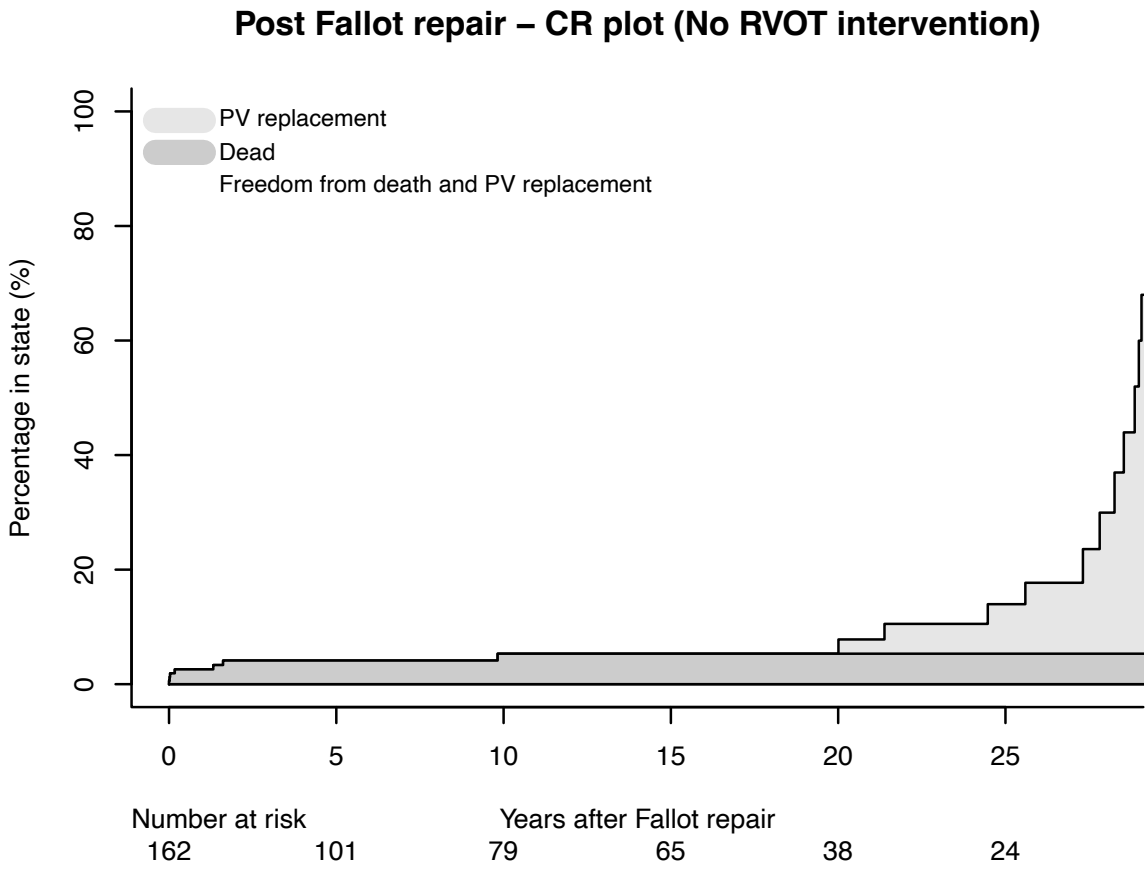

Figure 11 Stacked cumulative incidence curve of competing risk: death or pulmonary valve replacement after Tetralogy of Fallot repair including only those with annulus-sparing repairs.

