OPTIMISATION OF SURGICAL TIMING IN RHEUMATIC MITRAL VALVE DISEASE

A thesis submitted for the degree of Doctor of Philosophy

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The more that you read, the more things you will know.

The more that you learn, the more places you'll go.

Dr. Suess

1 Dedication

I dedicate this thesis to my patients.

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5 Thesis Summary

Rheumatic heart disease is a consequence of Group A streptococcal infections, and disproportionately affects the world's most disadvantaged people. Whilst the disease has been essentially eradicated from non-indigenous populations in Australia, Indigenous Australians continue to have some of the highest rates of rheumatic heart disease in the world. The mortality and morbidity associated with rheumatic heart disease primarily results from complications of valvular heart disease which include heart failure and stroke. Valvular surgery can reduce the risk of these, however it comes with its own short-term increase in risk and long-term sequelae.

Guidelines for the management of valvular heart disease primarily focus on North American and European populations which are generally older and with mainly single valve disease. Given the unique pathophysiology and demographics of rheumatic valvular disease, this may prove problematic. Rheumatic heart disease is epitomised by progressive mixed and multivalvular disease in children and young adults. Early intervention provides improved long-term outcomes following valvular surgery, especially in young adults. This thesis focuses on surgical delays, screening, and echocardiographic predictors as methods to reduce long-term risk in patients with rheumatic heart disease and optimise timing of tertiary intervention.

Chapter 1 reviews the current management of rheumatic heart disease and the pitfalls of existing international guidelines in patients with rheumatic heart disease including current evidence for timing and replacement of valves.

Chapter 2 reports on current surgical management of rheumatic heart disease in Australia and compares that to current guidelines. Given most patients come from remote communities, it further looks at delayed referrals and further, delayed surgery for those referred. It illustrates that there are many patients with guideline indications for surgery who fail to be referred or have surgery performed.

Chapter 3 examines the prevalence of rheumatic heart disease in Indigenous populations across different regions of South Australia. This provides guidance to the tailoring of screening programs as well as defining the prevalence of echocardiographic confirmed RHD in South Australia. This study shows the prevalence of RHD in remote areas are significantly higher than metropolitan or rural areas.

Chapter 4 quantifies sonographer sensitivity and accuracy using the World Heart Federation rheumatic heart disease echocardiographic screening criteria, as well as examining sonographer views of the echocardiographic parameters to enable further refinement of existing criteria. It confirms that sonographers have an extremely high sensitivity and reasonable specificity for RHD screening.

Chapter 5 demonstrates the potential role of the left atrium in the management of rheumatic mitral valve disease. It finds that left atrial ejection fraction is the strongest and most reliable predictor for developing a guideline indication for valve intervention in the subsequent two-years.

Finally, the insights gained in current management, screening, and echocardiographic assessment are placed in the context of previous literature in Chapter 6, before possible directions for future studies on optimising surgical outcomes and longevity of patients with rheumatic heart disease are discussed in Chapter 7.

6 Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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8 Abbreviations

3D	3-Dimentional
ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AHA	American Heart Association
AP	Anteroposterior
AR	Aortic regurgitation
ARB	Angiotensin II receptor blockers
ARF	Acute rheumatic fever
AS	Aortic stenosis
ASD	Atrial septal defect
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BP	Blood pressure
BMI	Body mass index
BMIc	Age and weight corrected body mass index
BMV	Balloon mitral valvuloplasty
BNP	Brain natriuretic peptide
BVF	Bioprosthetic valve failure
CI	Confidence interval
CKD	Chronic kidney disease
cm	Centimetre
CMR	Cardiovascular magnetic resonance
CT	Computed tomography

DBP	Diastolic blood pressure
DPI	Dimensionless pressure index
DVI	Dimensionless index
EACTS	European Association for Cardiothoracic Surgery
ePASP	Estimated pulmonary artery systolic pressure
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
GAS	Group-A streptococcus
GLS	Global longitudinal strain
HbA1c	Haemoglobin A1c
IE	Infective endocarditis
IHD	Ischaemic heart disease
INR	International normalised ratio
IQR	Interquartile range
LA	Left atrium
LA-Bicillin	Long-acting Bicillin (benzathine penicillin G)
LAEDV(i)	Left atrial end diastolic volume (index)
LAEF	Left atrial ejection fraction
LAESV(i)	Left atrial end systolic volume (index)
LIPV	Left inferior pulmonary vein
LSPV	Left superior pulmonary vein
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end diastolic diameter
LVEDP	Left ventricular end diastolic pressure
LVEDV(i)	Left ventricular end diastolic volume

LVESD	Left ventricular end systolic diameter
LVESP	Left ventricular end systolic pressure
LVESV	Left ventricular end systolic volume
MI	Myocardial infarct
mL	Millilitre
mm	Millimetre
mmHg	Millimetre of mercury
MMVD	Mixed mitral valve disease
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MS	Mitral stenosis
MVA	Mitral valve area
MVP	Mitral valve prolapse
MVR	Mitral valve replacement
MVRep	Mitral valve repair
NYHA	New York Heart Association
OR	Odds ratio
PBMV	Percutaneous balloon mitral valvuloplasty
PFO	Patent fossa ovale
PPM	Patient-prosthesis mismatch
PV	Pulmonary vein
RIPV	Right inferior pulmonary vein
RSPV	Right superior pulmonary vein
RV	Right Ventricle
RHD	Rheumatic heart disease
SAVR	Surgical aortic valve replacement

SBP	Systolic blood pressure
SE	Standard error of the mean
SEC	Spontaneous echocardiographic contrast
SVD	Structural valve degeneration
TAVI	Transcatheter aortic valve implantation
THV	Transcatheter heart valve
TR	Tricuspid regurgitation
TOE	Transoesophageal echocardiogram
TVRep	Tricuspid valve repair
VIV	Valve-in-valve
VHD	Valvular Heart Disease
VSD	Ventricular septal defect
WHF	World Heart Federation

9 Thesis Structure

This thesis is the culmination of work based around the management of end-stage rheumatic valvular heart disease. As per the University of Adelaide guidelines, the format of this thesis is ‘expanded publication’. This has allowed a more expansive description of methods, results and discussion than has been included in submitted manuscripts. Given the interrelationship between chapters, an attempt has been made to summarise and reference back to earlier chapters where appropriate.

CHAPTER 1

Management of Rheumatic Heart Disease in the Modern Era

Management of Rheumatic Heart Disease in the Modern Era

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1.1 Statement of Authorship

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Candidate	Dr Ross Roberts-Thomson
Contribution to the Paper	Primary contributor to the conception and design of the work; Drafted the work; Provided final approval of the version to be published; Accountable for all aspects of the work.
Overall percentage	90%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. THE CANDIDATE'S STATED CONTRIBUTION TO THE PUBLICATION IS ACCURATE (AS ABOVE);
ii. PERMISSION IS GRANTED FOR THE CANDIDATE IN INCLUDE THE PUBLICATION IN THE THESIS; AND
iii. THE SUM OF ALL CO-AUTHOR CONTRIBUTIONS IS EQUAL TO 100% LESS THE CANDIDATE'S STATED CONTRIBUTION.

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Contribution to the Paper	Helped revising it critically; Accountable for all aspects of the work

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1.2 Introduction

In assessing the best treatment for young patients with rheumatic heart disease (RHD), physicians must take account of patient preference, the surrounding healthcare environment and availability of resources. Quantifying and comparing the ongoing and cumulative risk of valve interventions over 10 or 20 years is difficult, and over 60 years it becomes almost impossible. Moreover, this assessment is made more complex by the availability of transcatheter techniques and innovations in leaflet technology that prolong the durability of surgical bioprostheses. Herein, we present the concept of cumulative lifetime interventional risk for young patients with RHD, examine strategies to reduce this risk, and review evidence underpinning the current choice (and sequence) of valve intervention.

1.3 Epidemiology and Aetiology

RHD is founded in social disadvantage, associated with poverty, under-employment and overcrowding (Noubiap et al. 2019). In 2017 RHD resulted in approximately 285,500 deaths compared to 144,900 deaths from non-rheumatic valvular diseases (Roth et al. 2018). The primary cause is a hypersensitivity reaction to certain Group-A streptococcal (GAS) species in genetically pre-disposed individuals (Guilherme, Ramasawmy, and Kalil 2007). Often manifesting as acute rheumatic fever (ARF), the accompanying valvulitis primarily damages the left sided heart valves. Over 60% of people with ARF develop RHD, and this progression is more likely in females, especially those who are young at first presentation and have recurrent ARF (Lawrence et al. 2013; Tibazarwa, Volmink, and Mayosi 2008). Remote domicile and distance from the nearest health centre are also independently associated with the

likelihood of developing RHD, adding further complexity to short- and long-term patient management (Okello et al. 2012; Roberts et al. 2015).

The prevalence of RHD is highest in low- and middle-income countries, and particularly high within underprivileged populations in high income countries.(Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, and Mensah 2017) Between 30-43 million people have RHD worldwide, accounting for 0.43% of the total global disability adjusted life years (84.9% of which are due to premature death) (Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, Mensah, et al. 2017). Prognosis is very poor and the Global Rheumatic Heart Disease Registry has demonstrated a median age at death from RHD of 29 years in Africa, Yemen and India (Zühlke et al. 2016). Even in high-income countries like Australia, the mean age at death is only 36 years (Carapetis and Currie 1999).

1.4 Valve Severity Assessment

1.4.1 Specific Difficulties

Although mixed lesions (stenosis and regurgitation) and multiple valve involvement are characteristic, RHD most frequently and severely affects the mitral valve, with evolving pathology over time (typically pure MR in young patients and increasing MS with age) (Zuhlke et al. 2015). The aortic valve is affected in approximately 50% of patients but resulting aortic regurgitation (typically central) is usually mild. Episodes of acute valve inflammation (with accompanying acute regurgitation) can punctuate the course of the disease and may partially recover with medical management alone.

Characterising ‘severe’ valvular pathology is challenging and often defined by parameters associated with poor outcomes with or without surgery – representing, in other words, a late disease state. These observations imply an element of stability of the valve disease that is not always certain. Indeed, rates of RHD progression are highly variable and unpredictable due to inter-individual differences in disease activity as well as variations in access to appropriate care. The application of natural history data from non-RHD cohorts to assess the severity and medium- to long-term prognosis of RHD is therefore inappropriate and access to earlier intervention (especially for primary MR) seems likely to improve outcomes for those with rapidly progressive RHD.

1.4.2 Multivalvular Disease

The assessment of mixed lesions affecting multiple valves is complex, even for experienced physicians, since each lesion creates volume and pressure changes that may be influenced by blood pressure, heart rate, volume loading, and left and right ventricular function (Gisbert et al. 2006). Comprehensive assessment requires use of echocardiographic indices that control for alterations in pressure and volume related to other valve lesions and provide an accurate assessment of lesion severity - Doppler velocity index (DVI) in aortic stenosis (AS), 3D planimetry in MS, and effective regurgitant orifice area (EROA) in MR (Otto 2019; Mannaerts, Kamp, and Visser 2004; Biner et al. 2010). However, characterising the severity of individual lesions may overlook the cumulative burden of multiple valve disease. Moderate mixed aortic valve disease, for example, has similar prognosis to severe isolated AS (Egbe, Poterucha, and Warnes 2016). Nevertheless, the mean gradient provides a

reasonable surrogate for the cumulative haemodynamic impact of mixed pathology affecting a single valve (Waisbren et al. 2008).

Importantly, improved haemodynamics following the correction of a single valve lesion can reduce the haemodynamic consequences of residual valve disease in some patients, notably reduction of secondary MR in patients with AS treated by means of surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) (Waisbren et al. 2008). Accurate assessment of each valve lesion is therefore crucial in the era of transcatheter valve intervention when valves can be treated one at a time without significant additional procedural risk. Beyond echocardiography, multimodality imaging, stress testing and invasive haemodynamic assessment may all provide useful additional information in complex valve disease, especially when symptoms are minimal or absent.(Baumgartner et al. 2017; Nishimura et al. 2017)

1.5 Medical Treatment

Primordial, primary, secondary and tertiary prevention all have a significant role in the management of RHD. From a valvular perspective, the valvulitis / carditis associated with ARF requires acute management. Once RHD is established, the primary aim is to prevent further valvular damage and progression of disease. Finally, managing the sequelae of significant valvular disease becomes the primary concern given the devastating impact this has on both mortality and morbidity.

There is currently no vaccine available for GAS and primordial and primary prevention strategies (including improved standards of living and reduced crowding)

remain the most effective way to reduce the incidence of RHD. Treatment with anti-inflammatories can reduce valve inflammation and the severity of symptoms in the acute phase but do not play a long-term role (Czoniczer et al. 1964; Herdy et al. 1999). Secondary prevention with LA-Bicillin aims to prevent immunological stimulation resulting from further GAS infection and is generally reserved for those with recent ARF, or those with moderate or severe RHD where further valve inflammation and disease progression is likely to impact on morbidity and mortality (Remenyi et al. 2016). The value of continued treatment after valve intervention is unclear, especially in those who have undergone both mitral and aortic valve replacement.

Loop diuretics may provide symptomatic improvement in patients with valvular heart disease but have no impact on mortality. Evidence to support the use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB) or beta-blockers in valvular heart disease has been conflicting. In patients with at least moderate AR, cohort analyses have shown ACEI to reduce the risk of AR-related clinical events and all-cause mortality, whilst a small randomised controlled trial showed no benefit in those with severe asymptomatic AR.(Elder et al. 2011; Evangelista et al. 2005) Guidelines therefore provide only limited recommendations for the use of ACEI and ARB in the management of AR (Baumgartner et al. 2017; Nishimura et al. 2017). Further, beta-blockade in mitral regurgitation or mitral stenosis has also had mixed results and are not currently recommended for patients in sinus rhythm (Slipczuk et al. 2019; Patel, Dyer, and Mitha 1995; Alan et al. 2002).

Mortality of both initial and subsequent interventions is higher in older patients who have reduced LVEF, pulmonary hypertension, end-stage renal failure or coronary artery disease (Onorati et al. 2018). Managing these risk factors throughout a patient's life is therefore crucial. Although clear benefits of smoking cessation, diet and exercise have not been shown in valvular heart disease cohorts, they remain an important treatment target given their overall association with poor prognosis. Careful monitoring and guideline-directed management of blood pressure, cholesterol, renal function and HbA1c are important steps to prevent renal failure, LV dysfunction and coronary artery disease, accompanied by removal of barriers to medication compliance (especially for patients requiring permanent anticoagulation after mechanical replacement).

1.6 Interventional Treatment

The engineering adage that "a structural problem requires a structural solution" holds true for valvular heart disease. Thus, once significant rheumatic valve disease is established, valve intervention is the only treatment.

1.6.1 Timing

Intervention is indicated when the risk is lower than that conferred with continued conservative management. Symptoms, pulmonary hypertension, atrial fibrillation (AF) and reduced LV ejection fraction are all late consequences of severe valve disease and are associated with high peri-operative morbidity and mortality, and poor long-term prognosis (Tribouilloy et al. 1999; Le Tourneau et al. 2010; Enriquez-Sarano et al. 2005; Badhwar, Peterson, et al. 2012). Early surgery provides superior

long-term outcomes to watchful waiting in carefully selected patients with asymptomatic severe valve disease, and these benefits may be particularly relevant in younger patients with RHD, the vast majority of whom undergo initial surgery before the age of 50 years (Kang et al. 2014; Kang et al. 2020; Tornos et al. 2006). Table 1.1 summarises the risk factors that are likely to reduce or remain unchanged due to early intervention in left sided valve replacement surgery.

Table 1.2 summarises the indications for surgery in left sided primary valve disease provided by the 2017 European Society of Cardiology (ESC)/European Association of Cardiothoracic Surgeons (EACTS) guidelines. These recommendations are less specific for mixed or multiple valve disease with greater emphasis on symptomatic status and objective haemodynamic consequences, thereby creating a management conundrum for many younger RHD patients. Whilst guidelines suggest watchful waiting for the development of symptoms, earlier intervention seems likely to provide better long-term outcomes in this cohort (Baumgartner et al. 2017). Screening can facilitate early detection in high-risk populations although the cost-effectiveness of such programmes remains uncertain (Marijon et al. 2007; Roberts et al. 2017).

Reduced Risk	Unchanged Risk
Emergency/Salvage/Unstable Higher NYHA Class Reduced LVEF Pulmonary Hypertension Atrial Fibrillation	Age Renal failure Obesity Ischaemic Heart Disease Infective Endocarditis Diabetes Immunosuppression

Table 1.1: *Impact of Early Surgery on Risk Factors Associated with Death Following Left Sided Valve Replacement*

These risk factors are based on the STS database are not specific to rheumatic heart disease (Mehaffey et al. 2018).

LVEF = left ventricular ejection fraction, NYHA = New York Heart Association.

	Symptoms	LVEF	LVESD	LVEDD	New-PASP	New-AF	Other
AS	✓	<50%			>60mmHg		MaxVel >5.5m/s; high BNP (>3x ULN)
AR	✓	<50%	>50mm	>70mm			
MS	✓				>50mmHg	✓	SEC/LA thrombus; previous embolism; desire for pregnancy
MR	LVEF >30% & >LVESD <55mm #LVEF 30% / LVESD >55mm	30-60%	>45mm	>60mm	>50mmHg	✓	*Flail leaflet; *LAVol >60mLs/m^2

Table 1.2: *2017 ESC/EACTS Guideline Indications for Surgery in Left Sided Primary Valvular Disease*

Green indicates Class I indications for surgery whilst yellow indicated class IIa indications for surgery
*Durable repair likely in low risk patient; # In low risk patient the indication is IIa for likely repair, IIb if unlikely repair
LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVEDD = left ventricular end-diastolic diameter, PASP = pulmonary artery systolic pressure, AF = atrial fibrillation, MaxVel = maximum velocity, BNP = natriuretic peptide, ULN = upper limit of normal, SEC = spontaneous echo contrast, LA = left atrium, LAVol = left atrial volume.

1.6.2 Lifetime Planning

Unfortunately, all treatment options for valve disease are fallible, especially for younger patients with RHD. Historically there have been limited interventional treatment options - balloon valvuloplasty for stenotic lesions in anatomically suitable patients, surgical valve repair or valve replacement – and experience with transcatheter approaches is limited in patients with RHD.

1.6.3 Percutaneous Balloon Mitral Valvuloplasty

Despite increasing prevalence with age, pure MS accounts for less than 10% of patients with RHD. Percutaneous balloon mitral valvuloplasty (PBMV) is a well-established treatment options for the 50% of such patients who have suitable valve morphology and no significant accompanying MR (mitral echocardiographic score ≤8) (Wilkins et al. 1988; Sutaria et al. 2006). Good immediate results are obtained in almost 90% of patients and over 50% of patients improve to New York Heart Association (NYHA) functional class I (Iung et al. 1999). Procedural mortality is <1% in young patients with rates of freedom from surgery of 89%, 68% and 51% at 5, 10 and 13 years, respectively (Chen, Cheng, and Group 1995; Fawzy et al. 2005). Thus, although PBMV is only effective for a small percentage of the total population with significant rheumatic valve disease, the low rates of procedural mortality and need for later surgery make it an ideal option in those selected patients.

