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ORIGINAL ARTICLE

Newly diagnosed rheumatic heart disease among indigenous populations in the Pacific

Mariana Mirabel,^{1,2,3} Muriel Tafflet,^{2,3} Baptiste Noël,⁴ Tom Parks,⁵ Olivier Axler,⁴ Jacques Robert,⁴ Marie Nadra,⁴ Gwendolyne Phelippeau,⁴ Elodie Descloux,⁴ Cécile Cazorla,⁴ Isabelle Missotte,⁴ Shirley Gervolino,⁴ Yann Barguil,⁴ Bernard Rouchon,⁶ Sylvie Laumond,⁷ Thierry Jubeau,⁸ Corinne Braunstein,⁴ Jean-Philippe Empana,^{2,3} Eloi Marijon,^{1,2,3} Xavier Jouven^{1,2,3}

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¹Département de Cardiologie, Hôpital Européen Georges Pompidou, Paris, France

²INSERM U970, Paris Cardiovascular Research Centre PARCC, Paris, France

³Université Paris Descartes, Sorbonne Paris Cité, Paris, France

⁴Department of Cardiology, Centre Hospitalier Territorial de Nouvelle Calédonie, Nouméa, New Caledonia

⁵University of Oxford, Oxford, UK

⁶Agence Sanitaire et Sociale de Nouvelle Calédonie, Nouméa, New Caledonia

⁷Direction des Affaires Sanitaires et Sociales, Nouméa, New Caledonia

⁸Département des Evacuations Sanitaires, Contrôle Médical Unifié, CAFAT, Nouméa, New Caledonia

Correspondence to

Dr Mariana Mirabel, Paris Cardiovascular Research Centre, Inserm U970, Hôpital Européen Georges Pompidou, 56 rue Leblanc, 75737 Paris, CEDEX 15, France; mariana.mirabel@inserm.fr

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ABSTRACT

Objectives Rheumatic heart disease (RHD) remains the leading acquired heart disease in the young worldwide. We aimed at assessing outcomes and influencing factors in the contemporary era.

Methods Hospital-based cohort in a high-income island nation where RHD remains endemic and the population is captive. All patients admitted with newly diagnosed RHD according to World Heart Federation echocardiographic criteria were enrolled (2005–2013). The incidence of major cardiovascular events (MACEs) including heart failure, peripheral embolism, stroke, heart valve intervention and cardiovascular death was calculated, and their determinants identified.

Results Of the 396 patients, 43.9% were male with median age 18 years (IQR 10–40). 127 (32.1%) patients presented with mild, 131 (33.1%) with moderate and 138 (34.8%) with severe heart valve disease. 205 (51.8%) had features of acute rheumatic fever. 106 (26.8%) presented with at least one MACE. Among the remaining 290 patients, after a median follow-up period of 4.08 (95% CI 1.84 to 6.84) years, 7 patients (2.4%) died and 62 (21.4%) had a first MACE. The annual incidence of first MACE and of heart failure were 59.05‰ (95% CI 44.35 to 73.75) and 29.06‰ (95% CI 19.29 to 38.82), respectively. The severity of RHD at diagnosis (moderate vs mild HR 3.39 (0.95 to 12.12); severe vs mild RHD HR 10.81 (3.11 to 37.62), $p < 0.001$) and ongoing secondary prophylaxis at follow-up (HR 0.27 (0.12 to 0.63), $p = 0.01$) were the two most influential factors associated with MACE.

Conclusions Newly diagnosed RHD is associated with poor outcomes, mainly in patients with moderate or severe valve disease and no secondary prophylaxis.

