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Review Article

RHEUMATIC VALVULAR VITIUM OF HEART

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ABSTRACT

Background:

Valvular heart disease is a leading cause of cardiovascular mortality, especially in China. More than a half of valvular heart diseases are caused by acute rheumatic fever. microRNA is involved in many physiological and pathological processes. However, the miRNA profile of the rheumatic valvular heart disease is unknown. This research is to discuss microRNAs and their target gene pathways involved in rheumatic heart valve disease.Rheumatic heart disease (RHD) remains a disease of international importance, yet little has been published about disease progression in a contemporary patient cohort. Multi-state models provide a well-established method of estimating rates of transition between disease states, and can be used to evaluate the cost-effectiveness of potential interventions. We aimed to create a multi-state model for RHD progression using serial clinical data from a cohort of Australian patients.

Methods and Results:

The Northern Territory RHD register was used to identify all Indigenous residents diagnosed with RHD between the ages of 5 and 24 years in the time period 1999–2012. Disease severity over time, surgeries, and deaths were evaluated for 591 patients. Of 96 (16.2%) patients with severe RHD at diagnosis, 50% had proceeded to valve surgery by 2 years, and 10% were dead within 6 years. Of those diagnosed with moderate RHD, there was a similar chance of disease regression or progression over time. Patients with mild RHD at diagnosis were the most stable, with 64% remaining mild after 10 years; however, 11.4% progressed to severe RHD and half of these required surgery.

Conclusions:

The prognosis of young Indigenous Australians diagnosed with severe RHD is bleak; interventions must focus on earlier detection and treatment if the observed natural history is to be improved. This multi-state model can be used to predict the effect of different interventions on disease progression and the associated costs.

INTRODUCTION

Rheumatic heart disease (RHD) remains a disease of international importance, yet little has been published about disease progression in a contemporary cohort. Much of our understanding of the natural history of the disease stems from seminal studies conducted over 50 years ago.1, 2, 3 While disease pathophysiology may have changed little since that time, the introduction of benzathine penicillin G (BPG) prophylaxis, as well as the availability of cardiac valve surgery in some settings, has changed the prognosis of established RHD considerably. An understanding of the current trajectory of RHD is important so that the potential impact of new interventions can be realistically estimated.

RHD is a disease of poverty, and the associations with overcrowding and lower socioeconomic status are well documented.4, 5 While it is now predominantly a disease of developing countries, the Indigenous population of Australia continues to experience rates of acute rheumatic fever (ARF) and RHD that are among the highest in the world.6 In the Northern Territory (NT) of Australia, there is an active RHD control program, and a computerized register was established in 1997. This register includes clinical information about individual patients' diagnosis, treatment, and clinical course, and provides the opportunity to evaluate local disease epidemiology in some detail. A number of audits have been undertaken using NT register data,6, 7, 8 but none to date have analyzed the progression of RHD from diagnosis to the occurrence of several important clinical events, including heart failure, surgical intervention, death, or disease remission.

In order to evaluate the potential health and economic impact of new interventions, a model of disease progression is required. As RHD is a chronic disease that can progress or regress over time, a multi-state model is well suited to this process (as opposed to a simple decision tree). The progression from diagnosis to heart failure, and the need for costly surgery, is of primary interest for economic modeling. Quantifying the probability of progression over time through standard Kaplan–Meier estimates (used in survival analysis) will be inaccurate due to the competing risk of death,9 which is higher in RHD patients compared to the general Indigenous population.8 A multi-state model overcomes this limitation because heart failure and death can be defined as mutually exclusive health states. Additionally, health states can also be included to represent the severity of RHD (ie, mild, moderate, or severe with and without surgery), allowing the natural history of disease to be expressed as time spent in these health states, as defined by state transition probabilities. Thus, the expected change in health states from an intervention that alters the natural history of disease can be estimated at an individual level by a change in the transition probabilities, or at an aggregated cohort level by a change in the initial distribution of RHD severity at diagnosis.

We therefore aimed to create a multi-state model for RHD progression using serial clinical data from a real cohort of Australian RHD patients. This model can then be used to evaluate the cost-effectiveness of a proposed school-based echocardiographic screening program in the contemporary Australian context.