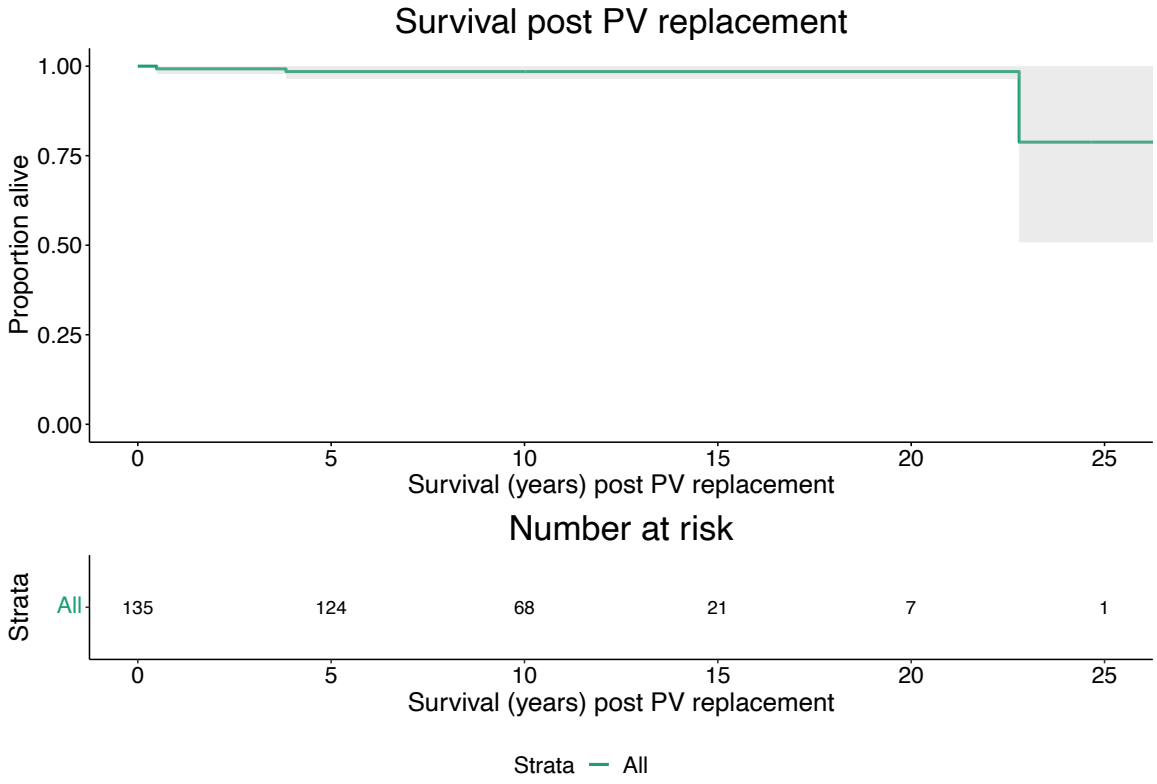

Figure 12 Kaplan-Meier plot showing survival following pulmonary valve replacement