INTRODUCTION

Rheumatic heart disease (RHD), a disease of poverty,¹ has almost disappeared from wealthy countries, but remains highly prevalent in developing countries and among indigenous populations in the Pacific.^{2–7} The burden of RHD is still a major challenge in the developing world with approximately 345 000 deaths per year worldwide.⁸ RHD is the result of an inadequate response to invasive group A streptococcal infections, namely acute rheumatic fever (ARF).⁹ Although they are part of a continuum, RHD and ARF have often been studied separately. The presentations do vary,

however, with some patients presenting with ARF and no overt cardiac involvement, and nearly half of those diagnosed with RHD at an advance stage having no history of ARF.^{10 11}

There is, however, limited contemporary data on the characteristics of patients with newly diagnosed RHD.¹⁰ Also, a handful of clinical studies assessing predictors of outcomes in ARF and RHD either present a highly selected population¹² or date back to the 1950s when access to interventions was extremely limited.¹³ The two contemporary hospital-based registers have so far described characteristics of patients with no or limited (up to 30 months) follow-up.^{10 11}

We present the results of a hospital-based cohort study in New Caledonia, a high-income country where RHD remains endemic among the indigenous population.⁶ The objective was twofold: to describe the characteristics and outcomes of patients with newly diagnosed RHD according to standardised and prespecified diagnostic criteria and to assess factors associated with outcomes, focusing on patients with no major cardiovascular events (MACEs) at entry.

METHODS

Settings

RHD remains prevalent in New Caledonia among Oceanic populations including Melanesians and Polynesians.⁶ New Caledonia (22.276 S, 166.458 E) is an overseas French territory of approximately 270 000 inhabitants located in the southwest Pacific Ocean.¹⁴ The Centre Hospitalier Territorial de Nouvelle Calédonie is the only centre that provides specialist Cardiology, Paediatrics and Infectious Disease services in the archipelago and uses computer-based notes. The New Caledonian social security system provides free of charge access to good quality medicine, imaging and microbiological diagnostic testing. Air transport for urgent referral for remote communities is widely available across the archipelago. Patients in need for heart valve surgery are referred either to neighbouring Australia or to mainland France with no additional cost for the patient.

Participants

Patients admitted with newly diagnosed RHD from 1 January 2005 to 31 December 2013 were



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considered eligible for the study. Hospital records of all individuals with a primary or secondary International Classification of Diseases, 10th revision separation diagnosis of ARF or RHD were examined. Patients who fulfilled World Heart Federation (WHF) criteria of 'definite' RHD¹⁵ with quantification of heart valve disease¹⁶ were included in the study (see online supplementary table S1). Patients were asked to give oral consent to be enrolled in the study at time of follow-up interview.

Data collected at the time of diagnosis

For each participant, the following data were retrospectively collected: demographics (age, sex), ethnicity, month and year of diagnosis, family history of RHD, ARF at presentation, valve disease on first echocardiogram and its severity,¹⁶ New York Heart Association (NYHA) class, LVEF on echocardiogram, pulmonary hypertension on echocardiogram (defined as pulmonary artery systolic pressure >35 mm Hg), presence of supraventricular arrhythmias (defined as paroxysmal or permanent atrial fibrillation, atrial flutter or atrial tachycardia). Mild heart valve disease included mild single left-sided valve disease and mild multiple heart valve disease (eg, mild mitral regurgitation and mild aortic regurgitation). Heart valve disease was considered moderate if one of the left-sided valves presented with moderate mitral regurgitation, mitral stenosis or aortic regurgitation. One single severe left-sided regurgitative/stenotic valve lesion was considered severe heart valve disease.¹⁶

Follow-up

Patients were invited to attend a specialist clinic from March 2013 to December 2013. If patients could not attend, a questionnaire was filled over the telephone either with the patient or the general practitioner, and the latest medical reports were collected.

Data on treatment included use of secondary prophylaxis (benzathine penicillin G injections or oral treatment) at any time from diagnosis and at the time of interview (ie, ongoing

secondary prophylaxis). The National Register of Secondary Prophylaxis was consulted when data were missing on the hospital chart. The population being captive, all major events (see below) such as heart failure, stroke or embolism would lead to admission to the single hospital in the archipelago. Vital status and cause of death were checked in the national register of the causes of death in March 2014 for patients lost to follow-up between March and December 2013. Use of cardiac interventions through the office in charge of overseas referrals was also checked in March 2014.