METHODS

Model Type:

Multi-state models provide a flexible framework that allows us to model a disease process by defining several health states of interest and describing the probability of transitioning from 1 state to another over time.10, 11, 12 If transition out of a health state is possible, the state is said to be transient. If transition is not possible, that state is said to be absorbing (for example, death). A multi-state model is a

particularly good model for RHD: a chronic process where patients may transition back and forth between different clinical states over time.

Our model is subject to the Markovian assumption that the transition process is "memoryless," meaning that the probability of transitioning from one state to another is not affected by time spent in previous health states. This is somewhat artificial, given that prior history often affects future prognosis. Despite this limitation, we chose a multi-state model because it permits a more useful and valid analysis of RHD progression than a simple survival analysis, which can only evaluate 1 event (eg, time to surgery, or time to death), and does not take into consideration competing risks where 1 event precludes the event of interest occurring (eg, death preventing surgery).9, 10

Data Source:

The NT RHD register includes data about patient demographics, clinical details, and investigations of all individuals diagnosed with ARF or RHD in the NT. Data are entered by register staff at diagnosis, and at each subsequent clinical review, based on clinician notes and/or laboratory or echocardiography reports. Hospital and primary care databases are regularly searched by register staff to ensure clinical information is as complete as possible. De-identified data were extracted from the RHD register and assessed for inconsistencies and completeness. A wavier of consent was sought for the use of existing data and the study was approved by the Human Research Ethics Committee of the Menzies School of Health Research.

Study Cohort:

Our study was based on a cohort of Indigenous persons identified from the NT RHD register. We selected NT residents aged 5 to 24 years diagnosed with RHD between January 1, 1999 and December 31, 2012, which was the date at which data were censored. We did not extract information about patients who had a diagnosis of ARF without RHD.

Health States:

Patients on the NT RHD register are categorized as having mild, moderate, or severe RHD (Priority level 3, 2, and 1, respectively), as outlined in the Australian RHD guidelines.13 We used this classification to describe disease severity (Table 1). Patients' priority levels are allocated by physicians, and are updated with each clinical encounter. It was assumed that patients remained in the same priority level each month between clinical encounters. Patients who require surgery are automatically assigned a "Severe" priority level (Priority 1) in the register; however, we modeled surgery as an explicit health state (Priority 1a). In cases where surgery was required at diagnosis, we modeled the assignment of the "Severe" priority level followed by a delay of less than 1 week before transition to the "Severe–Surgery" state. This change was required only at diagnosis to confine the initial states of RHD to mild, moderate, and severe.

Table 1: RHD Health State Definitions (Adapted From the Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease, 2012)13

According to the Australian RHD guidelines, a patient may transition to the "Inactive" state if they have completed a minimum of 10 years' antibiotic prophylaxis after their most recent episode of ARF, and if there are minimal valvular changes on echocardiogram at the time of final review. Possible transitions between RHD states are illustrated in Figure 1.

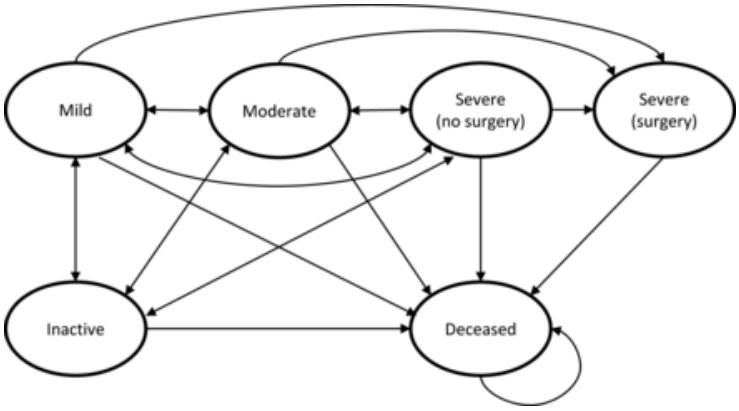


Figure 1: Potential health state transitions of patients on the NT RHD register. NT indicates Northern Territory; RHD, rheumatic heart disease.

Our analysis did not include 2 factors that could potentially affect the course of disease. Secondary prophylaxis data have only been entered into the register since 2007, and were therefore considered too incomplete to be useful. Recurrences of ARF were also difficult to capture, as they relied on a previous diagnosis of ARF, and some of our cohort had never had a previously recorded episode of ARF.