1.6.4 Mitral Valve Repair

While mitral valve repair confers mortality benefits in patients with primary (degenerative) MR when compared to valve replacement, these survival advantages are not replicated in RHD cohorts after adjustment for comorbidities, perhaps

reflecting ongoing valve degeneration driven by immune mechanisms (Mohty et al. 2001; David et al. 1993; Russell et al. 2017; Kim, Kim, et al. 2018). Surgical repair for rheumatic mitral valve disease is also associated with higher likelihood of repeat surgery (unadjusted freedom from re-operation at 10 years of 65–81%, 89-96% and 82-92% in reported series) (Choudhary et al. 2001; David et al. 2013; Mohty et al. 2001; David 2007; Sampath Kumar et al. 2006; David et al. 2003; David et al. 2005). Furthermore, surgery performed during an acute episode of ARF is associated with higher short and long-term mortality, and increased likelihood of repeat surgery (Chauvaud et al. 2001). Although mitral valve repair offers no survival advantage compared with valve replacement in RHD, other complications such as bleeding and embolic events are notably lower (Kim, Kim, et al. 2018). Nevertheless, although strongly recommended for rheumatic mitral valve disease when feasible, mitral valve repair still accounts for less than 25% of all rheumatic mitral valve surgery, even in experienced centres (Baumgartner et al. 2017; Nishimura et al. 2017; Yau et al. 2000). To ensure optimal results, valve repair should be performed by experienced surgeons in a ‘Heart Valve Centre of Excellence’ (Chambers et al. 2015). Although rheumatic aetiology remains a contraindication for using MitraClip for repair in MR due to the risk of MS, it has been used in the elderly with less active disease with good results (Wong et al. 2019).

1.6.5 Aortic Valve Disease

The interventional management of aortic valve disease in children and young adults is challenging. Mechanical valves require lifelong anticoagulation and are susceptible to pannus formation while biological valves exhibit accelerated valve deterioration and calcification in younger patients (Walker et al. 1983). Homografts and autografts

are a useful alternative but remain susceptible to rheumatic involvement and cautious use in patients with RHD is advised (Choudhary et al. 1999).

Aortic valve repair provides a durable treatment option for younger patients with significant rheumatic AR, with actuarial freedom from re-operation of 87.5% ± 3.9%, 80.7% ± 4.9%, and 75.3% ± 6% at 5, 10 and 15 years, respectively (Myers et al. 2010). However, valve repair is less durable for adults with rheumatic AR (re-operation rate of 4.26%/patient-year), and is associated with high incidence of late re-stenosis in adults with rheumatic AS (Bozbuga et al. 2004; Shapira et al. 1990). Experience with TAVI is limited in RHD and usually inappropriate in patients with dominant AR and minimal or no aortic annular calcification due to the high risk of embolisation (Bilge et al. 2014; Gunasekaran et al. 2018; Akujuo et al. 2015). SAVR using a bioprosthetic or mechanical valve therefore remains the principal interventional option for rheumatic aortic valve disease in adults.

1.6.6 Valve replacement and choice of prosthesis

There is surprisingly little high-quality evidence to support the almost universal preference for mechanical heart valves in younger patients (ESC/EACTS Guidelines level of evidence C), and very few randomised-controlled trials comparing mechanical and bioprosthetic valves over prolonged follow-up (Table 1.3) (Baumgartner et al. 2017). Importantly, patients under the age of 50 years were severely under-represented in the 3 available studies and none had a pre-specified and appropriately powered subgroup based on age (Oxenham et al. 2003; Hammermeister et al. 2000). Furthermore, information concerning the aetiology of valve disease is only available for one of the studies in which the rates of valve

replacement for rheumatic mitral and aortic valve disease were 94% and 30%, respectively (Oxenham et al. 2003). Unsurprisingly, mechanical valves were associated with lower rates of re-operation and increased frequency of bleeding in these studies with no difference in major embolic complications (Hammermeister et al. 2000; Stassano et al. 2009; Oxenham et al. 2003). Only one study showed any mortality advantage associated with use of a mechanical valve, and this benefit was restricted to those undergoing isolated AVR (Hammermeister et al. 2000).

Time Period	Follow-Up	N	Valve	All-Cause Mortality		Reoperation		Embolism		Bleeding	
				AVR	MVR	AVR	MVR	AVR	MVR	AVR	MVR
1975-1979 (Oxenham et al. 2003)	20 years	472		p=0.57	p=0.41	p<0.0001	p<0.0001	p=0.26	p=0.19	p=0.021	p=0.044
			Mechanical	72% ± 4	78% ± 4	7% ± 3*	13% ± 4*	10% ± 5	18% ± 5	38% ± 7.1*	47% ± 9*
			Bioprosthetic	69% ± 4	82% ± 4	56% ± 8*	78% ± 7*	15% ± 7	10% ± 3	32% ± 13*	10% ± 4*
1977-1982 (Hammermeister et al. 2000)	15 years	575		p=0.02	p=0.3	p=0.004	p=0.15	p=0.66	p=0.96	p=0.0001	p=0.01
			Mechanical	66% ± 3*	81% ± 4	10% ± 3*	25% ± 6	18% ± 4	18% ± 5	51% ± 4*	53% ± 7*
			Bioprosthetic	79% ± 3*	79% ± 4	29% ± 5*	50% ± 8	18% ± 4	18%s ± 6	30% ± 4*	31% ± 6*
1995-2003 (Stassano et al. 2009)	13 years	310		p=0.6		p=0.0003		p=0.3		p=0.08	
			Mechanical	27.5%		0.6%/pt year (0.2–1.1)*		0.5%/pt year (0.1–0.9)		1.5%/pt year (0.8–2.1)	
			Bioprosthetic	30.6%		2.3%/pt year (1.5–3.2)*		0.2%/pt year (0.00–0.5)		0.7%/pt year (0.3–0.2)	

Table 1.3: *Randomised Controlled Trials Comparing Mechanical and Bioprosthetic Valves*

Propensity-matched observational studies have also been reported but should be viewed with caution (de Lemos and Nallamothu 2020). This is because, particularly in cardiac surgery, there is significant selection bias from often unmeasured factors such as frailty which results in a failure to recreate the conditions of a RCT. One such study demonstrated mortality benefits for those less than 70 years of age undergoing mechanical MVR and those less than 55 years of age undergoing mechanical AVR (Goldstone et al. 2017). RCT sub-group and retrospective cohort analyses have also shown high rates of re-operation with bioprosthetic valves after AVR and MVR in patients under 60 and 65 years of age, respectively (Hammermeister et al. 2000; Weber et al. 2012). Furthermore, mechanical valves were associated with lower risk of re-operation and higher risk of bleeding and stroke (but no difference in mortality) compared with biological valves at 15 year follow up in patients aged 50-69 years undergoing isolated MVR, perhaps reflecting higher levels of mechanical stress and immune response in younger patients (Chikwe et al. 2015; Human and Zilla 2001; Z. Konakci et al. 2005). Rates of bioprosthetic valve failure in RHD patients have never been specifically studied. Furthermore, the risk of stroke and bleeding complications may be elevated in RHD patients with mechanical valves since optimal anticoagulation may be more difficult to achieve in regions with high RHD prevalence (Oldgren et al. 2014; Badhwar, Ofenloch, et al. 2012).

Valve selection is particularly complex in young women. A large historical cohort study has shown that pregnancy in RHD is associated with a complication rate of 21.4% (primarily driven by heart failure) and maternal mortality of 1.6% (Avila et al. 2003). Biological valves have obvious advantages in this situation (with no acceleration of degeneration during

pregnancy) whilst mechanical valves offer greater durability but are associated with high rates of termination, thromboembolic complications, maternal death, and warfarin complications including foetal toxicity (Sadler et al. 2000; De Santo et al. 2005). Ultimately these complex decisions should involve the patient under the guidance of a multidisciplinary cardiac and obstetric team.

1.6.7 Multivalve Surgery

Simultaneous surgery on multiple valves adds substantial risk to the procedure and increased likelihood of post-operative complications. In the German Society for Thoracic and Cardiovascular Surgery registry, the unadjusted in-hospital mortality rates for isolated aortic or mitral valve surgery were 4.1% and 7.4%, respectively, compared with 11.2% for combined aortic and mitral and valve surgery,(Beckmann et al. 2017) whilst in-hospital mortality triple valve surgery approaches 13% (Ohmes et al. 2017). Although repair procedures reduce this risk compared to triple valve replacement, in-hospital mortality remains high (Leone et al. 2018). Similarly, in series focusing on RHD, in-hospital mortality following combined mitral and tricuspid repair was almost double that of isolated mitral valve repair (Bernal et al. 1993). Furthermore, transcatheter approaches may not necessarily improve these outcomes. In the German transcatheter mitral valve interventions registry, 30-day mortality after MitraClip implantation in patients with a previous AVR (TAVI or SAVR) was 10.6%, albeit in a high-risk cohort. This data demonstrates the high surgical risk nature of multivalvular surgery, especially mitral valve surgery, and importance of reducing surgical risk.

1.6.8 Reintervention

Consideration of the potential options for future repeat procedures is essential at the time of initial valve intervention, particularly in younger patients. Age is clearly the strongest predictor of the future need for multiple valve interventions and rates of repeat intervention are increasing by approximately 10% per year as people with valvular disease are living longer (Mehaffey et al. 2018). Among those who survive, patients most likely to need 3 or more operations are those who have their first or second procedures before the ages of 45 or 56 years, respectively (Haydock et al. 2017). This consideration is therefore particularly relevant for RHD patients who have an average age of 22 years at the time of their first valve procedure (Rusingiza et al. 2018). Repeat surgery is associated with higher short- and long-term mortality, particularly in RHD populations who have a mean time to repeat surgery of only 6 years (Mehaffey et al. 2018; Keenan et al. 2019). Table 1.4 demonstrates the vast variation in outcomes of RHD patients following mitral valve surgery in sizeable studies (>200 procedures) with a minimum of 5-year follow-up.

Paper	Year	Country	MV Surgery	N	Age (years)	In-hospital mortality	Survival				Freedom from reoperation			
							5 yr	10 yr	15 yr	20 yr	5 yr	10 yr	15 yr	20 yr
Kim et al.	1997-2015	South Korea	Repair	294	44 ± 14	1.7%			57.6%				81.9%	
			Bio	303	52 ± 10	4.3%			29.2%				46.2%	
			Mech	1134	60 ± 13	6.6%			55.1%				96.5%	
Yau et al.	1978-1995	Canada	Repair	142	42 ± 1	0.7%	96.5%	88.2%			87%	72%		
			Bio	162	61 ± 1	5.6%	83%	70%			91%	69%		
			Mech	269	56 ± 2	5.2%	88%	73%			96%	95%		
Kumar et al.	1988-2003	India	Repair	610	22 ± 10	3.6%	93.8%	92%			95.5%	81.0%		
Chauvaud et al.	1970-1994	France	Repair	951	26 ± 18	2%		89%		82%		82%		55%
Yakub et al.	1997-2010	Malaysia	Repair	627	32 ± 19	2.4%	99.7%	98.1%			91.8%	87.2%		
Bernal et al.	1975-1990	Spain	Repair	327	45 ± 13	3.4%			78.1%				89.9%	
Gillinov et al.	1975-1998	USA	Repair + AVR	295	61 ± 13	5.4%	79%	63%	46%		97%	89%	75%	
			MVR + AVR	518	60 ± 13	7.0%	72%	52%	34%					
Talwar et al.	1995-2005	India	Bio + bAVR	293	33 ± 11	8.5%	81.6%				99.5%			
Panda et al.	1992-2006	India	Mech + mAVR	382	36 ± 12	4.2%	88%	74%	41%					
Ho et al.	1992-2001	Vietnam	Mech + mAVR	408	38 ± 9	0.7%		89.7%				89.7%		
Han et al.	1985-2005	China	Mech+ mAVR + TVRep	871	42 ± 11	8%	71%	59%				91%		

Table 1.4: *Differences in Survival and Reoperation Rates among Patients with Rheumatic Heart Disease Undergoing Mitral Valve Surgery*

MV = mitral valve, N = number of participants, yr = year, Bio = bioprosthetic, Mech = mechanical, AVR = aortic valve replacement, bAVR = bioprosthetic AVR, mAVR = mechanical AVR, TVRep = tricuspid valve repair.

Options for repeat valve intervention include redo sternotomy with valve re-repair or replacement, minimally invasive surgical approaches, or transcatheter valve-in-valve (VIV) or valve-in-ring (VIR) implantation. Transcatheter VIV and VIR procedures appear to have similar short-term outcomes to re-do valve surgery despite considerably higher pre-operative surgical risk (Kamioka et al. 2018; Neupane et al. 2018). Rates of pacemaker implantation are notably lower after aortic VIV implantation compared to re-do SAVR, and rates of patient-prosthesis mismatch (PPM) – which may be an issue due to annular constraint and underexpansion - are no higher than after re-do SAVR (are up to 33% in some studies) (Pibarot et al. 2018; Reardon et al. 2017). Whilst some newer surgical valves incorporate an expandable annular ring to avoid PPM following transcatheter VIV implantation, percutaneous valve cracking is also an option to reduce the risk of PPM for older valves (Chhatriwalla et al. 2017).

1.7 A Lifetime of Cumulative Risk

Predicting the risk of mortality, need for repeat intervention and major morbidity (including bleeding, stroke and heart failure) for an individual patient over a 20-60 year period is extremely difficult using available data. Rates of valve failure are significantly higher in younger populations undergoing valve repair or bioprosthetic valve replacement and may be influenced by ongoing risk of ARF or sub-clinical carditis in those with RHD.

Whilst PBMV or mitral valve repair are the preferred management options for rheumatic mitral disease, they are only applied in a small proportion of patients on account of anatomical considerations and resource limitations (Zühlke et al. 2016). The majority of young patients with RHD who require intervention therefore undergo mechanical valve replacement. Pregnancy in a patient with a mechanical mitral valve is associated with rates of survival, or freedom from stroke or any valve-related event of 94%, 61%, 33%, respectively at 10 year follow up (Vural et al. 2003). Biological valve replacement and subsequent transcatheter VIV implantation may provide a better alternative and mitigate the risk of repeat sternotomy.

The cumulative impact of sequential interventions needs to be accounted for when assessing overall risk for an individual patient. Current methods to evaluate risk in valvular heart disease interventions focus primarily on the inpatient or 30-day complications including death and stroke (Ad et al. 2016). For younger patients who operative risk is relatively low there is no current method of assessing 5 or 10 year risk, especially the cumulative risk of multiple procedures. Figure 1.1 demonstrates the theoretical cumulative lifetime risk of reintervention and death a 17 year old may face if they require mitral and aortic valve intervention. Beyond the risk of repeat intervention or death, assessment must also take account of substantial morbidity, including non-fatal major strokes, bleeding and heart failure, within the context of the individual patient's medical, socio-economic and geographical background, and available healthcare resources.

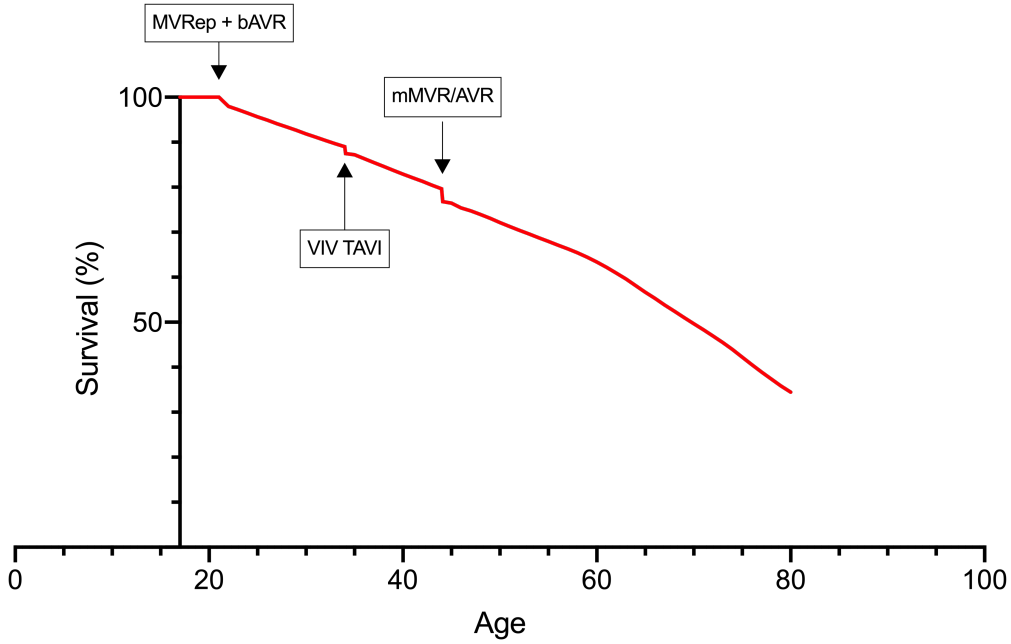

Figure 1.1: *Hypothetical Cumulative Risk Over a Lifetime of Valve Interventions*

MVRep = mitral valve repair, AVR = aortic valve replacement, VIV TAVI = valve-in-valve transcatheter aortic valve replacement, mMVR/AVR = mechanical mitral and aortic valve replacement

1.8 Role of Screening

Although its incidence is highest among children, ARF can occur at any age (Lawrence et al. 2013; Tibazarwa, Volmink, and Mayosi 2008; De Angelis et al. 2019). RHD screening in asymptomatic at risk populations has high yield but may not be cost-effective (Remenyi et al. 2012; Roberts et al. 2014; Ubels et al. 2017; Roberts et al. 2017). Australian and Brazilian studies have primarily focused on the ability of secondary prevention to prevent progressive valve disease and need for hospital admission. Regional variation in RHD prevalence and the cost of hospitalisation for acute episodes of ARF, heart failure or surgery mean that universal uptake of screening is

unlikely in the short-term. Alternative screening models could assist in the delivery of more sustainable programmes through lower costs and greater access (Engelman et al. 2016).

Whilst the primary measure of its effectiveness is prevention of RHD progression and reduced need for surgery, screening also allows early diagnosis and access to surgery for patients who meet criteria for valve intervention (many of whom may have minimal or no symptoms). Over time, this strategy would seem likely to substantially reduce the morbidity and mortality associated with valve intervention and contribute to the overall cost-effectiveness of screening programmes.

1.9 Early Markers of Valve Failure

The differentiation between severe valve disease *per se* and severe valve disease needing intervention is crucial. Thus, the ideal indicator would reliably predict poor survival without intervention (or the onset of factors associated with poor outcomes), without itself being associated with elevated procedural risk.

Brain natriuretic peptide (BNP), also known as B-type or ventricular natriuretic peptide, is released by cardiac myocytes in response to myocardial stretch resulting from pressure or volume overload, and predicts future symptoms in patients with valvular heart disease (Mukoyama et al. 1990; Suga et al. 1992; Pizarro et al. 2009; Bergler-Klein et al. 2004). However, an elevated BNP is

also associated with LV dysfunction and greater mortality and morbidity following mitral or aortic valve intervention (Magne et al. 2012; Bergler-Klein, Gyöngyösi, and Maurer 2014). Serial BNP monitoring in patients with valvular heart disease is therefore best used as a predictor of adverse outcomes rather than as an independent indicator for intervention (Klaar et al. 2011). AS remains the only valve disease for which elevated BNP is a IIa indication for surgery (Ozkan 2017; Nishimura et al. 2017).

Certain echocardiographic parameters (reduced left or right ventricular function and increased left atrial [LA] size) are associated with higher post-operative mortality in patients with MR undergoing valve replacement (Reed et al. 1991; Borer, Hochreiter, and Rosen 1991). Impaired LV global longitudinal strain is also associated with poor outcomes following intervention in patients with valvular heart disease, while impaired LA function is associated with higher rates of AF but no associated morbidity or mortality (Alashi et al. 2016; Mascle et al. 2012; Lafitte et al. 2009; Kim, Cho, et al. 2018; Alashi et al. 2020; Cameli et al. 2014).