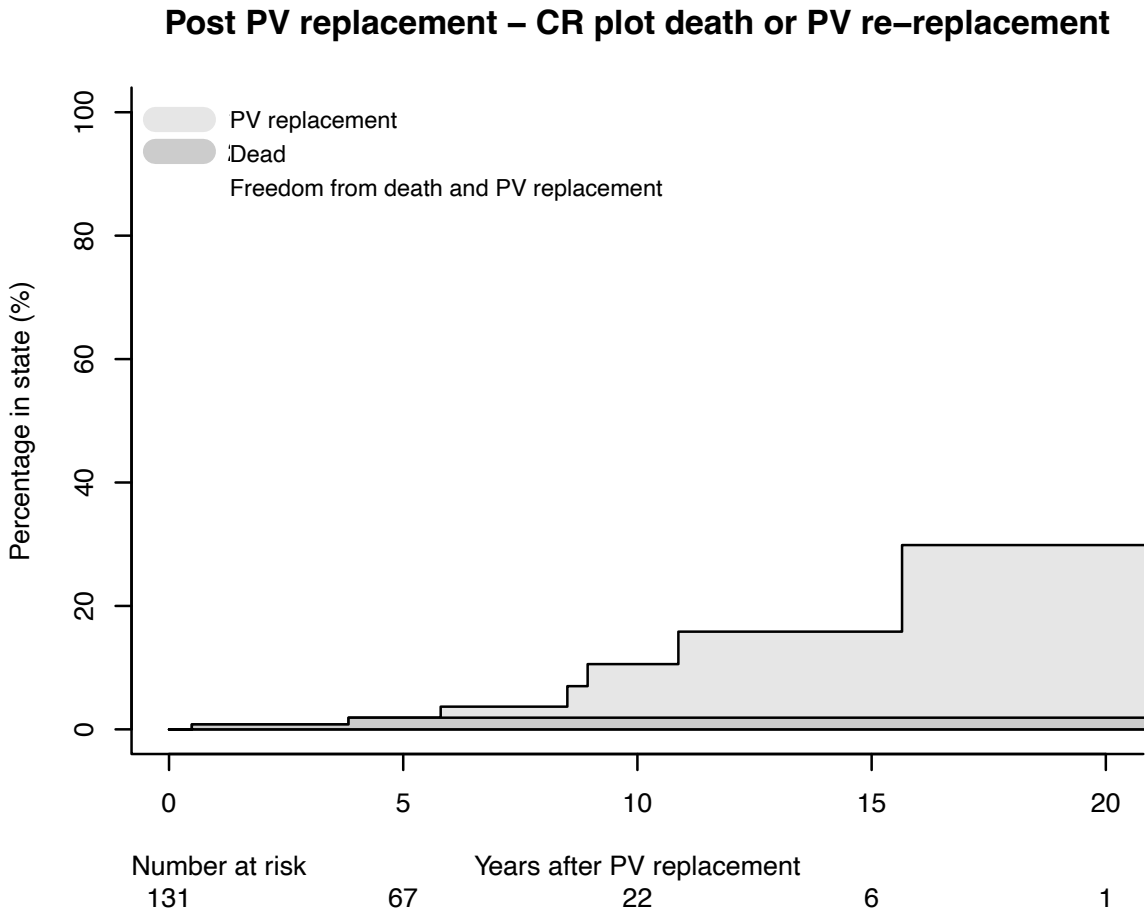

Figure 13 Stacked cumulative incidence curve of competing risk: death or pulmonary valve re-intervention (including percutaneous) after pulmonary valve replacement

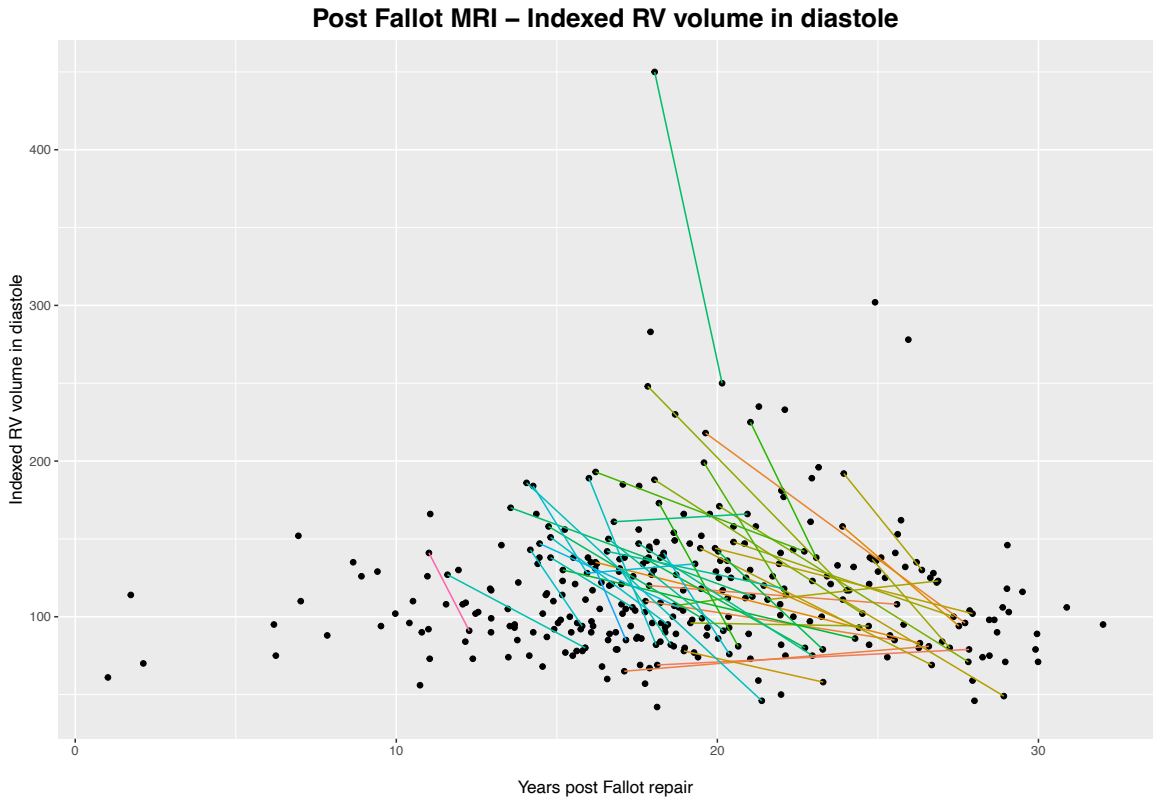

Figure 14 Scatter plot showing change in right ventricular end-diastolic volume indexed to body surface area (RVEDVi (ml/m^2)) following Tetralogy of Fallot repair over the whole follow-up period. Connecting lines denote the change in the volume within the same patient.