Data Quality Assessment and Exclusions:

The date of RHD diagnosis was defined as the date of diagnosis recorded on the register unless there were clinical reviews before the recorded diagnosis date, in which case the date of first review was used as a surrogate. If a priority level had not been assigned within 1 year of a recorded RHD diagnosis, individual clinical records were reviewed and, where possible, a priority level was allocated based on available clinical information (including clinician notes and echocardiogram reports) contained in the register. Cases were excluded if there was insufficient clinical information to permit allocation of a priority level at diagnosis.

Statistical Methods: All data analysis was performed in R (version 3.1.0, 2015). Age at diagnosis was categorized into 4 groups (5–9, 10–14, 15–19, and 20–24 years) for comparison with existing studies, and all data were summarized as frequency distributions. Chi-square tests (or Fisher's exact test where indicated) were performed to assess differences in RHD severity at diagnosis, valve surgery, and mortality between sex, and the age at diagnosis. Additionally, RHD severity at diagnosis was compared between sexes within 2 subgroups; children (5–14 years) and young adults (15–24 years).

The probabilities of being in a particular RHD health state at the end of each month following diagnosis were obtained from the Aalen-Johansen transition estimates calculated by the “msSurv” package (version 1.1-2, 2012), with corresponding 95% CI calculated from 200 bootstrap samples. Plots were constructed using the “ggplot2” package (version 1.0.1, 2015).

RESULTS

Data Set:

Information about 618 Indigenous persons aged 5 to 24 years inclusive, diagnosed with RHD between January 1999 and December 2012, was extracted from the NT RHD register (Figure 2). A detailed review of 272 records (44.0%) was required due to incomplete or inconsistent data. A priority level had not been allocated within 1 year of RHD diagnosis for 164 patients. Of these, sufficient clinical information was available to allow priority level allocation in 144 cases, but 20 were excluded due to inadequate information, including 3 deaths, which was the only data entry point for these patients.

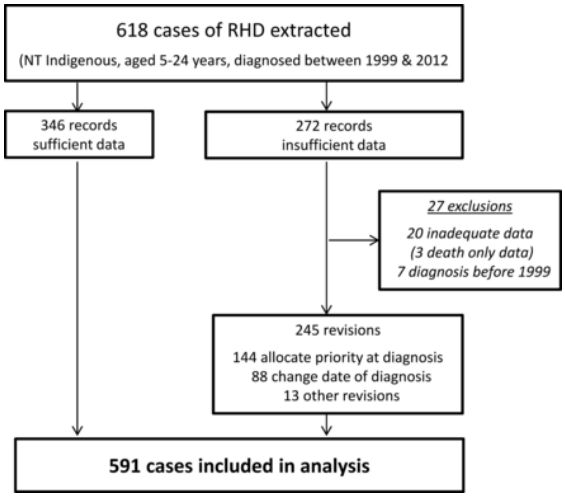


Figure 2: Selection of RHD cases included in analysis. NT indicates Northern Territory; RHD, rheumatic heart disease.

Ninety-five patients had clinical reviews recorded more than 1 year before their RHD diagnosis date; 7 of these were excluded due to an actual diagnosis date before 1999, and the remainder had their diagnosis date revised to correspond with the date of first clinical review. Other reasons for review included the following: surgery date before diagnosis date (n=2), interstate residence (n=3), and inconsistent sequences of records (for example, multiple priority transitions in <6 months; n=8).

After exclusions, 591 records were available for analysis with a median follow-up time of 7.5 years postdiagnosis (interquartile range 4.3–10.3).

Clinical Information Obtained from NT Register RHD incidence and severity:

Clinical information regarding 591 cases of RHD is presented in Table 2. There were more females than males, which was consistent within each age category (data not shown), and the highest number of RHD cases was reported in 10- to 14-year-olds.

Table 2: Clinical Information About Patients Aged 5 to 24 Years Diagnosed with RHD Between 1999 and 2012

At diagnosis, 96 (16.2%) patients had severe RHD, and over the 14-year study period 176 patients (29.8%) were diagnosed with severe RHD. The proportion with severe RHD at diagnosis did not vary significantly between sex (*P*=0.29) or age group (*P*=0.33; Table 2). However, within the subgroup of 5- to 14-year-old children, a greater proportion of girls than boys presented with severe disease (*P*=0.03; Figure 3).