1.10 Case Scenario

A 24-year-old woman is referred for a second opinion. She has New York Heart Association (NYHA) Class II symptoms and her echocardiogram shows moderate-severe rheumatic mitral stenosis (MS) and moderate mitral regurgitation (MR), with mild left ventricular (LV) dilatation (ejection fraction 60%). She has been advised that she should have a mechanical mitral valve

replacement but has concerns about the risk of stroke with two mechanical valves, as well as the difficulties of managing potential future pregnancies. She asks about other management strategies for her valve disease and whether current or future technologies may help her.

Physicians must take account of patients' wishes and the availability of resources when assessing the best treatment strategy for young patients with rheumatic valve disease. Quantifying and comparing the ongoing and cumulative risk of sequential valve interventions over 10 or 20 years is difficult, and almost impossible over 60 years. Furthermore, recent advances including transcatheter techniques and technologies to reduce valve degeneration have added complexity to this assessment.

Given the onset of mild symptoms, early LV dilatation and intended pregnancy, mitral valve repair (if anatomically feasible) and biological AVR would be a reasonable alternative to two mechanical valves for our patient. In her 20s, a biological AVR (with internal leaflets, and an expandable ring) would have a 50% freedom from operation of approximately 13 years and would therefore be likely to fail before the mitral repair. In her 30s and 40s, a VIV TAVI may then be a suitable option to delay surgery until the need for mitral and aortic valve replacement, thereby allowing her to avoid anticoagulation throughout her reproductive years. Lifelong LA-Bicillin prophylaxis would remain essential throughout.

1.11 Summary

RHD typically afflicts young women and frequently causes mixed multiple valve disease. Early intervention before the onset of irreversible left and right ventricular impairment is associated with improved long-term survival but current guidelines do not provide clear indications for referral. Earlier detection by means of screening, prompt diagnosis and access to specialist care are essential in reducing a lifetime of risk, especially in the context of mixed valvular disease.

The number of patients with suitable anatomy for PBMV or mitral valve repair is limited, and the role of transcatheter aortic and mitral interventions has not been evaluated in rheumatic populations. Many young patients (including women of childbearing age) therefore require surgical valve replacement. Assessment of the cumulative risk of death and need for re-intervention over the lifetime of an individual patient is complex and requires a tailored approach. This is a challenge for Heart Teams even when the full spectrum of modern cardiac care is available. The demographics, remoteness and health literacy of patients with RHD makes management of their valvular disease especially difficult. Lifelong planning of valve intervention is an essential element of decision-making and transcatheter technologies should be progressively incorporated alongside conventional surgery in contemporary management pathways.

CHAPTER 2

Concordance Between Practice and Guidelines in Rheumatic Mitral Valve Disease

Concordance Between Practice and Guidelines in Rheumatic Mitral Valve Disease

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Candidate	Dr Ross Roberts-Thomson
Contribution to the Paper	Primary contributor to the conception and design of the work; Drafted the work; Provided final approval of the version to be published; Accountable for all aspects of the work.
Overall percentage	90%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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2.2 Abstract

***Background*:** Rheumatic heart disease (RHD) affects young individuals from impoverished communities, whose median life expectancy is between 28 and 36 years. The barriers to intervention are complex but contribute to the high morbidity and mortality associated with RHD. The rates of guideline indicated intervention in patients with significant rheumatic valvular disease have not yet been reported.

Methods: 154 patients (mean age 38.5 ± 14.6, 66.1% female) with significant rheumatic mitral valve disease were identified from the Northern Territory Cardiac Database who fulfilled at least one AHA/ACC guideline indication for mitral valve intervention. Baseline clinical status, comorbidities, indication for intervention, referral and any interventions were recorded.

***Results*:** Symptoms, atrial fibrillation and pulmonary hypertension were the most common indications for surgery (74.5%, 48.1%, 40.9%). The median number of indications were 2 (range 1 - 5). 74 subjects (48.1%) had intervention on their mitral valve within two years of their surgical indication. 86% of referred and accepted patients received intervention. Multivariable analysis demonstrated that age and previous valvuloplasty were independently associated with future surgical intervention (Adj OR 0.95, 95% CI 0.91 - 0.98, *p=0.006*; Adj OR 2.9, 95% CI 1.00 – 8.2, *p=0.045*). The rates of accepted referral for patients with class I indications were 72.5% ± 4.2% while class IIa indications were 42.5% ± 9.0% (*p<0.001*).

***Conclusions*:** Among a young cohort of patients with significant rheumatic mitral valve disease who met AHA/ACC guideline indications for intervention, 52.6% received surgery or valvuloplasty within two-years at a single centre. A 30% difference in referral rates were found between Class I and Class IIa indications for valvular intervention.

2.3 Introduction

Rheumatic heart disease (RHD) affects between 30 and 43 million people globally, mostly from impoverished communities (Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, Mensah, et al. 2017). The valvular pathology of RHD is often complex and mixed mitral valve disease predominates (Remenyi et al. 2016). Morbidity and mortality are usually caused by heart failure, atrial fibrillation, pulmonary hypertension, stroke or infective endocarditis (Zuhlke et al. 2015; Remenyi et al. 2016). Surgical or percutaneous valve intervention remains the only robust treatment (Nishimura et al. 2017). Early surgery is associated with superior clinical outcomes and surgical delays can contribute to morbidity (Kang et al. 2014; Vincens et al. 1995; Tribouilloy et al. 1999).

Expected age of death for people with RHD varies greatly. However, without surgery it is rarely greater than 40 years (Gunther, Asmera, and Parry 2006). In low and middle income countries the median age of death is 28 years (Zühlke et al. 2016). Patients' baseline comorbidities, the type of and number of valve interventions also play a role in their long-term prognosis (Hernandez et al. 1999). Barriers to health care are multifactorial and differ considerably between regions (Harris et al. 2011; Peiris, Brown, and Cass 2008). In Australia, over 90% of cases affecting Indigenous people are outside major cities or inner regional centres (Katzenellenbogen et al. 2020). Although these barriers are acknowledged, they have not been quantified previously in RHD cohorts where they are likely to be significant.

Concordance between practice and established guidelines for mitral valve disease are known to be poor for Class I indications (Iung et al. 2019). In non-rheumatic populations, factors associated with a lower likelihood of surgery are advanced age, higher comorbidities and lower left ventricular ejection fraction (LVEF) (Mirabel et al. 2007). The rates of intervention for patients with guideline indicated surgery have not yet been studied in a rheumatic population.

This study aims to examine the rate of surgical intervention after two years from the onset of a surgical indication and the concordance between accepted referral and guideline recommendations for intervention in the Northern Territory, Australia.

2.4 Methods

2.4.1 Patients

A database search of 104,550 consecutive echocardiograms performed in the Northern Territory identified patients between 2007 and 2017 with at least progressive mitral regurgitation (MR), mitral stenosis (MS) or both. Patients aged 18 years or over at the time of the study with native valves were included. Consultation letters were then used to determine clinical indications for surgery. Those with an indication for surgical or percutaneous intervention were included. 11 had inadequate clinical data and were excluded. Severe aortic stenosis (AS) was found in three patients who were subsequently excluded. The study was approved by the Human Research Ethics

Committee of the Northern Territory Department of Health and Menzies School of Health Research. Individual patient consent was not obtained for this study.

2.4.2 Data Collection

The database was searched using the following criteria: free text search with the words “moderate” or “severe” with “mitral regurgitation” or “mitral stenosis” or “MR” or “MS”, mean mitral gradient >5mmHg, mitral valve area (MVA) <1.5cm^2, and effective regurgitant orifice area (EROA) >0.2cm^2.

2.4.3 Echocardiographic Assessment

The majority of echocardiograms were performed in remote communities using Vivid *q* or Vivid *i* (GE Healthcare, Freiburg, Germany). Images were acquired by sonographers who regularly work in areas with a high prevalence of RHD. All echocardiograms were re-reported from raw images by two blinded Cardiologists with expertise in echocardiography for the purposes of the study. The age, height and weight of the patient were provided to the reporting cardiologist. The cardiologist was blinded to any other information including any clinical information or the previous echocardiogram report. Severity of valvular disease was based on the 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines (Nishimura et al. 2017). Significant mitral valve disease was defined as progressive or severe MR or MS.

2.4.4 Surgical Indications

The AHA/ACC valvular guidelines were used to define surgical indications including dyspnoea, new-onset atrial fibrillation (AF) or estimated pulmonary arterial systolic pressure (ePASP) ≥50mmHg (Nishimura et al. 2017). Other surgical indications that were included as part of the analysis were: severe MR with left ventricular end-systolic diameter (LVESD) >40mm and/or LVEF 30-60%; and severe aortic regurgitation (AR) with LVESD >50mm, or LVEF <50%. Physician referral for surgery was not considered a guideline indication for surgery for the purposes of this study, however, these patients were included in the time from referral to intervention analysis as well as intervention type.

2.4.5 Statistical Analysis

Binary variables were compared using a Pearson Chi Squared analysis while continuous, normally distributed variables were analysed by unpaired parametric t-test. Multivariable analyses were performed using binary logistic regression. Variables with significant confounding were removed (left ventricular end diastolic diameter (LVEDD) Class II). Kaplan-Meier curves (1-survival) were used to illustrate time to referral or intervention. Log-rank Kaplan-Meier curves were used to compare time from referral to intervention by type of intervention. All curves included censoring for death and patients lost to follow-up. Data from this study were analysed using SPSS v25.(Corp)

2.5 Results

A total of 154 patients (mean age 38.5 ± 14.6, 66.1% female) with significant rheumatic mitral valve disease and a surgical indication were included in the baseline data. Table 2.1 demonstrates the differences in patient characteristics at baseline between those who did and did not undergo valve intervention. Symptoms, AF, and pulmonary hypertension were the most common indications for surgery (74.5%, 48.1%, 40.9% respectively). The median number of indications was 2 (range 1 - 5).

Table 2.1 demonstrates factors that were associated with having an intervention within two years. Multivariable analysis demonstrated that younger age (Adj OR 0.95, 95% CI 0.91 – 1.0, *p=0.04*), previous valvuloplasty (Adj OR 2.9, 95% CI 1.0 – 8.1, *p=0.04*) and greater LVESD (Adj OR 1.7, 95% CI 1.0 – 2.7, *p=0.03*) were independently associated with surgical intervention [Table 2.2]. Among those who had a previous valvuloplasty and did not undergo intervention, 10 (50%) were over the age of 40 years causing the association with intervention to change from a negative to positive once adjusted for age. The type and number of indications associated with referrals and intervention are shown in Table 2.3.

Concordance between practice and class I indications for valvular intervention was 72.5% ± 4.2% within two years (Nishimura and Otto 2014). The number of indications for each patient did not appear to change the accepted referral rate, however there was a 30% difference in the accepted referral rate between those patients with Class I and Class IIa indications (Class I 72.5% ± 4.2%, Class IIa 42.5% ± 9.0%, *p<0.0001*).

	No Intervention (85)	Intervention (69)	p value (mean difference)
Age (years)	42.3±15.2	32.9 ±12.3	<0.001 (9.36; 95% CI 4.88, 13.83)
Female	70.6% (60)	62.3% (43)	0.28
IHD	3.5% (3)	8.7% (6)	0.17
Symptomatic	70.2% (59)	79.7% (55)	0.18
AF	54.1% (46)	40.6% (28)	0.09
Diabetes	20.0% (17)	10.1% (7)	0.09
CKD	11.8% (10)	5.8% (4)	0.20
Smoker	31.8% (27)	33.3% (27)	0.84
Pregnant	4.7% (4)	7.2% (5)	0.45
Previous PBMV	23.5% (20)	10.3% (7)	0.033
Charleston Score	1.8 ± 1.5	1.2 ± 1.1	0.007 (0.61; 95% CI 0.17, 1.04)
Number of Indications	1.8 ± 0.9	2.1 ± 1.0	0.14 (-0.24; 95% CI -0.55, 0.08)
Class I indication	72.9% (62)	87.0% (60)	0.033
Class 2 (no Class I)	39.1% (9)	77.8% (7)	0.049
ePASP >50mmHg	37.6% (32)	44.9% (31)	0.36
Previous Stroke	5.9% (5)	0.0% (0)	0.04
Infective Endocarditis	3.6% (3)	4.4% (3)	0.80
MR & LVESD >4	3.5% (3)	15.9% (11)	0.008
MR & LVEF<60%	11.8% (10)	17.4% (12)	0.32
Isolated MS	16.5% (14)	14.4% (10)	0.83
Isolated MR	15.3% (13)	26.1% (18)	0.09
MMVD	68.2% (58)	59.4% (41)	0.21
LVEF (%)	56.4 ± 8.9	56.5 ± 11.9	0.94 (-0.1; 95% CI -3.5, 3.2)
LVEDD	4.8 ± 0.6	5.1 ± 0.8	0.001 (-0.38; 95% CI -0.61, -0.15)
LVESD	3.1 ± 0.8	3.6 ± 0.9	0.002 (-0.42; 95% CI -0.68, -0.15)

Table 2.1 *Patient Characteristics and Echocardiographic Parameters Among Patients with an Indication for Mitral Valve Intervention*

IHD = ischaemic heart disease; AF = atrial fibrillation; CKD = chronic kidney disease stage II-V; PBMV = percutaneous balloon mitral valvuloplasty; ePASP = estimated pulmonary artery systolic pressure; MR = mitral regurgitation; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; MS = mitral stenosis; MMVD = mixed mitral valve disease; LVEDD = left ventricular end-diastolic diameter.

	Adj. OR	95% CI	Significance
Age (yrs)	0.95	0.91-1.00	0.04
Class I	0.64	0.22-1.86	0.41
Charleston Score	1.13	0.67-1.90	0.65
Previous Stroke	0.40	0.07-2.19	0.29
Previous PBMV	2.88	1.03-8.09	0.04
LVESD (cm)	1.68	1.04-2.73	0.03
AF	1.04	0.45-2.39	0.93
Diabetes	1.56	0.48-5.04	0.46

Table 2.2: *Adjusted Odds Ratios for Factors Associated with Mitral Intervention within Two Years from Indication*

PBMC = percutaneous balloon mitral valvuloplasty; LVESD = left ventricular end-systolic diameter.

	Class 1 Indication(s)			Class IIa Indication(s) only (32)
	All (122)	1 Indication (38)	≥ 2 Indications (84)	
Referred (SE)	72.5% ± 4.2%	76.1% ± 7.4%	70.9% ± 5.1%	42.5% ± 9.0%*
Intervened (SE)	57.1% ± 4.8%	56.7% ± 9.0%	57.3% ± 5.7%	36.0% ± 9.6%*

Table 2.3: *Accepted Referral/Intervention Concordance with ACC/AHA Guidelines by Mitral Indication Class*

Class I category includes those with at least one Class I indication. Class IIa excludes those with a Class I indication. * = Significant difference (P<0.001) when compared to Class I indications.

Within two years from the onset of a surgical indication, 46.5% (73/157) of patients had intervention on their mitral valve [Figure 2.1]. Referrals were made and accepted for 62.4% (98/157) of patients within two years of a surgical indication (actuarial freedom from referral of 63.1%). Among the patients who developed a guideline indication for surgery and were referred, the median time to referral was 2.9 months (IQR 0.5 – 12.4 months). The median time from referral to intervention for all patients who underwent intervention was 3.9 months (IQR 1.5 – 8.0 months). Actuarial freedom from intervention following referral within two years was 15.7% [Figure 2.2]. Among the 74 procedures, four (5.4%) were referred without class I or IIA indication for intervention. These referrals were all based on a new increase in ePASP on echocardiography to 40-49mmHg.

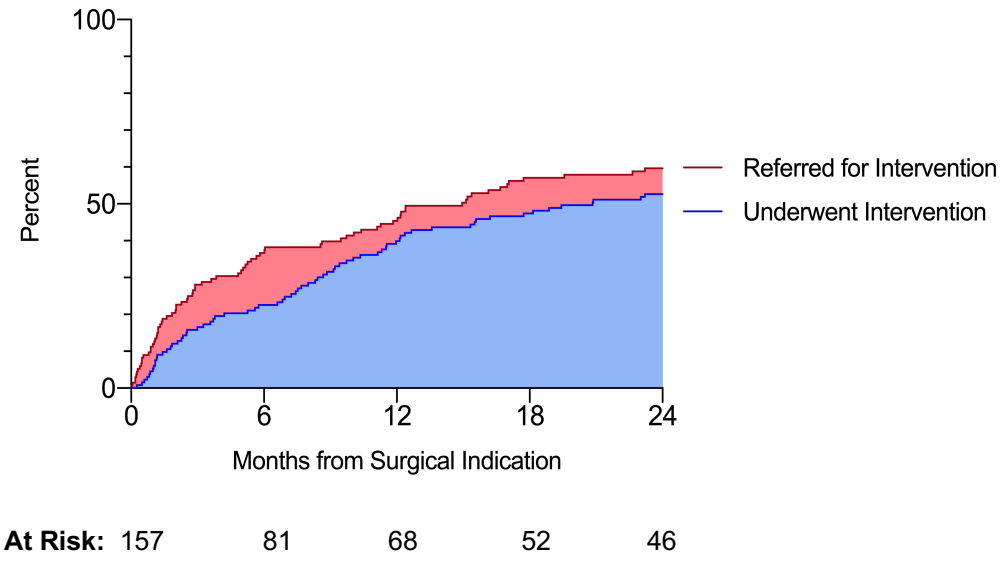

Figure 2.1: *Rates of Referral and Valve Intervention for Patients with Guideline Indications for Rheumatic Mitral Valve Surgery*

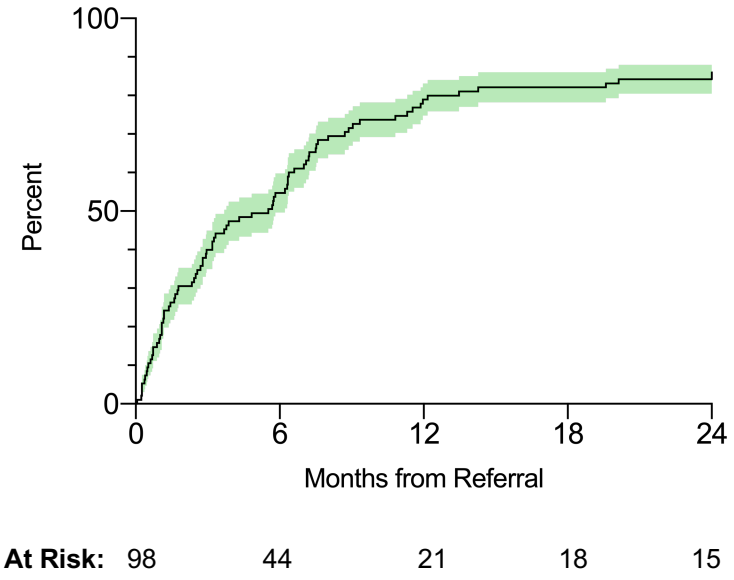

Figure 2.2: *Time from Accepted Referral to Valve Intervention in Patients with Rheumatic Mitral Valve Disease*

Percutaneous balloon mitral valvuloplasty (PBMV) procedures accounted for 18.9% of all interventions, with repair being undertaken in 27.1% of all operations [Table 2.4]. The most common additional procedure with surgery was an aortic valve replacement (AVR) in 16.8% of cases. A maze procedure was only undertaken in one case. The interventions for patients without a referral were not significantly different from those with a referral (one PBMV, one mitral valve (MV) repair, one bioprosthetic mitral valve replacement (MVR) and one mechanical MVR). There was no significant difference in the freedom from intervention from indication or time of accepted referral based on intervention type (*p = 0.16, p=0.8 respectively*) [Figure 2.3].