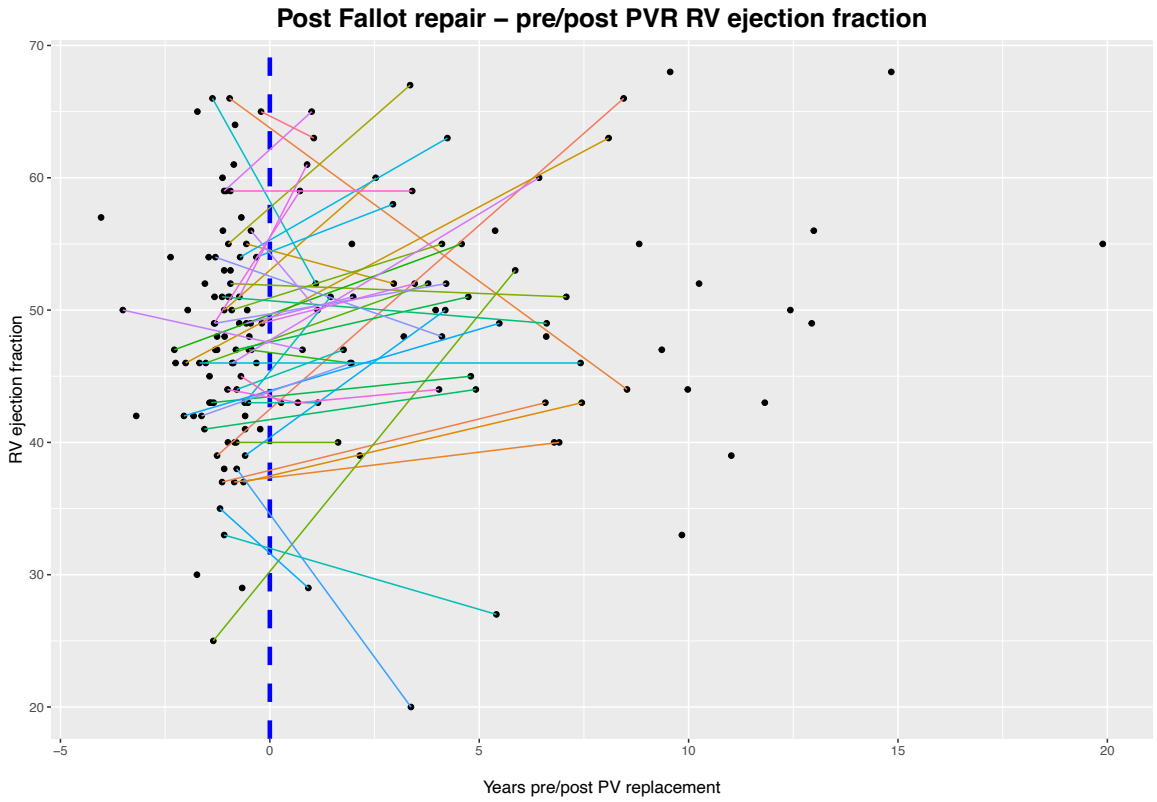

Figure 15 Scatter plot showing change in right ventricular ejection fraction (%) before and after pulmonary valve replacement.