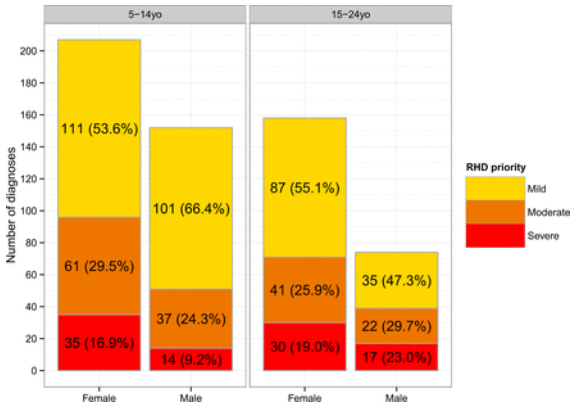


Figure 3: Number and severity at diagnosis of cases of RHD diagnosed between 1999 and 2012, by age and sex. RHD indicates rheumatic heart disease.

Surgery:

A total of 131 surgeries were performed in 97 patients; 83 valve repairs (63.4%), and 46 valve replacements (35.1%); surgery type was not specified in 2 cases. Seventy-three patients had a single procedure, 18 had 2 surgeries, and 6 had ≥3 surgeries. The number of patients requiring at least 1 surgery did not statistically differ between age groups (*P*=0.32) or sex (*P*=0.11). The median time to surgery for children diagnosed with severe RHD was 2 years. The age at first surgery is presented in Figure 4.

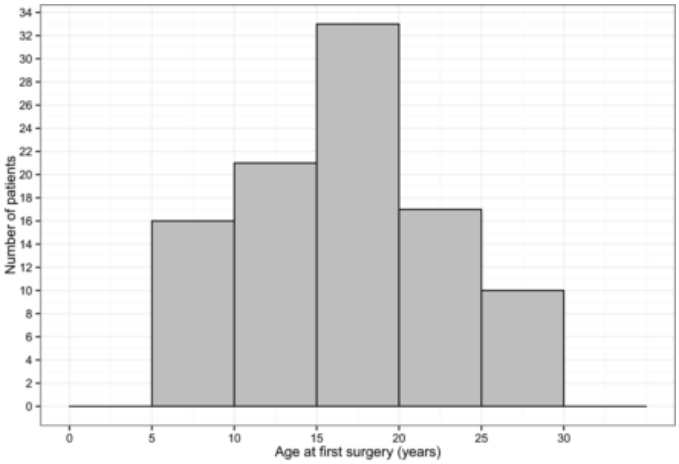


Figure 4: Age of RHD patient at time of first cardiac surgery. RHD indicates rheumatic heart disease.

Deaths:

There were 18 deaths during the study period. Of these, 10 had severe RHD at the time of diagnosis, and 16 had severe RHD at the time of death. Eleven had undergone surgery. There was no statistical difference in the number of deaths by age group at diagnosis (Fisher's exact test, *P*=0.11) or sex (*P*=0.58). The age at death is presented in Figure 5 and included 2 deaths in children under 15 years of age.

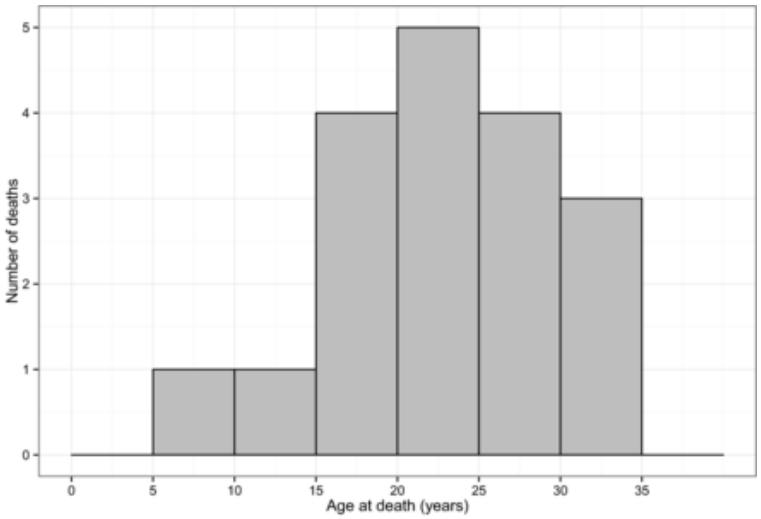


Figure 5: Age of RHD patient at time of death. RHD indicates rheumatic heart disease.