MV Intervention (73)	PBMV	Repair	Bioprosthetic	Mechanical	Total Operations
	18.9% (14)	21.6% (16)	24.3% (18)	35.1% (25)	80.8% (59)
+ AVR		6.3% (1)	16.7% (3)	24.0% (6)	16.8% (10)
+ TV Repair		6.3% (1)	16.7% (3*)	20.0% (5)	15.3% (9)
+ CABG		6.3% (1)	5.5% (1)	8.0% (2)	6.8% (4)
+ Other		PFO closure (1)	ASD Closure (1)	PFO + maze (1)	5.1% (3)

Table 2.4: *Type of Mitral Valve Intervention and Associated Surgery*

MV = mitral valve; PBMC = percutaneous balloon mitral valvuloplasty; AVR = aortic valve replacement; TV = tricuspid valve; CABG = coronary artery bypass grafts. *Includes one tricuspid replacement using bioprosthetic valve

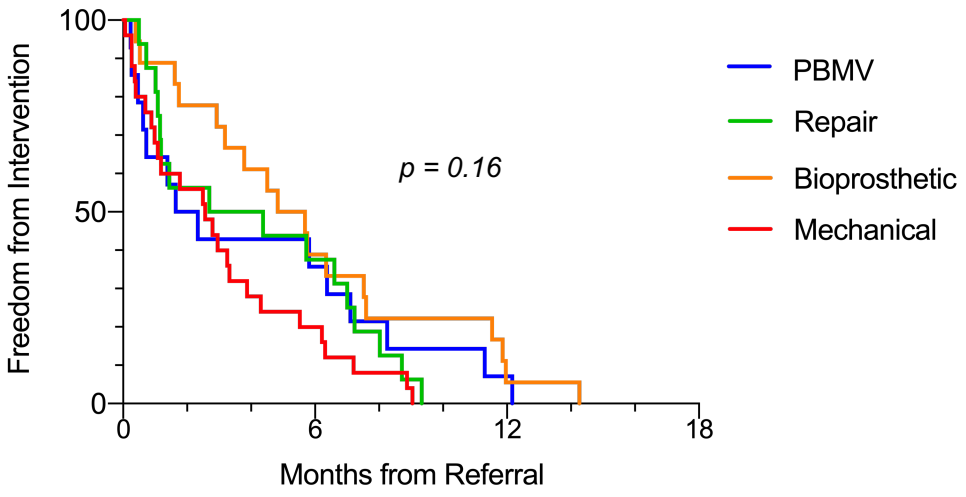

Figure 2.3: *Freedom from Intervention Following Accepted Referral by Type of Mitral Intervention*

2.6 Discussion

This is the first study to examine the rates of surgery in rheumatic mitral valve disease and the surgical waiting time. This study showed that in a comparatively young cohort of patients from predominantly remote communities, referrals for mitral valve intervention were low. In those who were referred however, the time to referral and intervention was comparatively short. There are likely significant barriers to referral in patients with rheumatic mitral valve disease.

Factors associated with a reduced likelihood of referral despite guideline indication in non-rheumatic MR populations have been found to be age, higher comorbidities and lower LVEF (Mirabel et al. 2007). Patients with RHD tend to be significantly younger than those with non-rheumatic valvular heart disease (VHD). Age as an independent predictor of surgery is consistent with other studies. It would be reasonable to conclude that patients who have had a previous PBMV are more likely to both be accepting of a procedure and also be considered suitable for intervention by a multidisciplinary cardiac team. The independent association with LVESD, but not LVEF was a surprising finding and has not been reported elsewhere. Beyond clinical, echocardiographic and comorbidity measures, the low rates of referral likely reflect patient wishes, cultural factors, and implicit bias.

There have been no studies to date assessing concordance between indications and practice for valvular intervention in RHD patients. A single European study of inpatients with severe symptomatic MR showed that

among those referred for surgery under 50 years of age, 63% were accepted (Mirabel et al. 2007). Primary MR is often undertreated in the community and associated with higher than expected mortality (Dziadzko et al. 2018). A recent study including both outpatients and inpatients with valvular heart disease has shown that North African patients (72% rheumatic) had a surgical rate of 25.9% after 6 months with planned intervention in a further 19.6% (Iung et al. 2019). The comparison with a 6 month versus two-year follow-up is difficult, however, these also appear to be in line with the findings of our study. The low referral rate for Class IIa indications compared with Class I indications has not previously been demonstrated. The 30% difference in concordance between practice and guidelines is not unexpected acknowledging the difference in weight of the recommendation by guideline authors. This is the first time that the real difference of clinical responses to Class I and Class IIa recommendations has been quantified and this should be taken into account when attributing the weight of any recommendation by future guideline authors.

Early surgery has consistently been shown to provide superior long-term outcomes to watchful waiting in those with asymptomatic severe valvular disease and no guideline indication for surgery (Kang et al. 2014; Kang et al. 2020; Tornos et al. 2006; Tribouilloy et al. 1999). Conversely, the period of time allowed to safely watch these patients is unclear and unnecessary valve surgery exposes individuals to avoidable harm. The median time from indication to accepted referral of 2.9 months appears favourable although comparative data is lacking.

There are few published studies on elective waiting times for valve surgery. Median wait times for aortic stenosis surgery in Canada have previously been shown to be 8.0 months (IQR 4.9 – 13.1 months) (Munt et al. 2006). One small Ugandan study showed that when surgery was performed by visiting NGOs, patients with predominantly RHD and heart failure had a waiting period of 10 months (IQR 6 – 21 months) however this comparison is difficult due to the differences in resource availability and visitation schedules. In Australia, patients with RHD are overwhelmingly Aboriginal with a low socioeconomic status (Brown, McDonald, and Calma 2007: 557). These factors are associated with longer surgical waiting times. However, there has been no published comparison of RHD to non-valvular waiting times to date (Pell et al. 2000; Health and Welfare 2018). Further, the referral centre is over 2500 kilometres from the surgical centre in this study and thus, patients are recommended to bring a family member along, both factors adding complexity to surgical planning. As RHD disproportionately affects those from remote communities, this reflects logistical difficulties found around the world. Acknowledging this, the median time from accepted referral to intervention of 3.9 months appears to be acceptable. Skin and oral infections are common in remote Aboriginal communities in the Northern Territory and are required to be treated before valvular surgery which can prolong the time from referral to surgery (Roberts-Thomson, Spencer, and Jamieson 2008; Hengge et al. 2006).

2.6.1 Limitations

This data is from the Northern Territory of Australia which has among the world's highest rates of RHD within remote Aboriginal communities (Roberts et al. 2015). Non-standardized follow-up may have impacted referral rates for surgery. There were not enough cases to investigate the temporal differences in intervention type or delays. The reasons for patients being censored or lost to follow-up within the two-year follow-up period were unknown. Although no studies to date have shown any benefit from medical therapy in mitral valve disease, this may have impacted patient outcomes and was not recorded.

2.7 Conclusion

This study shows that in patients with rheumatic mitral valve disease, the rate of intervention after two-years was approximately 52.6%. This indicates that there are substantial barriers to valvular treatment for relatively young patients with RHD which warrants further research. The 30% difference in accepted referral rates between Class I and Class IIa surgical indications should be taken into account by guideline authors when attributing weight to their recommendations. Patients who were ultimately referred and accepted were done so promptly and waiting periods for mitral valve intervention were low despite patients being from predominantly remote locations.

CHAPTER 3

The South Australian Childhood Rheumatic Heart Disease Screening Project (SACRHD)

The South Australian Childhood Rheumatic Heart Disease Screen Project (SACRHD)

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3.1 Statement of Authorship

Manuscript details

Title of paper	*The South Australian Childhood Rheumatic Heart Disease Screening Project (SACRHD)*
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Principal Author Contributions

Candidate	Dr Ross Roberts-Thomson
Contribution to the Paper	Primary contributor to the conception and design of the manuscript; Drafted the work; Provided final approval of the version to be published; Accountable for all aspects of the work.
Overall percentage	90%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

July 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Ms Sara Noonan
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July 2020

Co-Author Contributions (continued)

Name of Co-Author	Dr Gavin Wheaton
Contribution to the Paper	Involved in concept / design of the study and revising it critically; Accountable for all aspects of the work

July 2020

Co-Author Contributions

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Contribution to the Paper	Involved in concept / design of the study and revising it critically; Accountable for all aspects of the work

July 2020

3.2 Abstract

Background: Rheumatic heart disease (RHD) is the most common acquired childhood cardiac disease and although it has virtually disappeared from developed nations, Aboriginal and Torres Strait Islander populations of Australia continue to have among the world's highest rates of this chronic disease. Whilst the high prevalence of RHD in remote areas of Australia are well documented, the prevalence of RHD among Indigenous children living in metropolitan or regional communities remains unknown. Further, while echocardiographic screening has highlighted variation in rates across geographical regions in northern Australia, no such data exists for southern parts of the country.

Methods: A total of 26 schools in South Australia were identified based on Aboriginal enrolment and geographical location. Aboriginal and Torres Strait Islander students over five years of age underwent a limited screening echocardiogram. Australian Bureau of Statistics 2016 Census Data at a postcode level was used to establish people per bedroom and income.

Result: A total of 1989 Aboriginal or Torres Strait Islander school-aged children were screened. 1002 (50.4%) were male with an average age of 10.4 ± 3.3 years. The prevalence of RHD in metropolitan, rural and remote areas was found to be 3.5, 4.6 and 24.4 per 1000 respectively ($p < 0.001$). The association between RHD prevalence and remoteness remained significant

despite accounting for differences in age, gender, people per bedroom and income.

Conclusion: Remote Aboriginal children in South Australia demonstrated a high prevalence of RHD compared to their rural or metropolitan counterparts, and among the highest in the world. The association between remoteness and RHD was found to be independent of income and people per bedroom.

3.3 Introduction

Rheumatic heart disease (RHD) is the most common acquired childhood cardiac disease and primarily affects developing nations (Carapetis et al. 2005; Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, Mensah, et al. 2017). Although RHD has virtually disappeared from developed nations, Aboriginal and Torres Strait Islander populations of Australia continue to have among the world's highest rates of this chronic disease. Whilst the high prevalence of RHD in remote areas of Australia are well characterized, the prevalence of RHD among Indigenous children living in metropolitan or regional communities remains unknown (Kelly 2003; Roberts et al. 2014).

Historically, RHD has been associated with high-density metropolitan populations, particularly slums, due to the relationship between RHD, overcrowding and poverty (Land and Bisno 1983). Across both developed and developing countries, more recently the burden of disease had resided primarily in semi-urban and rural populations (Berry 1972; Land and Bisno 1983). This is likely due to a shift in the distribution of overcrowding and poverty away from inner city populations (Steer et al. 2002). Rural and remote populations have been shown to have poorer health and reduced life expectancy which is thought to be linked to reduced access to clean water, washing facilities and healthcare (Smith, Humphreys, and Wilson 2008). Whilst the association between RHD, poverty, nutrition, and overcrowding have been established, remoteness is yet to be studied as an independent risk factor for RHD (Lawrence et al. 2013; Carapetis and Currie 1997).

Australian registry data has shown a low prevalence of RHD in metropolitan and regional areas (AIHW 2013a). A low clinical suspicion and limited screening occurring in these areas may bias this data. The diagnosis of RHD through echocardiographic screening in children has been previously validated (Remenyi et al. 2012; Roberts et al. 2014). Studies involving school-aged Indigenous children in remote communities in the north of Australia showed 25 per 1000 have borderline or definite RHD (Roberts et al. 2015). As the long-term clinical significance of borderline RHD is unclear, its inclusion in screening studies remains important (Bertaina et al. 2017; Rémond et al. 2015).

The aim of this study was to determine the prevalence of RHD in metropolitan, regional and remote communities via echocardiographic screening of Indigenous school-aged children across South Australia. Establishing the impact of remoteness independent of nutrition, poverty and overcrowding will help to develop a better contemporary understanding of RHD, thus helping to refine and appropriately target primary prevention programs and aid disease eradication.

3.4 Methods

3.4.1 Recruitment

The South Australian Department of Education and Child Development (DECD) was engaged to support the project. Schools were identified based on Aboriginal enrolment and geographical location. A DECD Steering Committee provided guidance to support facilitation through the schools. Five areas of South Australia were identified; the Adelaide metropolitan area, the Port Augusta region, the wider Ceduna area, Coober Pedy region, and communities located in the far north-west of South Australia (Figure 3.1). Students were offered screening if they identified as Aboriginal or Torres Strait Islander; were aged 5 years and above; provided written informed consent from a parent or carer; and agreed to participate on the screening day. A small number of non-Aboriginal children and children aged under 5 years were included following discussions with individual school principals, however these children were not included in the data analysis. This study was performed over a one year period.

Figure 3.1: *Location of Schools (Included multiple schools at some sites)*

3.4.2 Image Acquisition

Experienced sonographers used GE Vivid i and Vivid q (GE Healthcare, Freidburg, Germany) cardiovascular ultrasound machines to collect the following images as per previously established screening protocols (Carapetis et al. 2008): two-dimensional and colour Doppler images in parasternal long axis; parasternal short axis and apical views with a focus on the mitral and aortic valves; spectral Doppler if regurgitation or stenosis was detected; and anterior mitral leaflet thickness if the valve appeared thickened. Two dimensional images and colour gain settings were optimized by the sonographers in line with World Heart Federation (WHF) screening guidelines (Remenyi et al. 2012). To minimize leaflet thickness measurement error, harmonics were not used.

Brief screening for congenital heart disease (CHD) included parasternal short axis view of the pulmonary artery with colour on (for detection of patent ductus arteriosus), and examination of ventricular and atrial septum in apical 4C view with colour on (for detection of atrial septal defect and ventricular septal defect).

Where RHD or another condition was suspected by the sonographer on screening images, a comprehensive echocardiogram study was immediately recorded and referred to a single paediatric cardiologist with expertise in RHD for confirmation of the diagnosis.

3.4.3 Reporting of Echocardiograms

Reporting of borderline and definite RHD was performed according to the WHF RHD screening guidelines (Remenyi et al. 2012). Non-rheumatic abnormalities were reported in line with the American Society of Echocardiography paediatric guidelines (Lopez 2010). Patent fossa ovales (PFOs) were identified but not considered CHD data for the purposes of the study. Nine percent (180) of screening echocardiograms that were classified as normal by the sonographers were examined by a cardiologist to evaluate the negative predictive value of screening in the study.

3.4.4 Body Habitus

Body mass index (BMI) was used to determine weight status and corrected for age and gender (Nihiser et al. 2007). A BMI percentile less than 5% was considered underweight, 5-85% normal, 85-95% was overweight and greater than 85% was obese (American Medical Association 2007).

3.4.5 Clinical Management

Children diagnosed with RHD or CHD requiring specialist review were seen by a visiting cardiologist at or near their home site. A few children were seen at the Adelaide Women's and Children's Hospital or Alice Springs Hospital. Children with definite RHD were managed in line with recommended care outlined in the national RHD guidelines (RHDAustralia (ARF/RHD writing group) 2012). These children were commenced on regular secondary prophylaxis treatment to prevent acute rheumatic fever (ARF) and referred to the South Australian RHD control program. Further investigation, secondary prophylaxis and follow-up of equivocal cases was determined by the treating cardiologist on an individual case by case basis in collaboration with the regular primary healthcare provider and the child's family.

3.4.6 Statistical Analysis

Remoteness was categorized using the Rural, Remote and Metropolitan Areas (RRMA) classification (AIHW 2004). Postcode linked data from the 2016 Australian Census, undertaken during the study period, was used to account for these variables. This data included only people who identified in the Census as either Aboriginal or Torres Strait Islander. For each postcode, the median weekly income, mean number of people and mean number of bedrooms per Aboriginal or Torres Strait Islander household were recorded. These are determined by the Australian Bureau of Statistics, acknowledging this limitation (Australian Bureau of Statistics 2016). Where the residential postcode was unknown, the postcode of the school was used which occurred

in 3 cases (0.2%). State based averages were also obtained from the Census data. ANOVA test was used for the analysis of ordinal variables whilst a binary linear regression was used for linear variables. Data from this study was analysed using SPSS v25.(Corp)

3.5 Results

A total of 1989 Aboriginal or Torres Strait Islander school-aged children were screened. 1002 (50.4%) were male. All children attended school with an average age of 10.4 $\pm$ 3.3 years. 285 (14.3%) of the Aboriginal children screened lived in a metropolitan area, 1088 (54.7%) lived in a rural area, and 616 (31.0%) lived in a remote area. Table 3.1 outlines the characteristics of each screening group. Age, income and people per bedroom were all independently associated with remoteness after multivariable analysis ($p = 0.014, p < 0.001, p < 0.001$ respectively).

	Metropolitan (285)	Rural (1088)	Remote (616)	p-value
Female	54.7% (156)	49.1% (534)	48.2% (297)	0.731
Mean age (years)	9.4 ± 2.9	10.2 ± 3.1	11.0 ± 3.5	<0.001^*#
BMIc Percentile	64.4 ± 30.0	61.8 ± 31.4	58.7 ± 32.7	0.012*
Underweight	3.9% (11)	4.9% (53)	6.6% (40)	0.181
Overweight	19.1% (54)	13.3% (144)	15.3% (93)	0.048^
Obese	16.6% (47)	20.4% (220)	16.1% (98)	0.063
All RHD	0.35% (1)	0.46% (5)	2.44% (15)	<0.001*#
Definite	0.0% (0)	0.09% (1)	0.97% (6)	0.006*#
Borderline	0.37% (1)	0.37% (4)	1.46% (9)	0.012*#
CHD	0.70% (2)	1.38% (15)	0.97% (6)	0.467
People per Bedroom	1.0 (1.0 - 1.0)	1.0 (0.9 - 1.0)	1.1 (1.1 - 1.7)	<0.001^*#
Income ($/week)	297	273	265	<0.001^*

Table 3.1: *Characteristics and Screening Outcomes of Aboriginal School Children in South Australia by Remoteness*

RHD = rheumatic heart disease, CHD = congenital heart disease, $ = Australian dollars, BMIc = Age and weight corrected BMI

*Significant between metropolitan and remote

Significant between rural and remote

^Significant between metropolitan and rural

Seven cases of definite RHD and 14 cases of borderline RHD were found during the screening. 15 (71.4%) of the cases were found in remote areas, five (23.8%) in rural areas and one (4.8%) was found in a metropolitan area. The prevalence of RHD in Aboriginal children living in metropolitan areas was significantly less than those in rural and remote locations (3.5 vs 4.6 vs 24.3

per thousand respectively, p<0.001) [Figure 3.2]. The characteristics of Aboriginal school children with and without RHD are shown in Table 3.2.