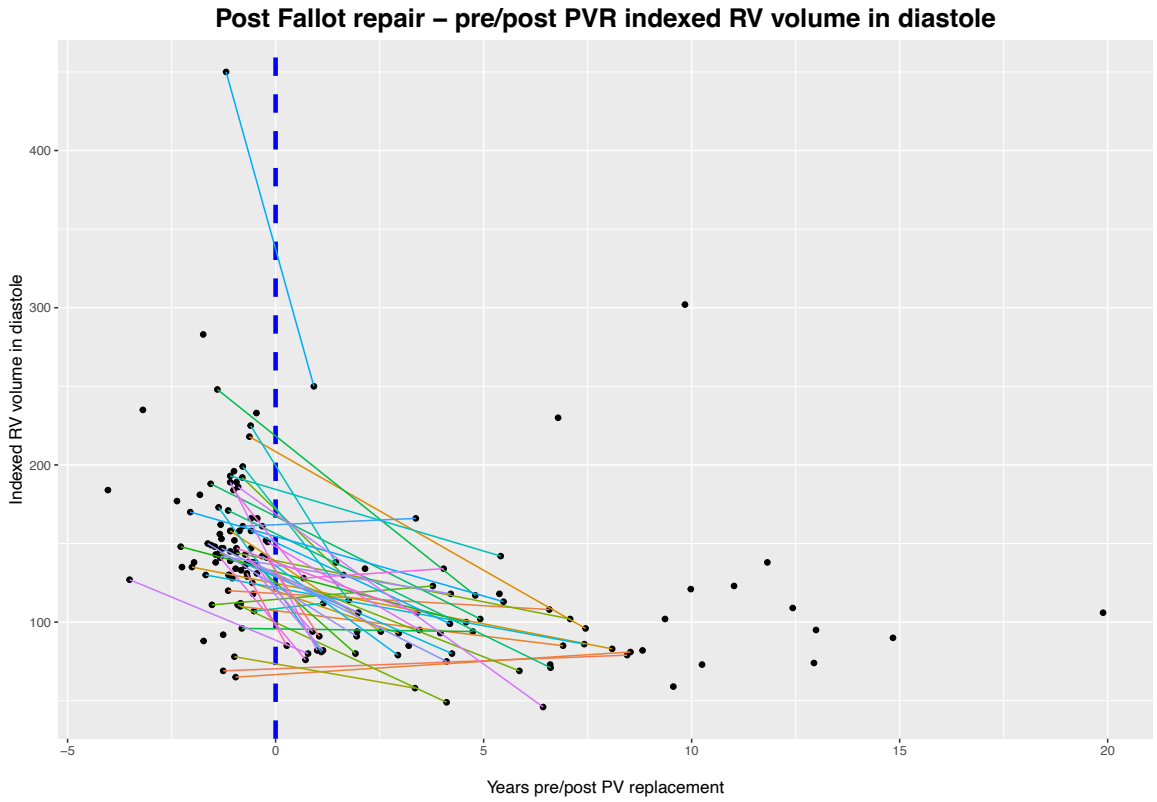

Figure 16 Scatter plot showing change in right ventricular end-diastolic volume indexed to body surface area (RVEDVi (ml/m^2)) following Tetralogy of Fallot repair.

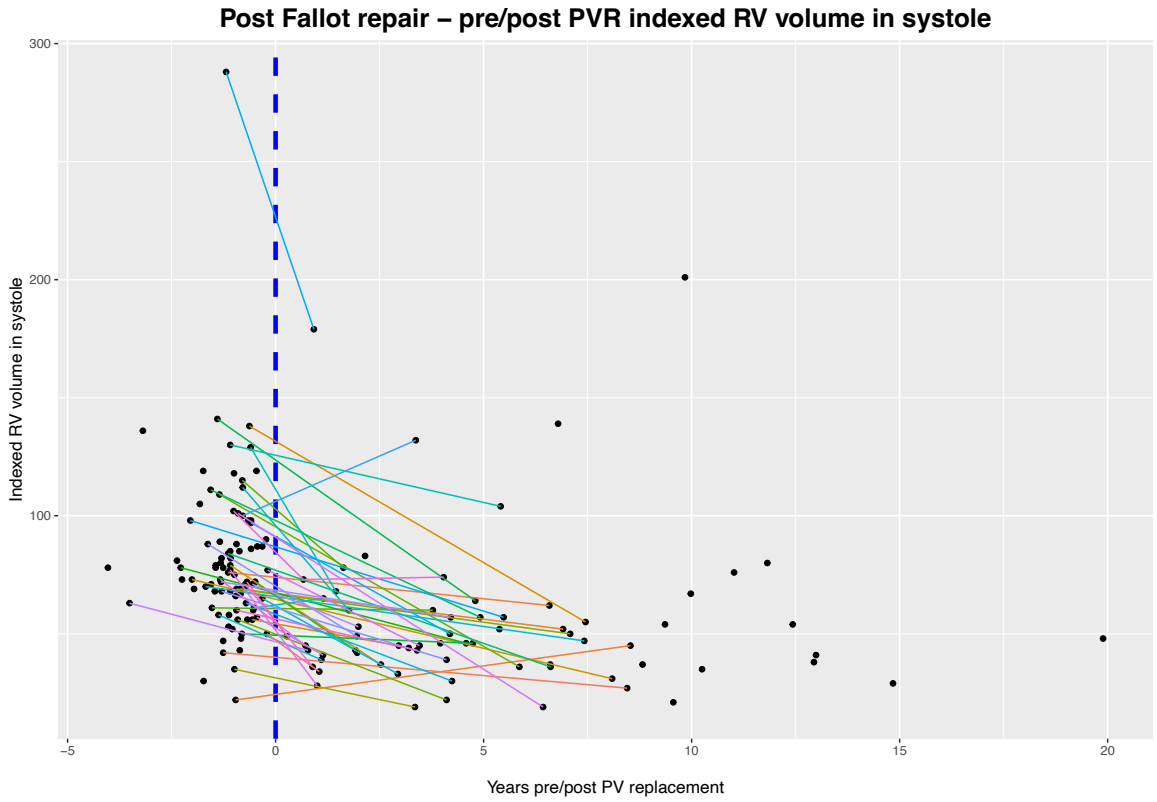

Figure 17 Scatter plot showing change in right ventricular end-systolic volume indexed to body surface area (RVESVi (ml/m^2)) following Tetralogy of Fallot repair

DISCUSSION

This thesis examines a large cohort of 821 patients with Tetralogy of Fallot over a very long period from 1988 to 2022, with follow-up over 30 years. It demonstrates not only low mortality and re-intervention rates, but also excellent overall outcomes into their fourth decade with survival at 92.5% at 30 years. Patients underwent a pulmonary valve replacement at a median interval of 18 years following Tetralogy of Fallot repair.