Disease Progression Over Time: A Multi-State Model for RHD:

Transition probabilities between all RHD health states were calculated for each month over the 14-year study period. The probabilities that a patient will be in a given health state 1, 5 and 10 years after RHD diagnosis are presented in Table 3. For example, of the patients diagnosed with mild RHD, 93.9% remained mild 1 year after diagnosis while 4.7%, 1.1%, and 0.3% progressed to moderate, severe, and severe with surgery, respectively. Probabilities for age groups 5 to 14 and 15 to 24 years are presented separately in Tables S1 and S2 and Figures S1 and S2.

Table 3: Estimated Severity of RHD Patients (Aged 5–24 Years at Diagnosis) 1, 5, and 10 Years After Diagnosis

Disease progression over time, based on RHD severity at diagnosis, is graphically represented in Figure 6.

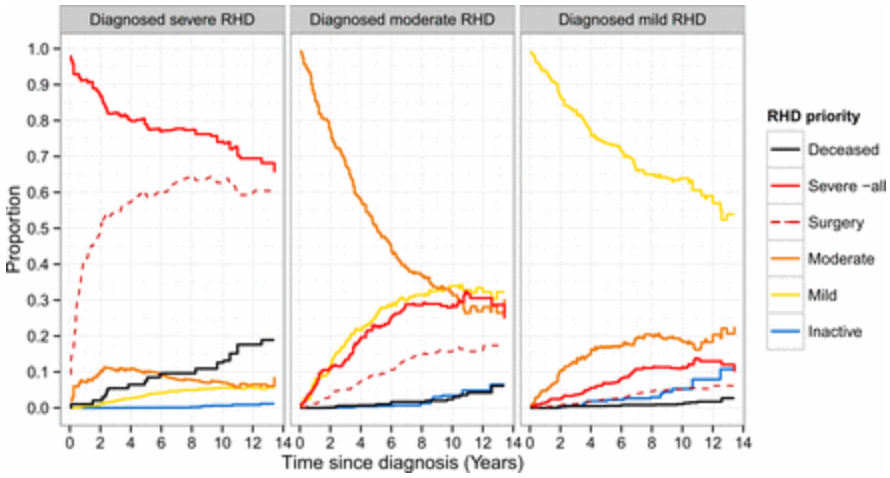


Figure 6: RHD prognosis over 14 years; probability that an individual will be in a particular health state over time, based on RHD severity at diagnosis. RHD indicates rheumatic heart disease.

Young people who had severe RHD at the time of diagnosis had rapid disease progression and a poor prognosis; 50% of this group had surgery within 2 years, and 10% were dead within 6 years of their diagnosis. Patients diagnosed with moderate RHD had a mixed prognosis; 10 years after diagnosis, roughly one third had progressed to severe RHD (with or without surgery), one third remained moderate, and one third had regressed to mild RHD. Those who had mild RHD at diagnosis had the most favorable prognosis, with over 60% remaining mild after 10 years, and 10% being inactive by the end of the 14-year study period. Nonetheless, nearly 30% of this group demonstrated disease progression (18.3% moderate, 11.4% severe, half of whom had surgery) by 10 years.

DISCUSSION

This is the first time a multi-state model for RHD progression has been developed using real patient data. The NT register contains the best available data on a contemporary cohort of RHD patients in the world, and we believe that our analysis provides an accurate picture of the trajectory of RHD for young Indigenous Australians today. Furthermore, we believe that our model may be informative for other populations in RHD-endemic settings who face similar socioeconomic disadvantage, poor adherence to BPG, and high rates of ARF recurrence.

Overall, 16.2% of our cohort had severe disease at diagnosis (Table 2). We were surprised that this proportion did not vary significantly between age groups, and that 15% of 5- to 9-year-olds presented with severe disease. This suggests either that the first episode of ARF is occurring very early (and is being missed), or that there is a group of children who have a fulminant presentation with ARF carditis that quickly progresses to severe RHD. This notion could be supported by a number of earlier studies describing presentations with congestive cardiac failure and/or cardiomegaly in 10% to 20% of first ARF episodes.1, 2, 3, 14, 15, 16 In all of these studies, severe carditis at presentation universally correlated with the poorest prognosis. Unfortunately, in this group of children, screening is unlikely to make a difference to their disease progression, although, in the Australian setting, where cardiac surgery is readily available, earlier surgery would be expected to improve clinical outcomes and reduce mortality.