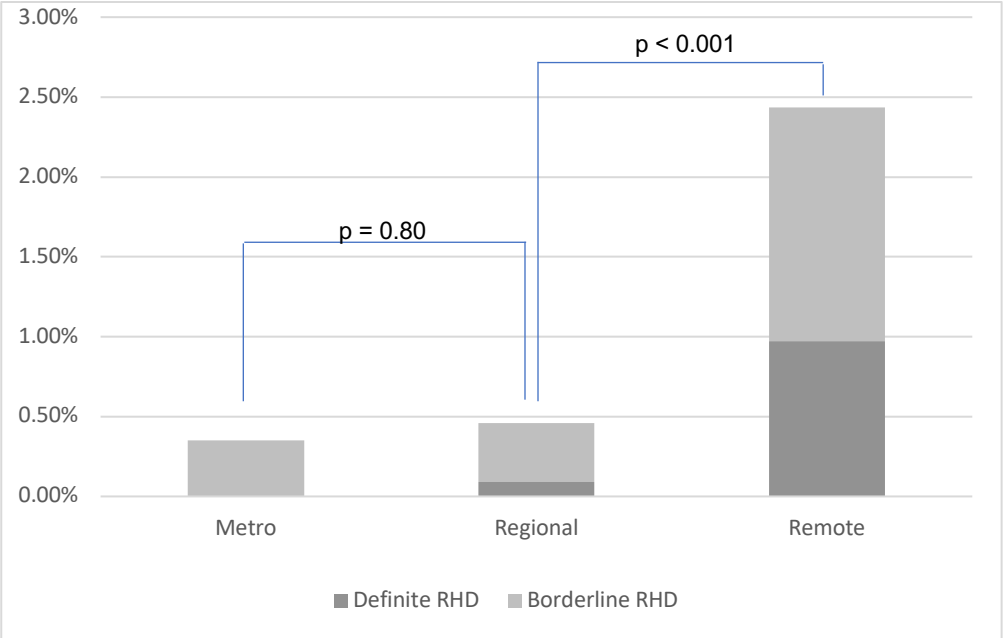

Figure 3.2: *Prevalence of Rheumatic Heart Disease in South Australia by Remoteness*

	No RHD (1869)	RHD (21)	Mean Difference (95% CI)	p value
Age	10.3 ± 3.2	12.3 ± 3.9	-1.9 (-3.3, -0.5)	0.008
Female	49.6% (927)	71.4% (15)	-	0.045
People per house	3.0 (2.9 - 3.2)	3.2 (3.0 - 4.6)		0.005
People per bedroom	1.0 (0.9 - 1.1)	1.1 (1.0 - 1.7)		0.002
Income ($/week)	274 ± 76	233 ± 44	41 (8, 74)	0.014

Table 3.2: *Factors Associated with Rheumatic Heart Disease Diagnosis During Screening of School Children*

As shown in Table 3.1, the number of people per bedroom increased and weekly income declined with remoteness. Age, gender, people per house, people per bedroom and weekly household income per person were all found to be significantly associated with RHD [Table 3.2]. Weight status was not found to be associated with RHD status (OR 1.54, 95% CI 0.97 - 2.44, *p=0.67*). A limited multivariable analysis showed that remoteness remained significant despite accounting for income and people per bedroom [Table 3.3].

	Odds Ratio	OR 95% CI	p value
Age	1.132	0.998 – 1.285	0.054
People per Bedroom	0.577	0.117 – 2.849	0.500
Income ($/week)	0.988	0.976 – 1.000	0.042
Remoteness	3.078	1.029 – 9.203	0.044

Table 3.3: *Multivariable Odds Ratios for Factors Associated with School Children Diagnosed with Rheumatic Heart Disease During Screening*

23 cases of congenital heart disease were found during screening. This included nine bicuspid aortic valves (BAV), four patent ductus arteriosus (PDA), three atrial septal defects (ASD), two ventricular septal defects (VSD), and five other abnormalities. The highest prevalence for these was in rural areas with 16 cases (1.4%) and there was a prevalence of 0.7% in metropolitan and remote areas which was not statistically significantly different.

A total of 180 (10%) echocardiograms that were deemed normal by the sonographer and not referred to the reporting cardiologist were randomly selected and reported. No echocardiogram that was not referred was found to have any significant abnormalities.

3.6 Discussion

This is the first screening study to determine the prevalence of RHD in Aboriginal school children across metropolitan, rural and remote areas. Previous published registry data has shown the majority of RHD cases in Australia are among Aboriginal people living in remote locations (AIHW 2013b). There had remained questions regarding the potential for clandestine disease, although less severe, to still exist among Aboriginal people living in metropolitan areas. This study demonstrates a high prevalence of RHD among Aboriginal school children in remote areas compared to metropolitan or rural areas. It also establishes remoteness as an important independent risk factor in Australia.

The rates found in remote communities in southern parts of Australia are not dissimilar with the prevalence rate of 25 per 1000 established from screening studies in Australia's northern remote communities (Roberts et al. 2015). The prevalence of RHD in this study was greatest in remote communities and lowest in metropolitan areas as indicated previously by registry data. Unlike previous screening studies, this is the first study to corroborate registry data on the distribution of RHD by remoteness.

Remoteness in Australia is strongly associated with a poor living environment and hygiene (Torzillo et al. 2008). Improvements in primordial prevention have thought to have contributed considerably to the reduction in RHD prevalence observed in many developed nations (Kaplan 1985). Further, poor living conditions are impediments to the successful implementation of public

health programs targeting common childhood diseases such as acute streptococcus pharyngitis (Bailie, Stevens, and McDonald 2012).

Remote communities are logistically difficult to provide for and access to healthcare services can be greatly diminished in many regions (Adanja, Vlajinac, and Jarebinski 1988; Vlajinac, Adanja, Marinkovic, et al. 1991). This creates significant barriers in obtaining appropriate diagnosis and management for acute streptococcal pharyngitis, as well as providing primary and secondary prophylaxis for ARF and RHD (Rémond et al. 2012: 635). One study showed that despite a concerted effort being made to improve the adherence to secondary prophylaxis, there was no change seen to the number of patients receiving over 80% of their prophylaxis, underlining the magnitude of these barriers (Ralph et al. 2013).

The most commonly stated and longstanding social determinant of ARF and RHD is overcrowding (DiSciascio and Taranta 1980: 636). An Australian study showed that although overcrowding was not associated with an increased number of Group A Streptococcal pharyngitis infections, there were still high rates of ARF within those communities (McDonald et al. 2006: 687). Although a higher number of people per bedroom was associated with RHD on a univariate analysis, on the multivariate analysis it washed out after accounting for age, income and remoteness. This may be a reflection of the study being underpowered. Despite this, overcrowding is still an important contributor to ARF and RHD in Australian remote communities.

Poverty has been historically less strongly associated with the development of ARF and RHD (Vlajinac, Adanja, Marinkovic, et al. 1991). The impact of household income per person found in this study is significant. Many postcodes which had high incomes among Aboriginal households were areas where mining companies also supported the community with educational, healthcare and general infrastructure. Despite this, having the financial means to overcome barriers to education, health care services, healthy diets and hygiene appears to be independently associated with a lower RHD prevalence (Chondur et al. 2014; Teng et al. 2014).

Australia is the only developed country with high rates of both undernutrition and obesity in its Indigenous population (Ruben 2009). Despite adjusting for remoteness and socioeconomic status, Aboriginal South Australian school children have higher rates of overweight and obesity than their non-Indigenous peers (Spurrier et al. 2012). The finding of a 5.3% rate of underweight Aboriginal children is consistent with other studies however, the rate of obesity of 18.5% is significantly higher than previous studies (Ruben 2009; O'Dea 2008). Historically rheumatic fever has been associated with underweight body weight, a marker of undernutrition (Vlajinac, Adanja, Marinković, et al. 1991). Once socioeconomic status and overcrowding are taken into account, more recent studies have shown this association to fall out, consistent with the findings in this study (Karthikeyan and Guilherme 2018).

The prevalence of CHD in this study was similar with a previous study on CHD identified in South Australia (Bolisetty et al. 2004). The prevalence was higher than other Australian states but lower than Central Australia. Interestingly, one large RHD screening study in Africa had significantly lower rates of CHD compared to Australian screening studies (Beaton et al. 2012). The reason for this is unknown.

3.6.1 Limitations

This study only screened children attending school. The association of increased poverty of children who don't attend school likely means these children are at greater risk and will have been missed by this study. Further, children who regularly do not attend school due to sickness could be missed and their recurrent illness may predispose them to a greater risk of RHD. The exact absenteeism rates during the study were not known. In addition, ABS data can be inaccurate in remote or transient populations, thus using the ABS 2016 Census data and residential postcode to determine the income status and number of people per bedroom and house has its limitations. Undertaking this at a postcode level may also be inadequate for communities which are relatively small with inherent potential ecological fallacy. The impact of transient populations was minimized however by the Census being undertaken during the study period.

This study highlights the importance of remoteness on the prevalence of RHD in Australia. The reason for this is multifactorial however health care access and the social environment likely play a dominant role. Future efforts to

reduce and eradicate RHD from communities should not only focus on these factors, but also the underlying social determinants associated with living in remote communities.

CHAPTER 4

Quantification of Sonographer Accuracy in Diagnosing Rheumatic Heart Disease in Children During Echocardiographic Screening

Quantification of Sonographer Accuracy in Diagnosing Rheumatic Heart Disease in Children During Echocardiographic Screening

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4.1 Statement of Authorship

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Principal Author Contributions

Candidate	Dr Ross Roberts-Thomson
Contribution to the Paper	Primary contributor to the conception and design of the work; Drafted the work; Provided final approval of the version to be published; Accountable for all aspects of the work.
Overall percentage	90%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

July 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

iv. the candidate's stated contribution to the publication is accurate (as above);
v. permission is granted for the candidate in include the publication in the thesis; and
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July 2020

4.2 Abstract

Background: Rheumatic heart disease (RHD) is the most common acquired childhood cardiac disease globally. Echocardiographic screening is becoming increasingly common in areas with high rates of RHD. Sonographer accuracy and confidence using the WHF criteria has not yet been established.

Methods: The South Australian Childhood Rheumatic Heart Disease Screening (SACRHD) project evaluated sonographer sensitivity and accuracy in diagnosing RHD using the WHF echocardiographic screening diagnostic criteria. A modified image acquisition protocol was used for the purposes of this study. 9% (180/1989) of the non-referred scans were reported by a cardiologist. All sonographers were surveyed following the screening period to evaluate confidence in using the World Heart Federation (WHF) criteria.

Result: Eight sonographers performed 1989 screening echocardiograms in Aboriginal school-aged children. Sonographers had an 84.1% agreement with the cardiologist with a kappa value of 0.45. Sonographer sensitivity was 100% (95% CI 83.9 – 100.0%) with a specificity of 82.6% (95% CI 76.9 – 87.4%). Sonographer accuracy was 83.2% (77.8% - 87.7%). Sonographers had less confidence in reporting morphological features, with lowest confidence levels reported with excessive leaflet tip motion of the mitral valve (-1.75, -2.5 - 1.0, p=0.011) compared to jet length >2cm. All sonographers agreed or strongly agreed that pre-screening training would improve their diagnostic accuracy and confidence.

Conclusion: Experienced sonographers have an excellent sensitivity and reasonable specificity in correctly diagnosing RHD using the WHF echocardiographic screening criteria. Sonographer confidence in reporting abnormalities were highest for pathological regurgitation and lowest for morphological features of RHD.

4.3 Introduction

Rheumatic heart disease (RHD) is the most common acquired childhood cardiac disease globally. RHD is increasingly becoming primarily an echocardiographic diagnosis. Historically echocardiograms have only been undertaken if the treating physician had a strong clinical suspicion based on symptoms or auscultatory signs. Unfortunately, auscultation is a poor indicator for RHD and symptoms are indicative of late stage disease, thus this approach delays diagnosis and access to preventative treatment (Beaton et al. 2012; Tribouilloy et al. 1999). Secondary prevention using LA-Bicillin can prevent valvular progression in many patients with RHD (Cannon et al. 2017). Screening echocardiography allows early detection of RHD, potentially facilitating reduced valvular progression, and early surgery with improved outcomes for those with severe disease.

The number of RHD screening projects have increased dramatically in the past 10 years, especially in high prevalence areas across Africa, Asia and Oceania (Engelman et al. 2016; Roberts et al. 2015; Saxena et al. 2011). In 2012 the World Heart Federation (WHF) published criteria for RHD diagnosis on screening in people under 20 years of age to standardize practice (Remenyi et al. 2012). These guidelines provided clear definitions for pathological regurgitation and morphological features of RHD for both the mitral and aortic valves. Sonographer accuracy and confidence in reporting to these guidelines has not yet been assessed.

In recent years there has been an increase in echocardiographic screening for RHD by untrained nurses or health care workers (Engelman et al. 2016; Beaton et al. 2015; Ploutz et al. 2016). This is essential for areas of need and workforce shortage. Further, simplified screening protocols, such as single image acquisition and regurgitation evaluation alone, have also been shown to be beneficial (Remenyi, Davis, et al. 2019). Although these studies appear to have reasonable positive and negative predictive values with non-sonographer screening, there is no benchmark by which to assess them.

This study aims to evaluate the concordance between sonographers and expert cardiologists, as well as sonographer confidence, in the echocardiographic diagnosis of RHD in school-aged children using the WHF criteria.

4.4 Methods

Participants were children attending schools participating in the SACRHD study. The inclusion criteria were as per the SACRHD study described in Chapter 3. Echocardiographers were all qualified cardiac sonographers who had varying experience in RHD screening. All referrals and responses were recorded.

4.4.1 Screening Protocol

Experienced sonographers used GE Vivid i and Vivid q (GE Healthcare, Freidburg, Germany) cardiovascular ultrasound machines to collect the

following images as per previously established screening protocols (Carapetis et al. 2008). Additional images to exclude congenital heart disease (CHD), in the form of patent ductus arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect (VSD) were taken. A patent fossa ovale (PFO) was not considered CHD data for the purposes of the study. The full imaging sequence is described in Chapter 3. Reporting of borderline and definite RHD was performed according to the WHF RHD screening guidelines (Remenyi et al. 2012). Screening scans took 5 minutes whilst those picked up on screening who required a full scan took approximately 30 minutes. Congenital abnormalities were reported in line with the American Society of Echocardiography paediatric guidelines (Lopez 2010). 180 of screening echocardiograms that were classified as normal by the sonographers were randomly selected and examined by a cardiologist who was aware they were a random sample of non-referred scans.

Echocardiogram settings

- Nyquist limits for color-Doppler echocardiography should be set on maximum to avoid overestimation of jet length.
- Images for assessment of valvular and chordal thickness should be acquired with harmonics turned off and probes with variable frequency set on ≥2.0 MHz. Low frequency settings and harmonics exaggerate valve and chordal thickness.
- Gain settings should be adjusted to achieve optimal resolution. Images acquired with an excessive gain setting will not be suitable for objective valve thickness measurements.
- All other settings (including depth, sector size, and focus) should also be optimized to achieve maximal frame rate (ideally 30–60 frames per s) and resolution.

Screening images

1. PLAX
2. PLAX + colour
3. PLAX Zoom MV
4. PLAX Zoom MV + colour
5. PLAX Zoom AV
6. PLAX Zoom AV + colour
7. PLAX + colour on interatrial and interventricular septum
8. PSAX MV
9. PSAX MV + colour
10. PSAX AV
11. PSAX AV + colour
12. PSAX PA + colour
13. A4C
14. A4C + colour
15. A4C Zoom MV
16. A4C Zoom MV + colour
17. A4C + colour on interatrial and interventricular septum

When to proceed to comprehensive study

- More than physiological MR (>2cm jet);
- More than physiological AR (>1cm jet);
- Any evidence of thickened/restricted anterior MVL; or
- Any concern or significant abnormalities seen.

Table 4.1: *Echocardiographic Screening Image Acquisition Protocol*

PLAX = parasternal long axis, PSAX = parasternal short axis, A4C = apical four chamber, MV = mitral valve, AV = aortic valve, MR = mitral regurgitation, AR = aortic regurgitation.

Pathological mitral regurgitation *(All four Doppler echocardiographic criteria must be met)*

1. Seen in two views
2. In at least one view, jet length ≥2 cm*
3. Velocity ≥3 m/s for one complete envelope
4. Pan-systolic jet in at least one envelope

Pathological aortic regurgitation *(All four Doppler echocardiographic criteria must be met)*

1. Seen in two views
2. In at least one view, jet length ≥1 cm*
3. Velocity ≥3 m/s in early diastole
4. Pan-diastolic jet in at least one envelope

*A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant colour.

Table 4.2: World Heart Federation Rheumatic Heart Disease Echocardiographic Screening Criteria for Pathological Regurgitation

4.4.2 Sonographer Survey

All sonographers were sent a survey following the SACRHD study. Eight sonographers (100%) filled in the survey. A Likert scale was used to determine agreement with statements regarding confidence of reporting echocardiographic parameters of the WHF screening protocol.

4.4.3 Statistical Analysis

Binary variables were compared using a Pearson Chi Squared analysis while continuous, normally distributed variables were analysed by unpaired parametric t-test. Multivariable analyses were performed using a binary logistic regression. Agreement between the sonographers and the cardiologist were assessed with sensitivity, specificity, accuracy, agreement and Cohen's kappa. These were calculated using the referred echocardiograms as well as the 180 echocardiograms that were not referred to the cardiologist. Confidence intervals for sensitivity, specificity and accuracy are "exact" Clopper-Pearson confidence intervals. Survey results (Likert scales) were compared using Wilcoxon signed-rank test and differences expressed as Related-Samples Hodges-Lehman median difference with 95% confidence intervals. Data from this study was analysed using SPSS v25.(Corp)

4.5 Results

A total of 1989 children (50.4% male, mean age 10.4 $\pm$ 3.3 years). 88 (4.4%) scans were referred by the sonographer for further evaluation by the pediatric

cardiologist. The sonographers were experienced with a mean number of years in practice of 18.1 ± 12.5 years. All of them primarily worked in adult cardiac centres.

Figure 4.1 demonstrates the referrals from sonographers and cardiologist agreement. 64.4% (38/59) of the scans considered borderline or definite RHD by the sonographer were deemed to be normal by the cardiologist. 20.7% (6/29) of the scans considered to have CHD by the sonographer were deemed to be normal by the cardiologist which was significantly better than RHD diagnosis (p = 0.0001). Overall, only 4.4% (88/1989) of the scans were deemed to be abnormal by the sonographers of which 50% (44/88) were considered normal by the cardiologist. Pathological aortic regurgitation (AR) was found to be negatively associated with cardiologist agreement. No other parameter was associated with cardiologist agreement [Table 4.4]. Pathological mitral regurgitation (MR) was the most common reason for referral.

In the echocardiographic diagnosis of RHD, sonographers had an 84.1% agreement with the cardiologist with a kappa value of 0.45. Sonographer sensitivity was 100% (95% CI 83.9 – 100.0%) with a specificity of 82.6% (95% CI 76.9 – 87.4%). Sonographer accuracy was 83.2% (77.8% - 87.7%) with an agreement of 84.1% and kappa of 0.45.