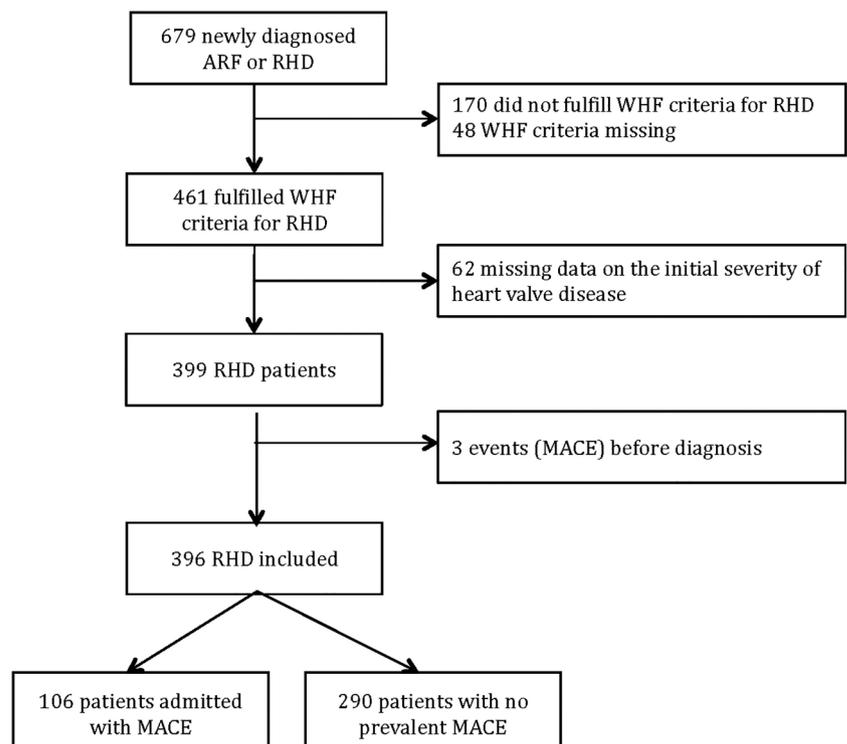
Outcomes and factors associated with events

MACEs, based on information available in the hospital chart, included heart failure (defined by NYHA class III or IV), peripheral embolism, stroke, heart valve intervention and cardiovascular death. Heart valve interventions included percutaneous mitral valvuloplasty and open-heart valve surgery. Additional adverse events were collected: severe haemorrhage (defined as leading to death, intracranial bleeding, bleeding associated with haemoglobin drop of ≥ 2 g/dL or need for transfusion of at least 2 red cell packs), infective endocarditis, heart valve thrombosis (in patients with a mechanical valve), cardiogenic shock and pregnancy-related complications (defined as maternal or foetal complications, including heart failure, need for surgery, termination of pregnancy, preterm birth and low birth weight). A team of two research nurses collected the data. A third party (MM) arbitrated in case of disagreement.

Statistical methods

Descriptive data were reported for the entire study population fulfilling the WHF criteria for RHD. Only patients with no MACE at hospital admission were further eligible for the analysis on incident MACE. The results are reported as median and IQR or as numbers and percentages. Categorical variables were compared using χ^2 test or Fisher's exact test, and continuous variables using Student's t test. The incidence of cardiovascular

Figure 1 Flow chart of the study. ARF, acute rheumatic fever; MACE, major cardiovascular event; RHD, rheumatic heart disease; WHF, World Heart Federation.



events was calculated per 1000 person-years. Factors associated with MACE were analysed using a Cox proportional hazard model. Time to event was calculated as time from diagnosis to first event or last follow-up. HRs for the Cox model were calculated accordingly with their 95% CIs. Sensitivity analysis was performed in regards to the use and duration of secondary prophylaxis as this information was missing in a significant number of patients; we, therefore, added the variable 'ongoing secondary prophylaxis at follow-up' in the final model. Significance was defined as p values <0.05 . All data were verified and analysed at the Paris Cardiovascular Research Centre, INSERM 970, Paris, France, with the use of Statistical Analysis System software (V9.3).