Over the 13-year study period, 176 patients (29.8%) were diagnosed with severe RHD, which is comparable to the 28% reported in Lawrence's audit of NT data,8 despite our younger cohort. It should be

noted that the majority of children with severe RHD in the Australian context would be considered New York Heart Association Functional Class I or II, as opposed to New York Heart Association Functional Class III or IV, as was the case in the recently published Global Rheumatic Heart Disease Registry (the REMEDY study)5 (a multi-center hospital-based registry of RHD patients in low- and middle-income countries). The ready availability of cardiac surgery in Australia means that children with severe RHD in New York Heart Association Class II automatically proceed to surgery.

The prognosis of patients diagnosed with severe RHD is bleak. Figure 6 shows the rapid progression to surgery, with 41.6% having surgery within 12 months of their diagnosis (Table 3). The proportion proceeding to surgery starts to plateau at about 60% by 4 years postdiagnosis, at which stage mortality starts to increase. This is particularly marked in the 15- to 24-year-old age group (Table S2) which had 13.7% mortality by 5 years (95% CI 3.4–24.0) and 22.0% by 10 years (95% CI 9.0–35.0). By 10 years postdiagnosis with severe RHD, over three quarters of 15- to 24-year-olds had progressed to surgery or death (Figure S2).

The implications of valve surgery in this population are particularly significant. Among Indigenous Australians receiving surgery for ARF or RHD, nearly 45% are under 25 years of age.17 The young age at surgery means that most of these patients will need multiple operations over their life, and that, while valve repair is the initial procedure of choice, mechanical valve replacement will be required in many, including women of childbearing age. The requirement for anticoagulation adds substantial risk, due to the challenges of international normalized ratio (INR) monitoring in this setting. A recent audit of Indigenous RHD patients on warfarin found that only 60% had adequate INR testing and that, of these, only 25% had INRs in the recommended range, putting these individuals at high risk for hemorrhagic or thromboembolic complications.18

The natural history of patients diagnosed with moderate RHD is the most dynamic, with roughly equal proportions likely to progress, regress, or remain moderate at 10 years. We have previously undertaken a large echocardiographic screening survey of Indigenous children in the NT,19 and of the 18 new cases of Definite RHD detected, 7 (39%) were considered to be moderate by the reporting cardiologist. Given that this group is asymptomatic, yet has established RHD on echocardiogram, these children may stand to benefit most from screening. Here, our data confirm that this group is capable of regressing or remaining static in the moderate state, and it would be hoped that early detection and instigation of regular secondary prophylaxis would further reduce the proportion progressing to severe disease.

Over half of all new RHD diagnoses in this cohort were categorized as mild. It is perhaps most pertinent to look at the prognosis of this group, as these are the children that are most likely to be detected by screening. The mild group was the most stable in terms of disease evolution, with the majority remaining mild over time (73.7% and 63.9% at 5 and 10 years, respectively, Table 3). However, the fact that over 10% had progressed to severe disease after 10 years, including 5.1% who underwent surgery, represents unacceptable morbidity in this group, which should have a benign prognosis.

Two Markov models looking at RHD progression have recently been published, but both rely on probability estimates derived from the literature, rather than data from an actual patient cohort. Manji et al20 compared 3 different strategies for RHD prevention, 1 of which was detection of early RHD using echocardiography, followed by lifelong secondary prophylaxis. Their model is limited by the fact that it only describes 2 states following diagnosis with RHD: RHD and death. There is no distinction made between mild and severe disease despite the significantly different clinical trajectories and associated costs of these 2 states.

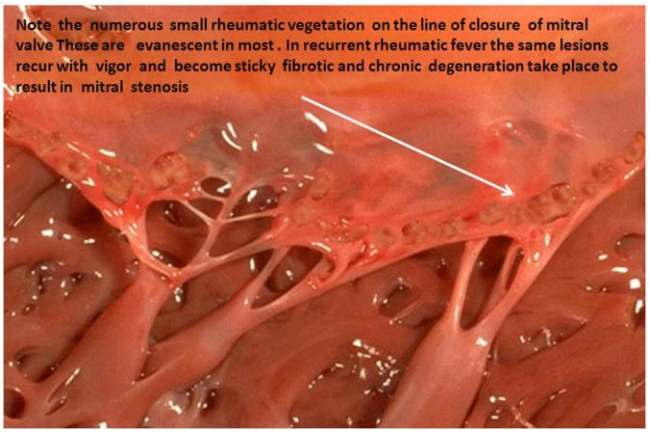
The model published by Zachariah et al last year21 aimed to evaluate the cost-effectiveness of RHD screening in the Northern Territory of Australia, and it is interesting to compare their theoretical work with ours. Following a diagnosis of RHD, they describe 6 clinical states, similar to ours. Definitions of severe disease were equivalent; however, their surgical state only considered valve replacement surgery, not valve repair that is the preferred intervention for young Indigenous patients in Australia. Zachariah's assumptions around the progression of severe disease do not appear to be appropriate for the current Australian context. They required that a patient be in the "RHD Congestive Heart Failure" state for at least 1 year prior to undergoing surgery. As previously outlined, our data suggest that disease progression is considerably more rapid than this.