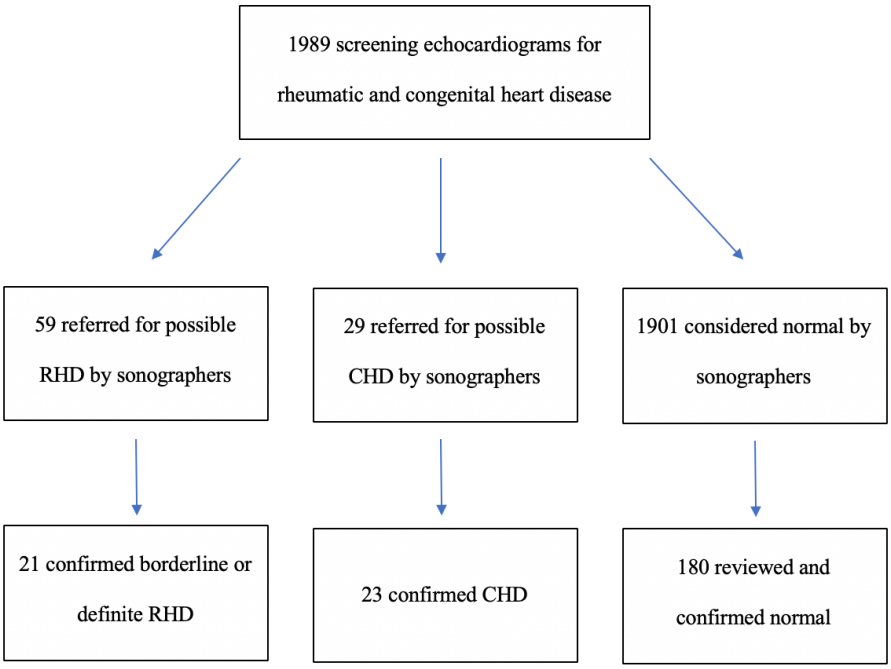

Figure 4.1: *Agreement Between Sonographer and Cardiologist*

RHD = rheumatic heart disease, CHD = congenital heart disease

	RHD	CHD	Any Abnormality
Sensitivity	1 (0.84-1)	1 (0.85-1)	1 (0.85-1)
Specificity	0.83 (0.77-0.87)	0.97 (0.93-0.99)	0.80 (0.75-0.85)
Positive Predictive Value	0.05 (0.04-0.07)	0.24 (0.12-0.41)	0.09 (0.07-0.12)
Negative Predictive Value	1	1	1
Accuracy (%)	82.7 (77.3-87.3)	96.8 (93.4-98.7)	80.8 (75.5-85.3)

Table 4.3*: Diagnostic Accuracy of sonographers in RHD and CHD compared to the Cardiologist*

RHD = rheumatic heart disease, CHD = congenital heart disease

	No RHD (38)	RHD (21)	kappa	p value
Pathological regurgitation				
Mitral valve	27 (71.1%)	19 (90.5%)	0.153	0.085
Aortic valve	14 (36.8%)	2 (9.5%)	-0.289	0.024
Morphological RHD Features				
Mitral valve	6 (15.8%)	7 (33.3%)	0.192	0.120
Aortic valve	3 (7.9%)	0 (0.0%)	-0.098	0.186

Table 4.4: *Likelihood of Agreement Between the Sonographer and Cardiologist by Screening Parameter Type*

Six (75%) of the sonographers felt that of the pathological MR or AR criteria, the pan-systolic jet in at least one envelope was the most difficult to obtain. Relative to their confidence in reporting a scan as normal, sonographers felt less confident in reporting a scan as borderline RHD or CHD [Table 4.5]. There was no difference in confidence in reporting definite RHD (-0.5, 95% CI -1.0 - 0.0, p = 0.16). Sonographers were less confident with all the aortic morphological features and two of the four mitral morphological features when compared to a >2cm MR jet. All sonographers agreed or strongly agreed that prescreening education would improve their confidence and accuracy for RHD screening.

	Mean Likert Scale	Estimated Median Difference (95% CI)	P Value
Normal	4.5 ± 0.9	reference	reference
Borderline RHD	3.5 ± 0.5	-1(-1.5 - -0.5)	0.023
Definite RHD	4.0 ± 0.8	-0.5 (-1.0 - 0.0)	0.157
CHD	4.0 ± 0.8	-0.5 (-1.0 - 0.0)	0.046
WHF Criteria			
- MR jet >2cm	4.6 ± 1.1	reference	reference
- Pathological MR	4.0 ± 1.1	-0.5 (-1.0 - 0.0)	0.059
- AR jet >1cm	4.4 ± 1.2	0.0 (-1.0 - 0.0)	0.317
- Pathological AR	4.0 ± 1.1	-0.5 (-1.0 - 0.0)	0.059
Mitral Morphological Features			
- AMVL thickening	3.9 ± 0.4	-1.5 (-1.0 – 0.5)	0.124
- Chordal thickening	3.1 ± 0.6	-1.5 (-2.5 - 0.5)	0.023
- Restricted leaflet motion	3.9 ± 0.8	-1.0 (-2.0 – 1.0)	0.230
- Excessive leaflet tip motion	2.9 ± 1.1	-1.75 (-2.5 - 1.0)	0.011
Aortic Morphological Features			
- Irregular or focal thickening	3.1 ± 0.6	-1.5 (-2.0 - 1.0)	0.014
- Coaptation defect	3.6 ± 1.2	-1.0 (-2.0 - 0.0)	0.039
- Restricted leaflet motion	3.8 ± 1.0	-1 (-1.5 - 0.0)	0.038
- Prolapse	3.3 ± 1.2	-1.5 (-2.0 - 1.0)	0.015

Table 4.5: *Sonographer Confidence in Reporting Echocardiographic Pathology on Screening Echocardiogram*

RHD = rheumatic heart disease, CHD = congenital heart disease, MR = mitral regurgitation, AR = aortic regurgitation, AVML = anterior mitral valve leaflet.

4.6 Discussion

This study illustrates that sonographers have an excellent sensitivity and reasonable specificity when performing RHD screening studies. Their confidence with the WHF RHD echocardiographic screening criteria is highest with pathological regurgitation and lowest with morphological features of the valves. This study provides a benchmark for RHD screening studies, as well as identifies training in RHD screening as highly desirable by sonographers to improve diagnostic confidence.

RHD commonly occurs in resource poor regions with limited health care infrastructure (Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, and Mensah 2017; Dodu and Bothig 1989; Blankart 2012). Screening programs need to be tailored to individual environments as each have their own unique sonographic expertise, infrastructure and requirements. Previous studies evaluating the accuracy of sonographers have not been done in relation to the WHF criteria, but in relation to specific parameters such as mitral jet length (Engelman et al. 2016). This study clearly demonstrates that the sensitivity of sonographer based screening is very high (Wong et al. 2002). Quality control evaluations of echocardiographic screening programs should use this as a standard. Although sonographer specificity and accuracy were relatively high, the involvement of clinicians to review images will remain. The commencement of secondary prophylaxis needs to take into account the clinical scenario, as well as echocardiographic findings to ensure best patient outcomes (Rémond et al. 2015).

The significant difference found between the diagnostic accuracy of congenital abnormalities and RHD features are due to the differences in pathology. Despite clear definitions of what constitutes pathological MR in the guidelines, MR severity is fundamentally linear, although categorized as mild, moderate or severe for the sake of practicality (Biner et al. 2010; Rosenhek et al. 2006b; Thomas, Foster, and Schiller 1998). In addition, many of the morphological features such as leaflet motion and thickening are either semiqualitative or linear. Congenital abnormalities on the other hand are more likely to be dichotomous (e.g. septal defects and PDAs are either present or absent).

A study comparing the diagnosis of RHD by international cardiologists using a standardized set of echocardiographic images from historical screening studies showed significant inter-rater variability (Remenyi, Carapetis, et al. 2019). This was especially true of borderline and normal scans. Although pathological AR was the only screening parameter associated with a lower cardiologist agreement in our study, other studies have found significant inter- and intra-rater variability with regard to morphological features of the screening criteria. The poor confidence by sonographers in correctly identifying the morphological features of RHD on echocardiography found in this study supports this. Educational tools and training to improve confidence and accuracy in identifying morphological features may be useful to the international screening community. These need to be made widely available, especially for those in countries with high RHD prevalence.

Recently a study of single parasternal sweep screening of the mitral valve against an WHF screening echocardiogram found relatively high sensitivity and specificity (Remenyi et al. 2020) with regard to RHD. This may be very useful in specific settings but the lack of CHD screening is somewhat limiting for an Australian context given the similar prevalence seen in this study as well as other studies (Bolisetty et al. 2004).

4.6.1 Limitations

Although a large number of screening scans were performed in this study, there was a relatively low event rate overall due to the inclusion of metropolitan and rural locations. The study was to compare the confidence of sonographers with their agreement between the cardiologist due to lack of power. Further, there were a limited number of sonographers involved in the study and thus the survey.

4.7 Conclusion

Experienced sonographers have an excellent sensitivity and reasonable specificity in correctly diagnosing RHD using the WHF echocardiographic screening criteria. The zero false negative and relatively low false positive rates mean there is a low probability of harm from screening. Sonographer confidence in reporting abnormalities were highest for pathological regurgitation and lowest for morphological feature of RHD. All sonographers agreed that prescreening education and training using the WHF criteria would

improve their confidence and accuracy for RHD diagnosis during screening projects.

CHAPTER 5

Left Atrial Ejection Fraction Predicts Future Need for Surgery in Asymptomatic Patients with Rheumatic Mitral Valve Disease

Left Atrial Ejection Fraction Predicts Future Need for Surgery in Asymptomatic Patients with Rheumatic Mitral Valve Disease

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Overall percentage	90%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

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i. the candidate's stated contribution to the publication is accurate (as above);
ii. permission is granted for the candidate in include the publication in the thesis; and
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5.2 Abstract

Background: Rheumatic heart disease is the most common acquired heart disorder in young adults and most frequently characterised by mixed mitral valve disease. The current indications for surgical intervention are complex and reflect when patients have reached a point where they ultimately do better with surgical intervention relative to continued conservative management. In those with an indication for intervention, outcomes are better in those who undergo intervention early. This study aimed to determine whether left atrial (LA) echocardiographic parameters could predict the development of guideline indicated intervention in asymptomatic patients with significant rheumatic mitral valve disease.

Methods: Patients with moderate or severe rheumatic mitral valve disease between 2007 and 2017 were identified from the Northern Territory centralised cardiac database. Conventional echocardiograms with additional LA parameters were analysed by two blinded cardiologists. The predictive value of clinical and echocardiographic factors for the development of any new surgical indication, referral for surgery or death within two years was investigated.

Results: A total of 256 patients (mean age 37.7±14.2 years) were identified, 107 (41.8%) of whom had no surgical indication at baseline. 22 of 107 (20.6%) asymptomatic patients developed an indication for surgery within two years. While LA volumes and mean mitral gradient were positively associated with incidence of surgical indication, the strongest predictor for the

development of a new surgical indication was a significantly reduced LA ejection fraction (LAEF < 40%) at baseline, with a bootstrapped 68·9 (95% CI 8·6 – 549·1, *p<0·001*; C-statistic 0.93, sensitivity 95.5%, specificity 81.2%). The 2-year event-free survival between those with LAEF greater than or less than 40% was 97·7% vs 33·6% respectively (*p<0·001*).

Conclusion: Determination of the LAEF at echocardiography is a simple measure that can be used to predict the future need for cardiac surgery in patients with asymptomatic rheumatic mitral valve disease. Patients with a LAEF <40% should be monitored closely and considered for early surgery.

5.3 Introduction

Rheumatic heart disease (RHD) affects between 30 and 43 million people globally (Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, Mensah, et al. 2017). Most affected individuals are young adults from impoverished communities, whose median age at death is approximately 28 years (Zühlke et al. 2016). The associated morbidity and mortality are usually due to heart failure, atrial fibrillation (AF), pulmonary hypertension, stroke or infective endocarditis, and at least one quarter of affected individuals will develop heart failure within five years from diagnosis (Zühlke et al. 2016; Zuhlke et al. 2015). However, currently there are no reliable means with which to identify patients without a surgical indication who are likely to require intervention in the near future.

RHD is often multivalvular with a combination of stenotic and regurgitant pathologies. The Global Rheumatic Heart Disease Registry showed that the mitral valve is affected in over 90% of cases, mostly with mixed mitral valve disease (MMVD), while both the mitral and aortic valves are involved in over 50% of cases (Zuhlke et al. 2015). The aortic valve disease is usually mild while approximately two-thirds of rheumatic mitral disease is classified as moderate to severe.

When patients meet criteria for mitral valve repair or replacement, surgical outcomes are superior for those who proceed to early surgery than for those who either defer surgery or present with advanced disease (Kang et al. 2014; Vincens et al. 1995; Tribouilloy et al. 1999). Symptoms, new onset AF and

high pulmonary pressures are common indications for surgery in both severe mitral stenosis (MS) and severe mitral regurgitation (MR) (Baumgartner et al. 2017). High risk features for an embolic event, such as dense spontaneous contrast in the left atrium (LA) or a history of embolism, are additional indications in MS while indications for intervention specific to MR include a reduced left ventricular ejection fraction (LVEF) or dilated left ventricle (LV) (Baumgartner et al. 2017). These clinical and echocardiographic features of rheumatic mitral valve disease are associated with a high post-operative mortality in the short and long-term (Ghoreishi et al. 2011; Grigioni et al. 2002). Indices that predict the development of a surgical indication may serve to better risk stratify individuals requiring earlier surgical intervention and thus improve patient outcomes.

The complex haemodynamics of multivalvular and mixed valvular pathology present additional diagnostic and therapeutic challenges, and current treatment guidelines support intervention for valvular disease based on criteria for single valvular disease with a single haemodynamic effect (e.g stenosis or regurgitation but not both) (Baumgartner et al. 2017). The haemodynamic consequences of valvular pathology are more important than the severity of valvular stenosis and regurgitation, although they often go hand in hand. Mean mitral valve gradient in MS is impacted by AF, cardiac output, heart rate, as well as many other variables. For MR, EROA (quantitative) is often difficult to measure while colour doppler (qualitative) is poorly reproducible highly dependent on blood pressure. A severe mitral valve pathology is not an indication to intervene. Further, in mixed mitral valve

disease, no marker of severity or indications are validated. While multimodality imaging is ideal, this is often unavailable in resource poor and remote communities. Portable transthoracic echocardiography remains the most practical and affordable method for assessing the severity of valvular and myocardial haemodynamics (Nishimura et al. 2017; Baumgartner et al. 2017).

The primary aim of this study was to assess the predictive value of simple echocardiographic parameters for the development of surgical indication within two years in patients with moderate or severe rheumatic mitral valve disease that can be applied in resource poor settings. The secondary aim was to examine clinical and echocardiographic differences between patients with and without an indication for mitral valve surgery at baseline.

5.4 Methods

5.4.1 Patients

This is a historical cohort analysis of consecutive patients in the Northern Territory, Australia who underwent a transthoracic echocardiogram between 2007 and 2017. Adult patients aged 18 years or older with at least moderate MR and/or moderate MS who did not meet any European Society of Cardiology / European Association for Cardio-Thoracic Surgery (ESC/EACTS) guideline indications for cardiac intervention were identified from a state-wide database of echocardiographic and clinical data. Where a patient had multiple echocardiograms, the earliest echocardiogram was

included. Patients with only mild disease, non-rheumatic disease, acute valvulitis, previous valve replacement, congenital heart disease, significant lung disease, or life-limiting comorbidities (a prognosis of less than two years not attributed to their valvular disease) were excluded. The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research. Individual patient consent was not obtained for this study as per the ethics committee.

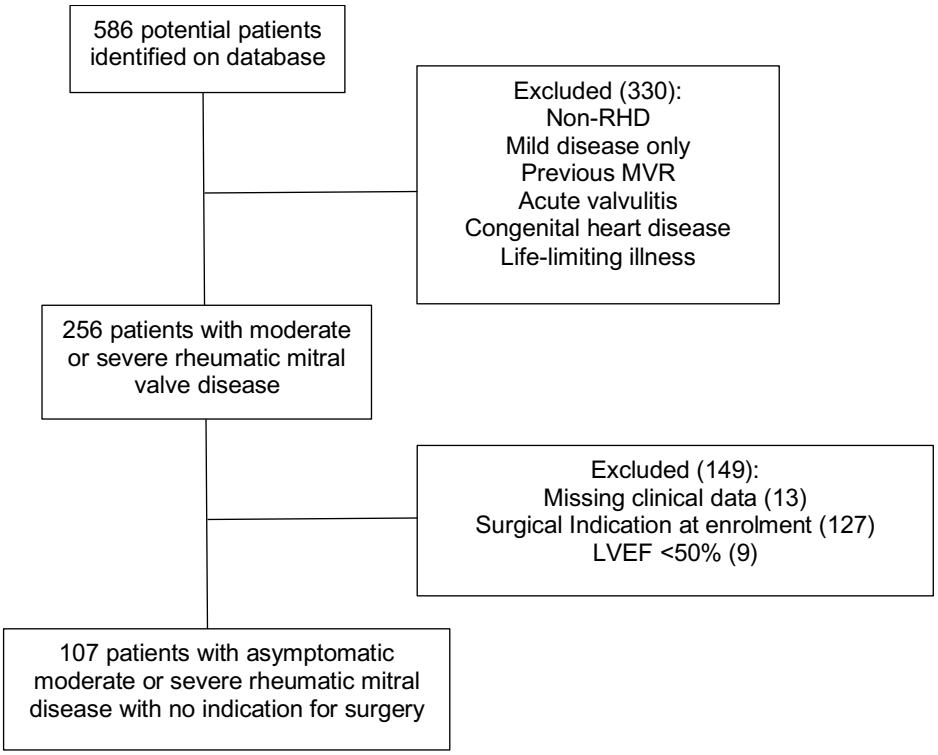


Figure 5.1: *Patient Selection and Inclusion*

5.4.2 Data Collection

The echocardiographic database was searched using the following criteria: free text search with the words “moderate” or “severe” with “mitral regurgitation” or “mitral stenosis” or “MR” or “MS”, mean mitral gradient >5mmHg, mitral valve area (MVA) <1.5cm^2, and effective regurgitant orifice area (EROA) >0.2cm^2. Baseline clinical data were obtained from clinical consultation letters where they had occurred on the day of, or within two days of the echocardiogram. Follow-up data were obtained from subsequent nurse or physician consultation records, hospital admissions records and echocardiograms. Despite most patients living in remote communities, the vast majority of those with moderate or severe valve disease underwent reviews with or without echocardiograms every 6-12 months.

5.4.3 Echocardiographic Assessment

The majority of echocardiograms were performed in remote communities using Vivid *q* or Vivid *i* (GE Healthcare, Freiburg, Germany). Images were acquired by sonographers who regularly work in areas with high prevalence of RHD. All echocardiograms were reviewed by two blinded cardiologists with expertise in echocardiography. Additional LA parameters were measured specifically for the purpose of this study. The age, height and weight of the patient were provided to the reporting cardiologist. The cardiologist was blinded to any other information including any clinical information or the previous echocardiogram report. Severity of valvular disease was based on the 2017 ESC/EACTS guidelines (Ozkan 2017). Significant mitral valve

disease was defined as moderate or severe MR or MS. Assessment of LA end-systolic volume (LAESV) and LA end-diastolic volume (LAEDV) was performed using apical four-chamber and two-chamber images. Left atrial ejection fraction (LAEF) was then calculated using the following formula: $LAEF = (LAESV - LAEDV)/LAESV$ (Morris et al. 2015). Patients with inadequate image quality to assess LA size and function were recorded but not included in the analysis.