RESULTS

Characteristics of patients with newly diagnosed RHD

Among the 679 patients with newly diagnosed RHD or ARF, 396 patients were included (figure 1). In total, 174 (43.9%) were male with a median age of 18 years (IQR 10–40). And 274 (71.9%) were indigenous Melanesians, 85 (22.3%) were Polynesians and 22 (5.8%) were of other ethnicity. Also, 205 (51.8%) presented with ARF. Based on standardised echocardiograms, 127 (32.1%) patients had mild heart valve disease, 131 (33.1%) had moderate valve disease and 138 (34.8%) had severe heart valve disease at the time of diagnosis. Mitral regurgitation was the most frequent heart valve disease, followed by aortic regurgitation and mitral stenosis (table 1). Multiple valve disease was present in 56.3% of cases. Moderate or severe tricuspid regurgitation was present in 4.5% of patients. 32 (8.1%) patients had permanent or paroxysmal atrial fibrillation. Thirty-seven (9.3%) patients had LVEF $<60\%$. Characteristics of patients did not vary according to the year of RHD diagnosis (data not shown). Female indigenous patients were more likely to be unemployed ($p=0.026$) and presented more often with mitral stenosis ($p=0.02$) on univariate analysis compared with their male counterparts.

Among the 396 patients included, 106 (26.8%) presented with MACE at entry. There were 83/106 patients admitted with heart failure, among which 12 leading to urgent valve intervention (ie, within 30 days), 5 with concomitant stroke and 1 with concomitant stroke and urgent intervention. In addition, 12/106 patients were admitted with stroke; 10/106 underwent urgent intervention and 1 was admitted with stroke and underwent intervention.

Patients with no MACE at presentation were eligible for further analysis. Characteristics of these 290 patients with no MACE at entry are depicted in online supplementary table S2. Briefly, median age was 13 (IQR 10–31) years, 131 (45.2%) were male and 185 (63.8%) presented with ARF. Patients with ARF were younger ($p<0.01$), had more often a family history of ARF ($p=0.01$), less atrial arrhythmias ($p<0.01$) and had different heart valve disease pattern ($p<0.01$) compared with those with no ARF.

Outcomes and their determinants in patients with no MACEs at entry

The 290 patients were followed up for median 4.08 (95% CI 1.84 to 6.84) years. Vital status and cardiac interventions data were available in all participants. Overall, there were 62 MACE; the annual incidence of MACE was 59.05‰ (95% CI 44.35 to 73.75); and median follow-up period to MACE was 10.49 (95% CI 2.04 to 35.03) months. Taken individually, the annual incidence of heart failure (34 patients) was 29.06‰ (95% CI 19.29 to 38.82). The annual incidence of stroke was 7.26‰

Table 1 Characteristics at diagnosis

Characteristics at diagnosis	All N=396
Age, median (IQR)	18 (10–40)
Male, n (%)	174 (43.9)
Ethnicity*	
Indigenous Melanesians	274 (71.9)
Polynesians	85 (22.3)
Other	22 (5.8)
Presentation with ARF	205 (51.8)
Family history of RHD or ARF†	114 (60.6)
Supra ventricular arrhythmias‡	32 (8.1)
Initial left-sided valve disease on echocardiogram	
Mitral regurgitation, n (%)	
Nil	69 (17.4)
Grade 1/4	162 (40.9)
Grade 2/4	110 (27.8)
Grade $\geq 3/4$	55 (13.9)
Mitral stenosis, n (%)	
Nil	265 (66.9)
Mild	42 (10.6)
Moderate	30 (7.6)
Severe	59 (14.9)
Aortic regurgitation, n (%)	
Nil	201 (50.8)
Grade 1/4	109 (27.5)
Grade 2/4	53 (13.4)
Grade $\geq 3/4$	33 (8.)
Aortic stenosis, n (%)	
Nil	370 (93.4)
Mild	10 (2.5)
Moderate	9 (2.3)
Severe	1 (0.5)
Multiple left-sided valve disease, n (%)	223 (56.3)
Overall severity of RHD§	
Mild	127 (32.1)
Moderate	131 (33.1)
Severe	138 (34.8)
Moderate or severe TR¶, n (%)	17 (4.5)
LVEF $<60\%$, n (%)	37 (9.3)
PASP >35 mm Hg, n (%)	74 (18.7)

*Missing data in 15 cases.

†Up to second-degree relatives; missing data in 208 cases.