Our study provides a reliable picture of RHD evolution in a contemporary cohort of Indigenous Australians. However, there are some limitations to our data. Firstly, patient severity levels, our outcomes of interest, are assigned by clinicians and are open to a degree of subjectivity. While specific echocardiographic definitions of RHD severity are provided in the Australian guidelines13 (Table 1), it is recognized that grading severity of mixed (stenotic and regurgitant) and multivalvular disease is challenging, and that clinical experience is important. It was noted in the data analysis process that there was some overlap between patients labeled as Priority 3 (mild RHD) and Priority 2 (moderate RHD) despite similar clinical and echocardiographic reports. Echocardiographic reports of Priority 1 cases (severe RHD) consistently demonstrated associated hemodynamic effect (eg, chamber dilatation, impaired left ventricular function, pulmonary hypertension) so we do not believe that severity was overestimated in this category. It is not possible to further analyze the potential impact of this suspected interobserver variability; however, it is reassuring that the patterns of disease progression we observed were what we expected based on our experience, and from the literature.

Detailed mortality information is another limitation of our data. Death in this age group remains a rare outcome, so complete ascertainment is important, yet we had to exclude 3 deaths due to incomplete information. We are therefore unable to make any comment about absolute survival rates, or about cause of death (ie, RHD- or non-RHD-related) as this was not consistently specified on the register. Similarly, we are unable to comment on other clinically significant outcomes such as infective endocarditis, atrial fibrillation, or stroke, as this information is presently not systematically recorded in the NT register. While these are of paramount importance in the adult RHD population, it is unlikely that the incidence of these outcomes would have been high enough in our young cohort to meaningfully incorporate into our model.

Our model has not explicitly taken into consideration adherence to secondary antibiotic prophylaxis or ARF recurrences, both of which obviously affect disease progression. However, these figures are available from previous reports based on the NT register, and we believe that it is reasonable to assume similar rates for our cohort. Effective BPG delivery remains a significant challenge in our setting, and while adherence has improved since 2005, in 2010, only 28.1% of patients on the NT RHD register were receiving >80% of prescribed BPG doses.6 Consequently, ARF recurrence rates remain high, consistently representing between one quarter and one third of ARF notifications over the last 10 years.6, 7 The disease trajectory that we have described, therefore, is more likely to reflect natural disease progression than disease modified by prophylaxis, supporting the notion that our model may be applicable to other disadvantaged populations.

It is highly likely that the trajectory of mild and moderate RHD would be improved with improved BPG adherence, and this is a parameter that will be varied in the sensitivity analysis as part of our proposed cost-effectiveness analysis. Clearly, improvement in BPG delivery must be a priority if RHD screening is to be implemented. Indeed, if RHD screening is to fulfill the international criteria for a disease suitable for screening, the delivery of successful treatment that improves the natural history of disease is a prerequisite.22



CONCLUSIONS

We have developed a robust multi-state model for RHD using data from a contemporary cohort of Indigenous Australian RHD patients. Our data highlight the bleak prognosis for young Indigenous Australians diagnosed with severe RHD, and reinforce the need to detect and treat the disease prior to this stage. Echocardiographic screening provides an opportunity for earlier detection, and our model of disease progression can be used to evaluate the cost-effectiveness of different screening strategies.