Pre-repair intervention

Our series has demonstrated a decreased use in pre-repair systemic-to-pulmonary shunts over time, though balanced by an increasing usage of stents in the right ventricular outflow tract. RVOT stents are intended to augment the pulmonary blood flow but without the added morbidity of cardiopulmonary bypass and prolonged general anaesthesia, as well as being a more physiological option for those who may be higher risk candidates for a surgical repair or a systemic-to-pulmonary shunt. In our centre, it has been shown to promote pulmonary artery growth up to an additional +0.6 to +0.75 z-scores compared to the modified BT-shunt[27]. UK data between 2000 and 2013 showed that pre-repair palliation was undertaken in 25.1% of patients in a group of 1,662 patients under 1 year of age[28], comparable to 24% of undergoing such procedures in our study. The proportion of those with a surgical shunt (18.7%) and RVOT stent (6.4%) is also similar to our results of 16.4% and 7.6%.

Age at repair

In the current era, It can be difficult to tease out the effect of the age at complete repair from the literature due to the confounding effect of symptoms being an indication for earlier repair. In a similar vein, onset of symptoms will be strongly linked to the effect of severity of the lesion. Many studies refer to an inflection point of between 2 and 3 months of age at the time of surgery up to which the post-operative morbidity is higher[29–32]. Most of these studies have short follow-up periods, and the effect of age at repair on longer term outcomes are unclear. However, older age at complete repair is a significant risk factor for sudden death if left unrepaired into adolescence[16]. A meta-analysis has recently reported that if repair is undertaken beyond a year of life, there is a slight risk (odds ratio of 1.04) of ventricular tachycardia or mortality[14]. It is reasonable to conclude that ToF be repaired beyond the neonatal period but no later than infancy, to achieve a balance of benefit from repair and minimisation of cyanosis against the morbidity associated with surgical repair.

Previous studies have already established the impact of prematurity and low birth weight as significant risk factors for mortality. For example, database analysis of Paediatric Cardiac Care Consortium revealed an odds-ratio of 12.5 by multivariate analysis, though the number of patients with weight of less than 2.5kg was very small: 15 in a cohort of 3,894.[4] Generally, elective repair between the ages of 3 and 6 months is advocated by several series and the latest consensus documents.[33,34] Though some series do report not overall early mortality differences in the younger age group[35], younger patients had longer operations including duration of cardiopulmonary bypass,

longer post-operative course including ventilator and inotrope use and higher complications, particularly in those less than 3 months[29,31,36–39]. The data from these studies will be affected by centre-specific preferences for early repair and pre-repair palliation.

Teams from Boston[40], Michigan[41] and Linz[42] have reported low early mortality rates of between 2-3% when undertaking primary repair in the neonatal period. When symptomatic with severe cyanosis or cyanotic spells, it is reasonable to undertake primary repair as a neonate. [33,43]However, if there are high risk features such as low birthweight (less than 3kg), small branch PAs, syndromic or genetic co-morbidities, repair may be better staged by undertaking a catheter intervention or shunt. Neonatal repairs are associated with prolonged hospital stays including intensive care usage, and higher mortality – this may reflect the underlying phenotype and risk profile of the patient who requires surgery in the neonatal period.[44]

Approach to VSD repair

Any Fallot repair should address fully the ventricular level shunting and the right ventricular outflow tract obstruction, though the level of residual pulmonary regurgitation will be determined largely by the intrinsic anatomy. A ventriculotomy incision may be used to primarily approach the septal defect which was used in the first repairs.[7] This remained a standard approach into the late 20th century[45,46] as it provided excellent visualisation of the lesions to be corrected with some studies showing little difference in post-operative complications[47]. The results may be

confounded by the definition of the "ventriculotomy" group including an atrial incision for access as well. However, generally a ventriculotomy approach usually necessitates at larger incision for visualisation than one that is limited to the infundibulum just below the pulmonary valve annulus.

A transatrial approach utilises a right atrial incision to visualise the ventricular septal defect below the tricuspid valvar septal leaflet. It was realised early on that ventriculotomy carried a morbidity in particular with respect to RV function and arrhythmias when compared to a transatrial incision.[48]. This finding was replicated in several studies[49,50] showing very low rates of in-hospital and late sudden deaths with 96.9% survival at 25 years[51]. Our approach in the series described in this thesis has been consistently transatrial except for a few outliers in the early part of the study.