5.4.4 Clinical Endpoint

The clinical endpoint of interest was the onset of any new surgical indication, referral for surgery, or death within two years in patients with a LVEF > 50% and no surgical indication at baseline. ESC/EACTS valvular guidelines were used to determine surgical indications including dyspnoea, AF, estimated pulmonary arterial systolic pressure (ePASP) ≥50mmHg, new infective endocarditis (IE), or cardioembolic thromboembolism (Baumgartner et al. 2017). Other surgical indications that were included as part of the analysis were: severe AS; severe MR with left ventricular end-systolic diameter (LVESD) >40mm or LVEF <60%; and severe AR with LVESD >50mm, left ventricular end-diastolic diameter (LVEDD) >70mm, or LVEF <50%. The discrepancy between the number of patients who had an indication for surgery and those who received surgery meant that time to surgery was not an adequate reflection of clinical severity or clinical need. A referral to surgery within 14 days of the baseline echocardiogram was considered a referral at baseline. For the primary analysis, LA volumes were evaluated against

indexed LA volumes to ensure this had no impact on the results. The development of a clinical endpoint will hereafter be referred to as an event.

5.4.5 Statistical Analysis

Prior to the analysis of the asymptomatic patients, patients with and without an indication for surgery at baseline were compared using Pearson's Chi Square or Fisher's Exact Test for categorical variables and unpaired t-tests for continuously-measured, normally distributed variables. These results were used to inform which baseline factors might also be useful for differentiating asymptomatic patients with respect to their risk for development of surgical indication in the future.

To identify and quantify simple measures that predict a patient's risk for needing surgery, univariable binary logistic regression was used to determine which single baseline factors (if any) were able to differentiate asymptomatic patients according to their risk for developing a surgical indication. Predictors that were strongly associated with the outcome ($p<0.05$) in the univariable models were assessed for confounding by age, gender, and other selected variables in multivariable models. LA variables were evaluated independent of one another in multivariable analyses due to the significant confounding between them, however other echocardiographic measures were included. A simple predictor model was chosen over a more complex model in order to allow its practical application in remote and underprivileged communities.

ROC curves were generated for the individual baseline measures for which there was little evidence of confounding by other factors. The optimum cut-point was then determined by the highest Youden Index, and both adjusted and unadjusted odds ratios calculated, with simple bootstrap resampling performed for internal validation. A Kaplan-Meier curve was used to illustrate the time to first events.

5.5 Results

A total of 586 patients satisfying the criteria of moderate or severe MR or MS were identified from the database search of 104,550 echocardiograms performed during the study period. After excluding those with mild disease, non-rheumatic disease, acute valvulitis, previous valve replacement, congenital heart disease, significant lung disease, or life-limiting comorbidities, 256 patients were included [Figure 5.1]. 13 patients with missing clinical data and nine with an LVEF <50% and no surgical indication were excluded from the follow-up analysis [Figure 5.1]. The average age at enrolment was 37·7±14·2 years and 169 (69·8%) were female. 127 (52·3%) had a surgical indication at the time of their baseline echocardiogram. 175 (68·4%) patients had MMVD with isolated MR or MS present in the remaining 17·2% and 14·5% of the cohort respectively. Concomitant aortic valve involvement was present in 126 (49·2%), however only nine (3·5%) of these were severe. Moderate or severe tricuspid regurgitation (TR) was present in 51 (19·9%) patients. Two patients had pulmonary regurgitation and two had tricuspid stenosis, with none of these lesions being severe.

Of the 127 patients with a surgical indication at baseline, 57 (46·0%) had more than one indication at baseline. The most common surgical indications at baseline were the presence of symptoms (56·7%), AF (44·1%), pulmonary hypertension (29·1%), and severe MR with LVEF <60% (22·0%). Table 5.1 demonstrates the clinical and echocardiographic characteristics of patients with and without a surgical indication at baseline. Those with a surgical indication showed significantly higher mean mitral gradient, ePASP, LAESV and LAEDV, whilst exhibiting significantly lower atrial and ventricular ejection fractions.

	No Surgical Indication (107)	Surgical Indication (127)	p value (mean difference, 95% CI)
Age (years)	37.1 ± 13.1	38.3 ± 15.0	0.52 (1.21; 95% CI -2.46, 4.87)
Female	74 (73.8%)	82 (64.6%)	0.16
Indigenous	106 (99.1%)	126 (99.2%)	0.90
IHD	5 (4.7%)	8 (6.3%)	0.78
Diabetes	12 (11.2%)	22 (17.3%)	0.20
CKD	7 (6.5%)	12 (9.4%)	0.48
Smoker	31 (29.0%)	38 (29.9%)	0.89
Previous Stroke	2 (1.9%)	7 (5.5%)	0.19
Previous BMV	17 (15.9%)	21 (16.7%)	1.00
Isolated Mitral Stenosis	13 (12.1%)	20 (15.7%)	0.46
Isolated Mitral Regurgitation	18 (16.8%)	24 (18.9%)	0.61
MMVD	76 (71.0%)	83 (65.3%)	0.46
Mitral Gradient (mmHg)	7.7 ± 2.6	10.9 ± 5.5	<0.001 (3.1; 95% CI 2.0, 4.3)
LVEF (%)	61.8 ± 5.2	55.3 ± 10.6	<0.001 (-6.4; 95% CI -8.6, -4.2)
LVEDD (cm)	4.8 ± 0.6	4.9 ± 0.8	0.10 (0.2; 95% CI -0.03, 0.3)
LVESD (cm)	3.1 ± 0.7	3.4 ± 0.9	0.005 (0.3; 95% CI 0.1, 0.5)
ePASP (mmHg)	29.3 ± 9.3	47.4 ± 18.7	<0.001 (18.1; 95% CI 13.0, 23.3)
LAESV (mLs)	84.9 ± 39.1	117.0 ± 58.4	<0.001 (32.2; 95% CI 18.9, 45.5)
LAEDV (mLs)	49.9 ± 34.4	86.3 ± 52.3	<0.001 (36.4; 95% CI 24.5, 48.2)
LAEF (%)	44.5 ± 17.0	28.0 ± 14.9	<0.001 (-16.5; 95% CI -20.7, -12.3)

Table 5.1: *Comparison of clinical and echocardiographic characteristics of patients with and without a surgical indication at baseline*

IHD = ischaemic heart disease. CKD = chronic kidney disease stage II-V. BMV = balloon mitral valvuloplasty. MMVD = mixed mitral valve disease. LVEF = left ventricular ejection fraction. LVEDD = left ventricular end-diastolic diameter. LVESD = left ventricular end-systolic diameter. ePASP = estimated pulmonary arterial systolic pressure. LAESV = left atrial end-systolic diameter. LAEDV = left atrial end-diastolic diameter. LAEF = left atrial ejection fraction.

107 patients without a surgical indication were included in the primary analysis. Mean follow-up time was 3·8±2·9 years after the baseline echocardiogram. 106 (99·1%) were Aboriginal or Torres Strait Islanders. The overall two-year and five-year event free survival rates were 75·4% and 51·1%, respectively [Figure 5.2]. MMVD comprised 71·0% of the mitral valvular disease and three patients (2·8%) did not have image quality sufficient to perform LAEF analysis. 22 patients (21·2%) developed an indication for surgery within two years. The indications for intervention during follow-up were symptoms (45·5%), AF (22·7%), physician directed surgical referral (22·7%), and pulmonary hypertension (9·1%). All five physician directed referrals for surgery were based on a new increase in the ePASP from below 40mmHg, to between 40mmHg and 50mmHg. There were no deaths, embolic events, or IE prior to the development of any surgical indication.

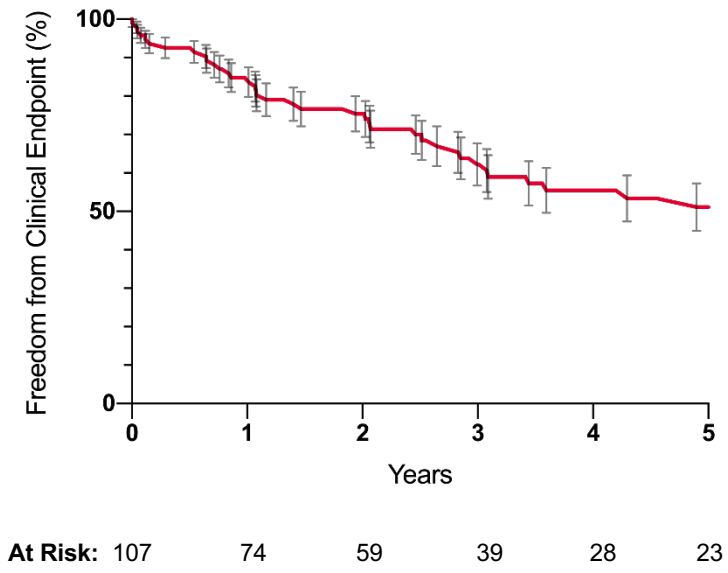


Figure 5.2: *Five-Year Freedom from Clinical Endpoint in Moderate or Severe Asymptomatic Rheumatic Mitral Valve Disease*

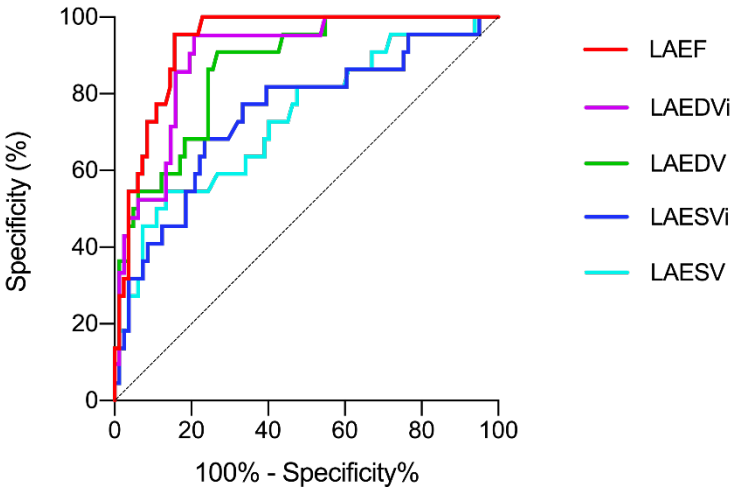
The differences in baseline characteristics between those who developed a surgical indication and those who remained event free are shown in Table 5.2. Multivariable analyses showed that the effect of LAESV (*p=0·002*), LAEDV (*p<0·001*), LAESVi (*p=0·003*), LAEDVi (*p<0·001*) and LAEF (*p<0·001*) were largely unchanged after adjustment for mitral gradient, age and gender.

	No Events (n=85)	Events (n=22)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age (years)	36.7 ± 13.2	38.9 ± 12.6	1.01 (0.98-1.05)	0.48	0.96 (0.91-1.01)	0.10
Female	64 (75.3%)	15 (68.2%)	0.70 (0.25-1.96)	0.50	3.00 (0.63-14.34)	0.17
Indigenous	84 (98.8%)	22 (100.0%)	--	1.00	--	
IHD	5 (5.9%)	0 (0.0%)	--	0.58	--	
Diabetes	11 (12.9%)	1 (4.5%)	0.32 (0.04-2.63)	0.29	--	
CKD	5 (5.9%)	2 (9.1%)	1.60 (0.29-8.86)	0.59	--	
Smoker	25 (29.4%)	6 (27.3%)	0.90 (0.32-2.56)	0.84	--	
Previous Stroke	1 (1.2%)	1 (4.5%)	4.00 (0.24-66.62)	0.33	--	
Previous BMV	11 (12.9%)	6 (27.3%)	2.52 (0.81-7.83)	0.11	--	
Mitral Stenosis	9 (10.6%)	4 (18.2%)	1.88 (0.52-6.78)	0.46	--	
Mitral Regurgitation	15 (17.6%)	3 (13.6%)	0.74 (0.19-2.81)	0.66	--	
MMVD	61 (71.8%)	15 (68.2%)	1.19 (0.43-3.27)	0.74	--	
Mitral gradient (mmHg)	7.4 ± 2.5	9.2 ± 2.7	1.33 (1.09-1.63)	0.005	1.13 (0.86-1.49)	0.38
LVEF (%)	61.4 ± 5.3	62.7 ± 4.3	1.04 (0.96-1.14)	0.36	--	
LVEDD (cm)	4.7 ± 0.5	4.9 ± 0.8	1.51 (0.69-3.29)	0.30	--	
LVESD (cm)	3.1 ± 0.6	3.1 ± 0.8	1.11 (0.55-2.24)	0.77	--	
ePASP (mmHg)	29.3 ± 7.9	29.3 ± 13.0	0.99 (0.94-1.06)	0.98	--	
LAESV (mLs)	77.2 ± 32.0	113.4 ± 49.8	1.02 (1.01-1.04)	0.001	1.02 (1.01-1.04)	0.002
LAESVi (mLs)	44.5 ± 19.2	66.2 ± 27.9	1.04 (1.01-1.06)	0.001	1.04 (1.01-1.06)	0.003
LAEDV (mLs)	39.8 ± 23.4	87.7 ± 42.3	1.05 (1.02-1.07)	<0.001	1.04 (1.02-1.06)	<0.001
LAEDVi (mLs)	22.8 ± 13.9	51.1 ± 25.1	1.08 (1.04-1.12)	<0.001	1.04 (1.04-1.12)	<0.001
LAEF (%)	50.1 ± 13.9	23.7 ± 9.3	0.88 (0.84-0.93)	<0.001	0.87 (0.82-0.93)	<0.001

Table 5.2: *Comparison of Baseline Clinical and Echocardiographic Characteristics Among Asymptomatic Patients Who Did and Did Not Reach Clinical Endpoint within Two-Years*

IHD = ischaemic heart disease. CKD = chronic kidney disease stage II-V. BMV = balloon mitral valvuloplasty. MMVD = mixed mitral valve disease. LVEF = left ventricular ejection fraction. LVEDD = left ventricular end-diastolic diameter. LVESD = left ventricular end-systolic diameter. ePASP = estimated pulmonary arterial systolic pressure. LAESV(i) = left atrial end-systolic diameter (index). LAEDV(i) = left atrial end-diastolic diameter (index). LAEF = left atrial ejection fraction.

Figure 5.3 illustrates the ROC curves for baseline echocardiographic parameters associated with incidence of the clinical endpoint(s) of interest. The indices with the highest C-statistics were LAEF, LAEDVi and LAEDV respectively. A LAEF less than 40% provided sensitivity of 95·5% and specificity of 81·2% in predicting a new surgical indication within two-years, with an adjusted odds ratio of 68·9 (95% CI 8·6 – 549·1, *p<0·001*) and an unadjusted odds ratio of 74·7 (95% CI 9·4 – 593·6, *p<0·001*). After bootstrap resampling the unadjusted 95% CI were 16·1 - 130·3 (*p<0·001*). The relationship between indexed LA volumes and LAEF is shown in Figure 5.4. Figure 5.5 demonstrates the 97·7% vs 33·6% 2-year event-free survival between those with LAEF greater than or less than 40% (*p<0·001*). The analysis remained significant when restricted to either patients with MMVD (*p<0·001)* or patients without MMVD (*p<0·001*) [Figures 5.6 - 5.8].



Predictive Factor	C-Statistic	95% CI
LAEF	0.93	0.89 – 0.98
LAEDVi	0.88	0.81 - 0.95
LAEDV	0.87	0.80 - 0.95
LAESVi	0.75	0.62 - 0.87
LAESV	0.74	0.61 - 0.86
Mitral Gradient	0.69	0.55 – 0.83

Figure 5.3: *Receiver Operating Curves and C-Statistic for Left Atrial Predictors of an Event Within Two-Years*

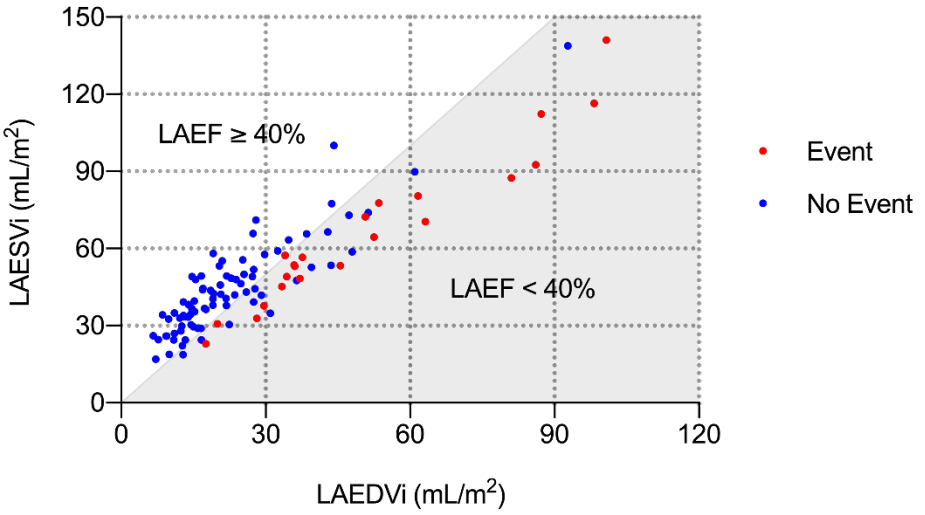
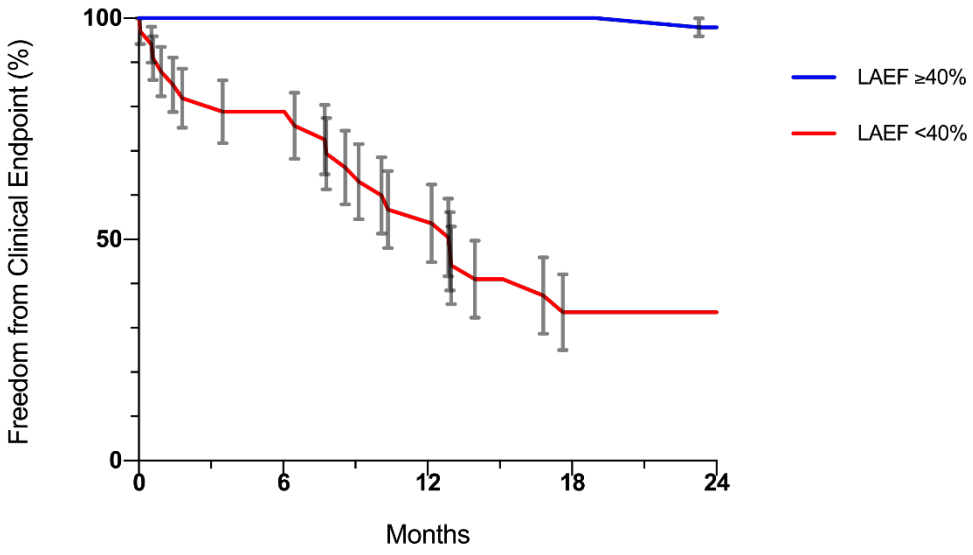


Figure 5.4: *Relationship between indexed Left Atrial End-Systolic Volume and indexed Left Atrial End-Diastolic Volume in patients with rheumatic mitral valve disease*



At Risk

LAEF ≥40%: 65	56	53	51	48
LAEF <40%: 39	26	18	9	9

Figure 5.5: *Event-free survival based on a 40% Left Atrial Ejection Fraction cut-off for asymptomatic patients with rheumatic mitral valve disease*