REFERENCES

1. BlandE, JonesT. Rheumatic fever and rheumatic heart disease. A twenty-year report on 1,000 patients followed since childhood. Circulation. 1951;4:836–843.
2. The natural history of rheumatic fever and rheumatic heart disease. Ten-year report of a cooperative clinical trial of ACTH, cortisone, and aspirin. Circulation. 1965;32:457–476.
3. TompkinsDG, BoxerbaumB, LiebmanJ. Long-term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. Circulation. 1972;45:543–551.
4. JaineR, BakerM, VenugopalK. Acute rheumatic fever associated with household crowding in a developed country. Pediatr Infect Dis J. 2011;30:315–319.
5. ZuhlkeL, EngelME, KarthikeyanG, RangarajanS, MackieP, CupidoB, MauffK, IslamS, JoachimA, DanielsR, FrancisV, OgendoS, GituraB, MondoC, OkelloE, LwabiP, Al-KebsiMM, Hugo-HammanC, ShetaSS, HaileamlakA, DanielW, GoshuDY, AbdissaSG, DestaAG, ShashoBA, BegnaDM, ElSayedA, IbrahimAS, MusukuJ, Bode-ThomasF, OkeahialamBN, IgeO, SuttonC, MisraR, AbulFadlA, KennedyN, DamascenoA, SaniM, OgahOS, OlunugaT, ElhassanHH, MocumbiAO, AdeoyeAM, MntlaP, OjjiD, MucumbitsiJ, TeoK, YusufS, MayosiBM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J. 2015;36:1115–1122.
6. Australian Institute of Health and Welfare .Rheumatic heart disease and acute rheumatic fever in Australia: 1996–2012. Cat. no. CVD 60. 2013.
7. ParnabyMG, CarapetisJR. Rheumatic fever in indigenous Australian children. J Paediatr Child Health. 2010;46:527–533.
8. LawrenceJG, CarapetisJR, GriffithsK, EdwardsK, CondonJR. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. Circulation. 2013;128:492–501.

9. WolbersM, KollerMT, StelVS, SchaerB, JagerKJ, LeffondreK, HeinzeG. Competing risks analyses: objectives and approaches. Eur Heart J. 2014;35:2936–2941.
10. PutterH, FioccoM, GeskusRB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389–2430.
11. Meira-MachadoL, de Una-AlvarezJ, Cadarso-SuarezC, AndersenPK. Multi-state models for the analysis of time-to-event data. Stat Methods Med Res. 2009;18:195–222.
12. HougaardP. Multi-state models: a review. Lifetime Data Anal. 1999;5:239–264.
13. RHD Australia (ARF/RHD writing group) National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand .Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. 2nd ed. Menzies School of Health Research: Darwin; 2012.
14. MajeedHA, YousofAM, KhuffashFA, YusufAR, FarwanaS, KhanN. The natural history of acute rheumatic fever in Kuwait: a prospective six year follow-up report. J Chronic Dis. 1986;39:361–369.
15. VeasyLG, TaniLY, HillHR. Persistence of acute rheumatic fever in the intermountain area of the United States. J Pediatr. 1994;124:9–16.
16. SanyalSK, BerryAM, DuggalS, HoojaV, GhoshS. Sequelae of the initial attack of acute rheumatic fever in children from north India. A prospective 5-year follow-up study. Circulation. 1982;65:375–379.
17. Australian Institute of Health and Welfare ,FieldB. Rheumatic heart disease: all but forgotten in Australia except amongst Aboriginal and Torres Strait Islander peoples. AIHW Cat. No. AUS 48. 2004.
18. RemondMG, SeverinKL, HodderY, MartinJ, NelsonC, AtkinsonD, MaguireGP. Variability in disease burden and management of rheumatic fever and rheumatic heart disease in two regions of tropical Australia. Intern Med J. 2013;43:386–393.
19. RobertsK, MaguireG, BrownA, AtkinsonD, RemenyiB, WheatonG, KellyA, KumarRK, SuJY, CarapetisJR. Echocardiographic screening for rheumatic heart disease in high and low risk Australian children. Circulation. 2014;129:1953–1961.
20. ManjiRA, WittJ, TappiaPS, JungY, MenkisAH, RamjiawanB. Cost-effectiveness analysis of rheumatic heart disease prevention strategies. Expert Rev Pharmacoecon Outcomes Res. 2013;13:715–724.
21. ZachariahJP, SamnalievM. Echo-based screening of rheumatic heart disease in children: a cost-effectiveness Markov model. J Med Econ. 2015;18:1–10.
22. RobertsK, ColquhounS, SteerA, RemenyiB, CarapetisJ. Screening for rheumatic heart disease: current approaches and controversies. Nat Rev Cardiol. 2013;10:49–58.