Right ventricular outflow tract intervention

The use of a transannular patch during complete repair of tetralogy of Fallot in a recent analysis of the UK audit database (National Congenital Heart Disease Audit) was lower at between 42% and 47% than in our cohort (74.4%)[28]. The variation may be explained by the selection criteria for the analysis which only included 1662 infants, and limited to the most recent time period of 2000 to 2013. An analysis of the European database (European Association of Cardiothoracic Surgery Congenital Database) between 1999 and 2011 showed trans-annular patching with ventriculotomy was undertaken in 57.5% of 6654 operations for ToF[52]. This analysis also included another category of ToF repair with a ventriculotomy but without a

trans-annular patch, which comprised 19.7% of repairs. Similarly, the Society of Thoracic Surgeons Database analysis of 10,272 patients between 2010 and 2020 showed the transannular patching rate with ventriculotomy was 44.6%, and ventriculotomy without transannular patch was undertaken in 24.8%[53]. In both the European and American analyses, the ToF repair requiring any ventriculotomy with or without transannular patching were 77.2% and 69.4% respectively. The difference from our cohort may be due to our standardised approach in ensuring any ventriculotomy is limited, confined to a small incision immediately below the annulus and undertaken solely to relieve RVOT obstruction (and not for access to the VSD).

There will be those patients with varying degrees of severity of infundibular, annular, and valvar stenosis that is not reflected within a single parameter of the RVOT or z-score cut-off for annular size. The z-score, for example, may be confounded by differences in reference data adopted for the score, be it peer-reviewed or institutional databases. The post-repair z-score, taken as surrogate for acceptable repair, varies between 0.34 to -1.2[37,54,55]. In our study, we did not have measurements of z-scores for the whole cohort. The principle remains to avoid any residual RVOTO as that can prolong the post-operative support with complications, as well as adversely impact right ventricular function and remodelling [56–59].

Though some groups have reported benefits in short-term outcomes such as post-operative recovery in those who have a monocusp valve reconstruction[60,61], larger analyses have failed to prove a significant difference in re-intervention rates or long-

term survival[62–65]. Though some have shown improved survival and fewer re-intervention in those with a valve-sparing approach[66], it is difficult to tease out the obvious confounder being that of a less severe phenotype lending itself to a valve-sparing approach.

Long-term outcomes

Over the last twenty years, 30-day mortality for repair of Tetralogy of Fallot has improved from less than 3% in 2000-01 to 0.8% in 2021-22[67,68]. Long-term survival has been reported by several groups. In comparison to other groups, our overall cohort survival of 92.5% at 29.5 years ranks among the highest. Published worldwide figures range between 69% and 91%[51,52,64,69–71]. The Taiwan registry reported 90.5% at 30 years in a cohort of 819 patients between 1970 and 2002.[72]

In our data, we showed no difference in survival between groups depending on the type of RVOT intervention at complete repair, i.e., between valve-sparing and transannular patch. Though there are techniques that allow for a conduit-less repair in the setting of an anomalous coronary crossing the RVOT, in our series this was an indication for conduit placement. Our analysis showed no significant difference in survival between the three groups, though the survival curves diverged in the first decade of life. This probably reflects the cumulative risk of multiple re-operations for conduit replacement. As with other groups, risk of re-intervention is much higher as demonstrated in the results of the regression analysis.

Pulmonary valve replacement

Our results shows that pulmonary valve replacement is rarely undertaken until late adolescence. Long-standing volume overload of the right ventricle results from the significant regurgitation in the absence of a competent pulmonary valve. Transannular patch, though it relieves the RVOT obstruction, leaves significant pulmonary regurgitation. Though it appears to be well-tolerated, there is a growing risk of RV failure, arrhythmias and sudden cardiac death, with symptomatic and prognostic benefits shown after PVR[73–75]. This data is extremely useful to counsel families about the need for potential re-intervention, in adolescence or early adulthood.

The morbidity of a transannular incision not only relates to the loss of pulmonary valve competency, but also to the ventriculotomy however limited it may be. MRI-based analysis have demonstrated increased scarring (through late gadolinium enhancement) that affects the RVOT in particular[49,76]. Large-scale multi-national cohorts have shown RV hypertrophy (ratio of RV mass to volume) as well as ventricular dysfunction (RV or LV) were predictors of death and ventricular tachycardia[77], a signal that both diastolic and systolic dysfunction are important for better outcomes.

Magnetic Resonance Imaging

Several studies have tried to define cut-offs for MRI parameters of RV dilatation to determine the threshold at which reverse remodelling may take place if a PVR were to be undertaken[25,78]. These studies examining right ventricular end-systolic and end-diastolic volumes indexed to body surface area measured before and after PVR showed that ventricular remodelling becomes unlikely at pre-PVR cut-offs of 80ml/m^2 and 160ml/m^2 respectively[25,79]. These cut-offs have been reflected in several national and international guidelines[80–82].