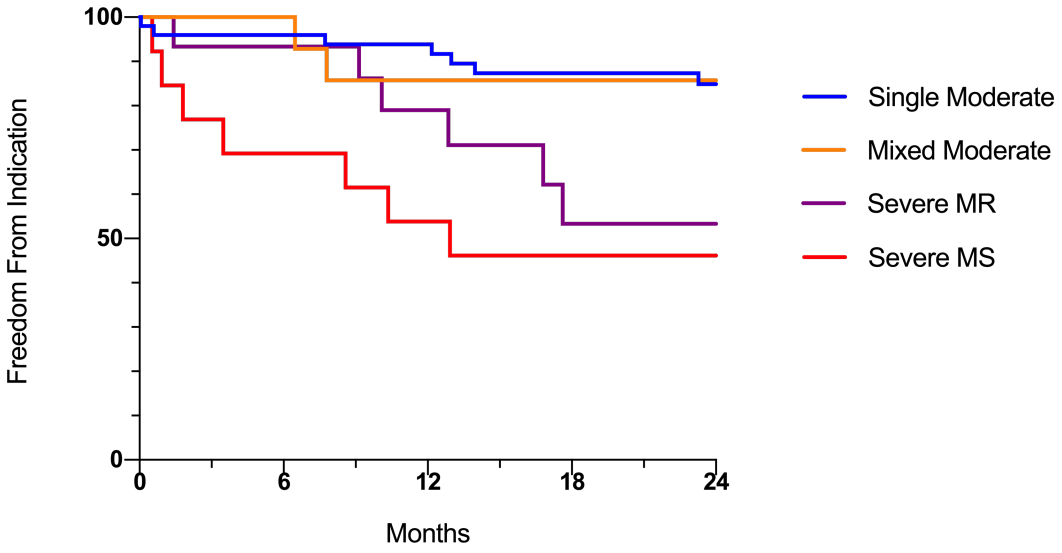


Figure 5.6: *Freedom from Clinical Endpoint by Mitral Pathology*

Single moderate = moderate mitral regurgitation or stenosis (excluding any severe disease), Mixed moderate = moderate mitral regurgitation and stenosis, MR = mitral regurgitation, MS = mitral stenosis

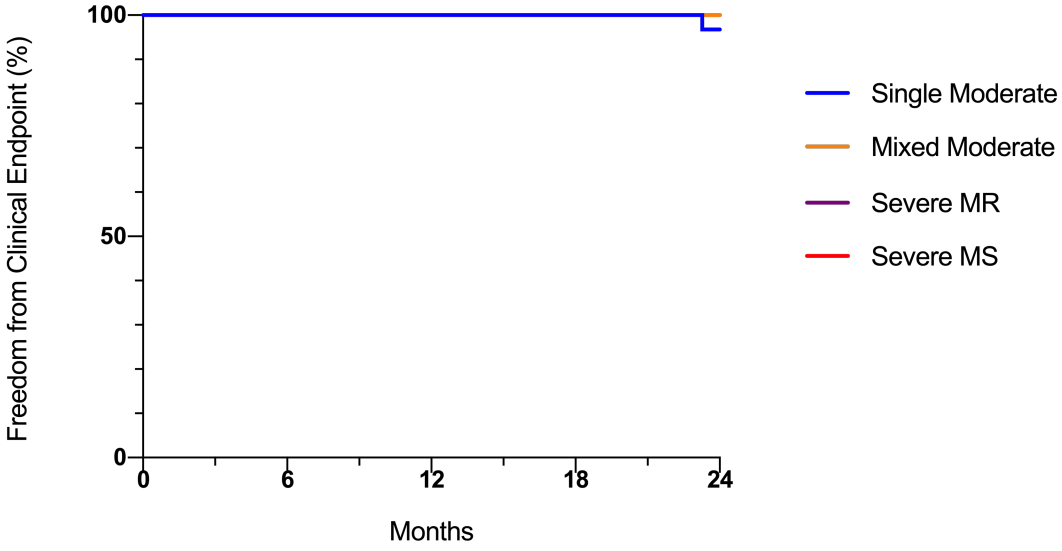


Figure 5.7: *Freedom from Clinical Endpoint by Mitral Pathology with Left Atrial Ejection Fraction >40%*

Single moderate = moderate mitral regurgitation or stenosis (excluding any severe disease), Mixed moderate = moderate mitral regurgitation and stenosis, MR = mitral regurgitation, MS = mitral stenosis.

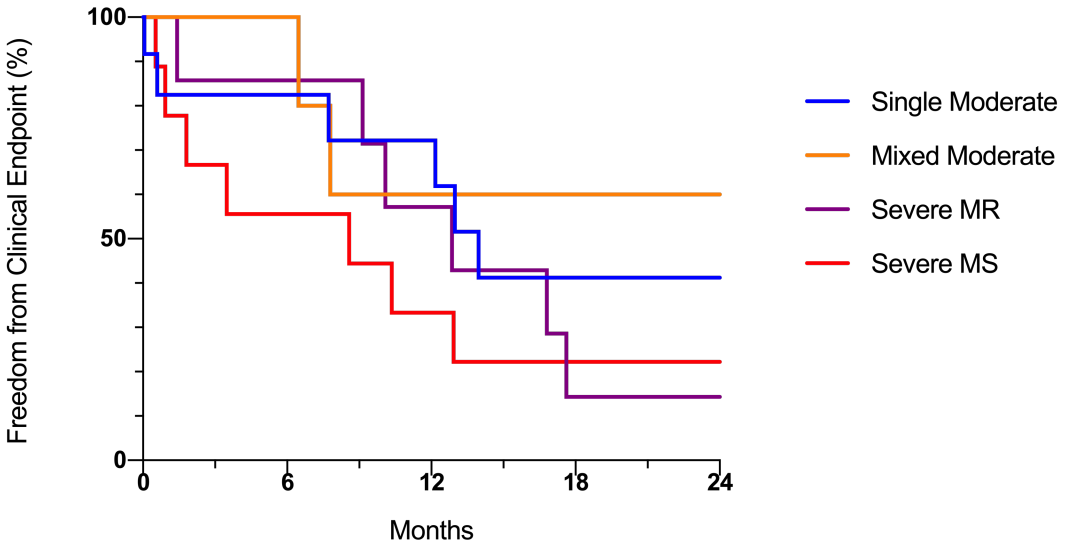


Figure 5.8: *Freedom from Clinical Endpoint by Mitral Pathology with Left Atrial Ejection Fraction <40%*

Single moderate = moderate mitral regurgitation or stenosis (excluding any severe disease), Mixed moderate = moderate mitral regurgitation and stenosis, MR = mitral regurgitation, MS = mitral stenosis.

5.6 Discussion

This is the first study to illustrate contemporary outcomes of asymptomatic patients with moderate and severe rheumatic mitral valve disease in individuals who do not meet standard clinical and echocardiographic indications for cardiac surgery based on ESC/EACTS guidelines (Baumgartner et al. 2017). Our asymptomatic cohort demonstrated very high overall event rates at both two and five years. This retrospective cohort study found that a reduced LAEF (< 40%) predicted the development of a new surgical indication with high sensitivity and specificity, within two years. Interestingly, the mean baseline LAEF seen in asymptomatic patients who develop a surgical indication was very similar to the mean LAEF in patients who already had a surgical indication. This suggests that a reduced LAEF may be the first sign of cardiac compromise in rheumatic mitral valve disease.

RHD is associated with considerable morbidity and early mortality (Carapetis et al. 2016). The high event rates seen in this study are significantly worse than those documented within longitudinal studies of asymptomatic non-rheumatic severe mitral regurgitation (Rosenhek et al. 2006a; Enriquez-Sarano et al. 2005). In aortic valve studies there is good evidence that mixed valvular disease has a worse prognosis compared to isolated stenotic or regurgitant valvular pathology (Egbe, Poterucha, and Warnes 2016). There is little longitudinal data currently describing the outcomes of MMVD and this study is the first to provide insight into this patient population. It would be reasonable to assume that the added effect of MR with LA end-systolic volume overload to MS or conversely, the added effect of MS with raised end-

diastolic pressures to MR, would cause more rapid decompensation than otherwise seen in the setting of isolated MS or MR (Kennedy et al. 1970). Following mitral valve surgery, some studies have shown an early improvement in LA function, reflecting that a reduced LAEF is predominantly due to volume and pressure overload rather than an intrinsic atrial cardiomyopathy (Dardas et al. 2004; Antonini-Canterin et al. 2008). However, over time with severe disease, LA fibrosis and myocardial loss have been shown to occur in both MS and MR and act as a substrate for future AF and are likely irreversible (John et al. 2008; Boldt et al. 2004). Significant valvular disease left untreated for a long period of time may impact LAEF recovery and remodelling, as well as contribute to the poor prognosis associated with AF after mitral surgery. LAEF-directed early intervention in moderate or severe mitral disease, prior to the onset of these poor prognostic markers, may improve both the short and long-term survival for these patients.

Whilst there is understandably an association with valve severity and haemodynamic consequence, figures 5.6-5.8 show that the haemodynamic changes associated with valvular disease, as indicated by LAEF, much more accurately predict the onset of an indication for surgery than just severity alone. In fact, measurements like gradients across the valve simply reflect flow rates and valve area. Flow rates can often decline due to loss of or reduced LA contraction, thus underestimating the haemodynamic impact of the pathology. This may explain why mean mitral gradient does not perform as other LA parameters for predicting the onset of surgical indications.

The presence of any surgical indication portends a higher mortality and morbidity in the short and long-term after valve replacement (Tribouilloy et al. 1999; Ghoreishi et al. 2011). Therefore, markers that can predict the development of a surgical indication have the potential to improve outcomes after valve surgery, whilst also minimising the performance of what may be considered unnecessary surgery. There is an increasing trend towards earlier surgery, which has the potential to contribute to improved long-term prognosis (Montant et al. 2009; Baumgartner et al. 2017). Invasive haemodynamics, echocardiographic strain analysis, exercise testing and cardiac magnetic resonance (CMR) imaging can provide supplementary information but are not readily available for patients residing in resource-poor and remote settings (Magne, Lancellotti, and Pierard 2010; Myerson et al. 2016).

In non-rheumatic primary MR, LAESV is a validated prognostic factor and now appears in both the American Heart Association / American College of Cardiology (AHA/ACC) and ESC/EACTS valvular guidelines (Nishimura et al. 2017; Baumgartner et al. 2017). Both LA size and function are reproducible measurements and have shown promise as predictors of outcomes in coronary disease, atrial fibrillation, heart failure and stroke (Hoit 2014; Pellicori et al. 2014; Santos et al. 2014). The normal LAEF in healthy populations is ≥50% (Morris et al. 2015; Hoit 2014). There are no known differences between males and females, and it has been shown to decline after 60 years of age (Morris et al. 2015). In primary severe mitral regurgitation, a reduced LAEF has been shown to have the strongest relationship to the presence of a surgical indication compared to other

echocardiographic parameters (Ring et al. 2014). This is consistent with findings of the present study, where patients with a surgical indication at their baseline echocardiogram had a significantly reduced LAEF compared to those without a surgical indication. Our study is the first to show prognostic and predictive utility of LAEF in patients without a surgical indication. The predictive value of LAEF shown in our study provides evidence for the utility of this measurement in patients with rheumatic mitral valve disease.

Reversal of LAEF has been shown to be possible with mitral valve intervention. This is best assessed with percutaneous balloon mitral valvuloplasty (PBMV) which does not distort the architecture of the LA or mitral annulus (Inoue et al. 1984; Wilkins et al. 1988). Successful PBMV procedures are known to result in an immediate reduction of left atrial pressure (LAP). LA kinetic energy (active LA contraction) is associated with symptoms in patients with MS and heart failure patients (Stefanadis, Dernellis, Lambrou, et al. 1998). A lower LAEF correlates with symptoms in heart failure patients (Roşca et al. 2010). This improves significantly following PBMV and on a four-chamber area basis this was quantified at 15.1% $\pm$ 4.9% (Stefanadis, Dernellis, Stratos, et al. 1998). Other echocardiographic changes post PBMV include improved right ventricular (RV) function, however this was not evident in the mid-term in those with pulmonary hypertension (İnci et al. 2015). This is presumably due to the aetiologic heterogeneity of pulmonary hypertension and RV dysfunction in patients with valvular heart disease (Magne et al. 2015). Left ventricular and right ventricular strain have also

been shown to improve statistically, but not by a clinically significant margin (Roushdy et al. 2016).

There are very few diseases that so glaringly represent the inequitable distribution of health within the same national borders as RHD among Indigenous and non-Indigenous Australians (Kim et al. 2019; Azzopardi et al. 2018). Globally, RHD continues to be highly prevalent in the world's poorest regions, with associated barriers to healthcare delivery (Watkins, Johnson, Colquhoun, Karthikeyan, Beaton, Bukhman, Forouzanfar, Longenecker, Mayosi, Mensah, et al. 2017). Remote echocardiographic assessment has been established through screening programs in many countries with a high prevalence of RHD. The high applicability of LAEF as a prognostic tool to supplement current practice models may afford unique benefit to patient populations who are impoverished and often living in remote locations with limited access to healthcare and healthcare infrastructure. The ability to identify high risk patients allows limited resources to be directed to those who will likely need them most.

5.6.1 Limitations

Several potential limitations should be noted. The data is from a single location with rates of RHD that are among the highest in the world (Kim et al. 2019). Despite the event rates in this study being high, the non-standardised follow-up may have inadvertently underestimated the frequency of events. The absolute number of events was relatively low, and the statistical modelling approach was relatively simple for practical purposes. Medication

data were not recorded and although no studies to date have shown any benefit from pharmacotherapy, this may have impacted patient outcomes. The echocardiograms were obtained for clinical purposes by sonographers experienced in RHD assessment, however image acquisition was not standardized. While the findings of the present study suggest early surgery in selected patients may be associated with improved outcomes, there was no external validation and future research is needed to evaluate the post-surgical outcomes of patients with a reduced LAEF and no current standard surgical indication compared to those with an indication. Reproducibility between the cardiologists was not assessed. a retrospective study, the percentage of scans with dedicated LA views was not assessed. However, in the context of RHD, Northern Territory sonographers tend to regularly assess LA volumes using dedicated views which may limit applicability in other settings.

5.7 Conclusion

LAEF is a widely available and reproducible method of evaluating the large number of patients with moderate-severe rheumatic mitral valve disease. It is a strong predictor for the development of a new surgical indication in a population with a high event rate. It can be easily applied to current RHD management models and can be performed in remote and resource poor settings. Patients with a preserved LAEF can be safely monitored while those with a LAEF <40% should be followed closely and considered for early surgery.

CHAPTER 6

Final Discussion

This thesis has examined the optimisation of surgical timing in patients with rheumatic mitral valve disease. It has provided new information related to the differences in geographical burden, sonographer screening, current rates of surgical referral and concordance with guidelines, as well as identified a novel strong predictor for needing surgery in the near future. This is in context of the low rates of surgery for patients with rheumatic mitral valve disease that have a surgical indication already. These findings provide further insight into how we can improve outcomes from significant rheumatic mitral valve disease in the future.

Early valvular intervention is associated with improved long-term outcomes for patients. Recent improvements in valve technology may provide alternative approaches to long-term valve planning for these patients. The first valvular intervention for rheumatic heart disease patients commonly occurs in early adulthood. This is associated with significant long-term morbidity, especially if they present late. The identification of asymptomatic patients required targeted screening. There are no current indications for surgery that are not associated with reduced mortality and morbidity post-operatively.

In Chapter 2, we characterise the rates of accepted referral and intervention in patients with significant rheumatic mitral valve disease. Although there were no Australian or international comparators, the rates of valve surgery appear low for such a young cohort. The low median time from indication to accepted referral and subsequent intervention indicates that those who were

considered for surgery were acted upon in a timely manner. This raises questions regarding the cohort who did not have an accepted referral that requires further study. Did the patients not want to be referred for surgery, if so, why? Did their cardiologists believe the surgery would be futile in the context of the patients' other comorbidities, or not think they would benefit from surgery? Chapter 3 examines the prevalence of rheumatic heart disease found through echocardiographic screening of school-aged children in South Australia. It also examines geographical differences and associations by postcode. This is the first comparison between metropolitan, rural and remote prevalence of RHD in Indigenous children using echocardiographic screening and confirms registry data.

We have seen no decline in the incidence of acute rheumatic fever or prevalence of RHD in the last 10-15 years in Australia (Katzenellenbogen et al. 2020). Sustainable screening programs are essential to the ongoing identification of asymptomatic disease. Chapter 4 evaluates sonographer performance in reporting rheumatic heart disease on screening, as well as sonographer confidence with the international screening criteria. This is the first evaluation of the criteria by experienced sonographers and validates sonographer led screening, with cardiologist referral of only abnormal scans. Despite their significant experience, confidence with the screening criteria was significantly different between the pathological regurgitation parameters and morphological parameters used as part of diagnosis. This is important for future iterations of the criteria and these data also serve as a benchmark for all non-sonographer echocardiographic screening studies. Some studies

outside of Australia have utilized single sweep views of the mitral valve with simplified criteria to detect rheumatic heart disease which may be appropriate in some environments (Remenyi et al. 2020). However, in the Australian context, and outlined in Chapter 3, we detected several congenital abnormalities (Bolisetty et al. 2004). The future consequences of a negative screening echocardiogram, such as delayed diagnosis for those with congenital heart disease, remains unknown.

In Chapter 5, various echocardiographic and clinical parameters were compared for their ability to identify people with rheumatic mitral valve disease who require valve intervention in the near future. LAEF was shown to be the strongest and most robust predictor. This is not necessarily unexpected as reduced LAEF has previously been shown to predict people having a surgical indication (Ring et al. 2014). It has also been used in people with heart failure with both preserved and reduced ejection fraction to predict hospitalisations (Reddy et al. 2020)(Pellicori et al. 2014). This novel finding that has wide reaching implications to not only RHD, but also mitral valvular disease more generally. Its utility in predicting need for surgery in mixed mitral valve disease, in which there are no established surgical indications, is likely its most novel impact. Against more traditional surgical indications for single valve pathologies, its role is less clear and requires more research. In addition, the simplicity of determining LAEF means that it is able to be utilized in resource poor regions with high rheumatic heart disease prevalence. The outcome of patients with reduced LAEF compared to those with preserved ejection fraction have not yet been studied.

The optimisation of surgical timing in rheumatic mitral valve disease requires a multifaceted approach. Ultimately, early diagnosis and close monitoring of individuals who will likely need surgery in the near future is key. In resource limited settings, these basic tools are key to ensuring better outcomes for patients in long-term and can be easily implemented into current practice.

CHAPTER 7

Future Directions

Understanding current referral and intervention practice for rheumatic heart disease in Australia is crucial to improving systems, practice, and ultimately patient outcomes. There are a large number of patients who do not have valvular intervention despite it being indicated. Understanding the reasons behind this may help to overcome barriers to surgery for these patients and improve outcomes. Further, understanding the impact of delays on outcomes is important to advocate for early intervention and streamlined processes for these patients. The study did not have enough cases to examine temporal differences in referral and intervention practice. This, alongside an examination of changes in healthcare access and resources, may also assist in understanding the barriers to treatment.

Screening has resulted in many asymptomatic people with rheumatic heart disease being identified. This allows not only secondary prophylaxis administration reducing disease progression, but also the monitoring of valve integrity and early intervention. Screening programs are likely to be tailored to individual environments, each with their own unique sonographic expertise, infrastructure and requirements. Every screening region will likely require their protocol to be validated with ongoing inbuilt quality control features.

Finally, left atrial ejection fraction has been shown to identify patients who will develop an indication for surgery within two years. This raises a number of questions. The impact of a reduced left atrial ejection fraction on surgical outcomes following mitral surgery needs evaluation. Whether left atrial ejection fraction recovers following mitral intervention, and its impact on long-

term mortality and morbidity, is also unknown. Ultimately, in order to definitively determine whether left atrial ejection fraction is an early predictor for surgery in patients with rheumatic mitral valve disease; a prospective randomised controlled trial is needed.

8 REFERENCES

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And so for a time it looked as if all the adventures were coming to an end;

but that was not to be.

C.S. Lewis