‡Defined as paroxysmal or persistent atrial fibrillation, flutter or atrial tachycardia.

§Defined as mild RHD if single or multiple left-sided valve disease graded as mild; moderate RHD defined as at least mitral or aortic moderate valve disease (regurgitation or stenosis); severe RHD defined as at least mitral or aortic severe valve disease (regurgitation or stenosis).

¶Missing data in 22 cases.

AR, aortic regurgitation; ARF, acute rheumatic fever; PASP, pulmonary artery systolic pressure; RHD, rheumatic heart disease; TR, tricuspid regurgitation.

(95% CI 2.52 to 12.01) (see online supplementary table S3). The survival rate was 97.89% (CI 95% 95.97 to 99.64) at 4 years, and 96.21% (CI 95% 89.95 to 98.60) at 8 years after diagnosis. During the study period, seven patients (2.4%) died, of whom four from cardiovascular death (ie, incidence of RHD-attributable mortality of 3.16 ‰ (95% CI 0.06 to 6.26) per year). Causes of cardiovascular death included heart failure (N=2), stroke (N=1) and infective endocarditis (N=1). Other events were noted during the study period: atrial fibrillation in seven patients (2.4%), infective endocarditis in eight patients (2.8%), cardiogenic shock in two patients (0.70%) and major haemorrhage in eight patients (2.8%). Among the 59 women in

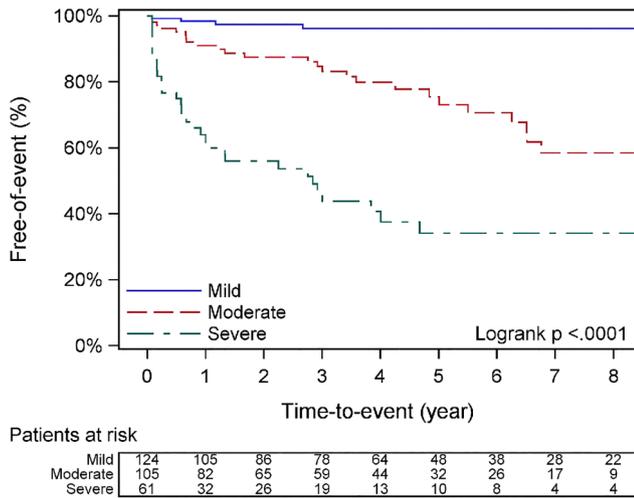


Figure 2 Kaplan–Meier survival free of major cardiovascular events (including heart valve interventions, heart failure, stroke, peripheral embolism and cardiovascular death) according to the severity of heart valve disease on echocardiogram at diagnosis.

childbearing age (ie, 15–45 years of age), 9 (15.2%) developed complications during subsequent pregnancies.

Among the 290 patients, secondary prophylaxis was prescribed at least at one point in time in 235 (83.0%) patients, no secondary prophylaxis was ever prescribed in 48 (17.0%) patients (missing data in 7 cases). Continuation of secondary prophylaxis was reported in 159 out of 222 (71.6%) patients (missing data regarding timing of prophylaxis in 61 cases). The use of secondary prophylaxis at the time of interview varied according to age (7.5% in patients aged >40 years; 94.7% in patients aged 5–20 years old).

In addition to patients (24/396) in need for urgent heart valve interventions within 30 days of diagnosis, 40 patients (13.8%) underwent either percutaneous or surgical procedures during the study period. The annual incidence of heart valve interventions was 36.47‰ (95% CI 25.17 to 47.77). In total, 59 heart valve interventions were undertaken in these 40 (13.8%) patients, including 7 (2.4%) percutaneous mitral

Table 3 Multivariate analysis of factors associated with major cardiovascular events in 280 patients (missing data in 10/290 patients in regards to ethnicity)

Factor	Multivariate HR (95% CI)	Multivariate p value
Mild RHD	1	<0.001
Moderate RHD	3.36 (1.10 to 10.34)	
Severe RHD	10.54 (3.50 to 31.75)	
ARF vs no ARF	0.46 (0.24 to 0.89)	0.02
Sex (male)	0.81 (0.48 to 1.36)	0.43
Melanesian	0.66 (0.37 to 1.18)	0.16
Age group (years)		
5–20	1	<0.001
21–40	2.88 (1.34 to 6.22)	
>40	5.15 (2.44 to 10.88)	

ARF, acute rheumatic fever; RHD, rheumatic heart disease.

valvuloplasty, 5 (1.7%) mitral valve repair, 23 (7.9%) mitral valve replacement and 18 (6.2%) aortic valve replacement.