A recent updated meta-analysis showed that post-PVR RV remodelling takes place, as demonstrated by cardiac MRI, usually by way of RV end-diastolic volumes[83]. However, the normalisation of RV volumes is less likely when the pre-operative RV volumes are higher. In those patents with a pre-operative RVEDV of less than 160ml/m^2, remodelling to a normal volume happened in more than 70% of patients. However, age at PVR was not a predictor of normalisation, indicating that maintaining favourable ventricular loading conditions over a longer period may be a strategy to adopt.

In an animal model of ToF where the RV was subjected to pressure overload (though not cyanosis) followed by post-repair volume overload and later correction by valve implantation, increased fibrosis was seen in the myocardium[78]. In a recent histological analysis of patients with ToF undergoing PVR, the authors showed greater fibrosis in those who suffered cardiac adverse events[84]. Older age at PVR has been shown to be an independent risk factor for adverse events[85] though this recent analysis with

histology suggests the risk starts in early adulthood[84]. This is correlated also with symptomatology and patient-reported quality of life measures surveyed in patients with ToF [86] where drop in quality of life scores happens in the teenage years after which it remains steady. This dropped further especially after 40 years of age when pain and mobility problems increased. Patients reported quality of life scores to be greatest when asymptomatic, unsurprisingly.

Limitations

There are limitations to this study. Granular detail into the peri-operative management including length of stay in intensive care, duration of ventilation and morbidities associated with surgery were not collected or analysed. We already know that caregivers including parents and clinicians place importance on overlapping but different morbidities.[87] These include neurological insults, feeding problems, renal replacement therapy, necrotising enterocolitis, infection and prolonged pleural effusion – data that was not captured by this study. This could be important in counselling when detailing options relating to catheter or surgical-based approaches.

Further interrogation of the data could include comparison of interval to re-intervention and life-time re-intervention rates. It would be useful to evaluate the relationship between mild residual gradient that is usually accepted and long-term results.

Our cohort was subjected to a consistent technique over four decades which is a strength as variations in surgeon technique within a single institution have been previously shown to produce wide variability in outcomes, and in particular re-intervention rate[88]. However, it is subject to the era effect where peri-operative care and patient selection would have been different.

The use of cardiac MRI in routine practice has been predominantly implemented in the latter half of the follow-up period. Also, the timing of MRI is not consistent as there are no clear guidelines on follow-up MRI in the interval between complete repair and PVR, and post-PVR. It is often dictated by symptom status, or echocardiographic evidence of dysfunction, stenosis, or severe RV dilatation – usually PR is severe in follow-up of patients with a transannular patch.

Another limitation is that some patients may have significant delays between surgery for PVR and the pre-PVR MRI. It is possible that the ventricular volumes may have increased significantly by the time of surgery, such that the potential for remodelling is impacted.

The transition of patients from the paediatric to adult follow-up usually happened in the 16-to-18-year age group. Although there were different institutions and physicians for adult and paediatric groups, leading to potential differences in decision-making for PVR and imaging follow-up, the surgical team remained constant.

Future Work

It is no longer satisfactory to determine primary clinical outcomes solely by survival in an era where surgical mortality is already very low. Meaningful outcomes for patients would include freedom from complications and measures of quality of life. By moving towards an individualised patient profile that could predict the extent of reversible remodelling after ToF repair, the congenital team can plan for timely RVOT re-intervention.

Healthcare delivery and analysis has substantially changed in the timespan of this database. The marriage of 'big data' from electronic records that are capturing all aspects of a patient's journey from birth, and newer analytical techniques such as machine learning, can glean valuable insights for future direction of work.

Machine learning is already giving a greater insight into prognosticating and aiding decision-making in patients with ToF[89,90]. Wearable and remote technologies are also allowing for better capture of clinically relevant endpoints[91]. A combination of these technologies could allow prediction of adverse events, stratification of patient variables into predictive groups, and re-intervention balanced with the risk of repeat interventions over a lifetime.

Standardising timing of follow-up imaging following Tetralogy of Fallot repair will enable better characterisation of RV remodelling at various timepoints including after pulmonary valve replacement. In the future, it may be possible to determine from

tissue or genetic analysis from tissue biopsied at initial repair what kind of trajectory the RV will take in response to volume or pressure overloading. This may allow individualised patient pathway that optimises RV remodelling potential.

CONCLUSIONS

In a large cohort of patients with Tetralogy of Fallot, we demonstrate excellent long-term survival into adulthood with a low rate of mortality. The rate of pulmonary valve implantation for these patients increases during adolescence and into adulthood. When patients undergo pulmonary valve replacement, MRI data shows reverse remodelling.

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