Characteristics significantly associated with MACE on multivariate analysis were the severity of heart valve disease at diagnosis (moderate vs mild HR 3.36, 95% CI 1.10 to 10.34; severe vs mild RHD 10.54, 95% CI 3.50 to 31.75, $p<0.001$), ARF at diagnosis (HR 0.46, 95% CI 0.24 to 0.89, $p=0.02$) and older age (21–40 vs 5–20 years old, HR 2.88, 95% CI 1.34 to 6.22; >40 vs 5–20 years old, HR 5.15, 95% CI 2.44 to 10.88, $p<0.01$) (figure 2, tables 2 and 3). After sensitivity analysis including secondary prophylaxis at the time of interview, two factors remained associated with outcomes: the severity of heart valve disease at diagnosis (moderate vs mild HR 3.22, 95% CI 0.90 to 11.49; severe vs mild RHD HR 11.07, 95% CI 3.21 to 38.22, $p<0.001$) and ongoing secondary prophylaxis at the time of interview (HR 0.33, 95% CI 0.14 to 0.79, $p=0.013$) (table 4).

DISCUSSION

We present here contemporary longitudinal data of patients admitted for RHD with the longest follow-up published to date. A significant proportion of patients (~25%) are still diagnosed at the onset of complications or at a stage when heart valve interventions are urgently needed. Half our patients presented with ARF. Approximately 20% needed heart valve intervention during the study period (median follow-up ~4 years). The annual incidence of complications and RHD-related mortality is high even in young patients who are initially admitted with uncomplicated RHD (~59‰ per year). We identify factors associated with outcomes: the severity of heart valve disease at diagnosis and continuation of secondary prophylaxis. Our results suggest that early diagnosis and secondary prophylaxis is cornerstone to reducing the burden of RHD.

Our study population is young and mainly indigenous, in keeping with population-based studies in the region.^{2 6 17} The characteristics of our population are overall consistent with the two other RHD hospital-based registers published to this date.^{10 11} Half our patients had ARF, as in other upper-middle-income settings.¹¹ A history of ARF is more often reported in wealthier settings,¹¹ suggesting the impact of health-care services in the ability to diagnose the condition. The heart valve disease pattern is slightly different from that described in the heart of Soweto study,¹⁰ with a higher proportion of mild mitral and aortic regurgitation in our study, likely due to the

Table 2 Univariate analysis of factors associated with major cardiovascular events in 280 patients (missing data in 10/290 patients in regards to ethnicity)

Factor	Univariate HR (95% CI)	Univariate p value
Mild RHD	1	<0.001
Moderate RHD	8.1 (2.8 to 23.3)	
Severe RHD	24.9 (8.8 to 70.8)	
ARF vs no ARF	0.17 (0.09 to 0.30)	<0.001
Sex (male)	0.8 (0.5 to 1.3)	0.34
Melanesian*	0.6 (0.4 to 1.1)	0.09
Age group (years)		
5–20	1	<0.001
21–40	6.1 (2.9 to 12.41)	
>40	15.2 (8.0 to 28.8)	
Ongoing secondary prophylaxis at FU*	0.13 (0.07 to 0.23)	<0.001

*Analysis for 217 patients.

ARF, acute rheumatic fever; FU, follow-up; RHD, rheumatic heart disease.

Table 4 Sensitivity analysis of factors associated with major cardiovascular events in 217 patients (overall missing data in 73/290 patients in regards to secondary prophylaxis in 63 cases and ethnicity in 10 cases)

Factor	Multivariate HR (95% CI)	Multivariate p value
Mild RHD	1	<0.001
Moderate RHD	3.22 (0.90 to 11.49)	
Severe RHD	11.07 (3.21 to 38.22)	
ARF vs no ARF	0.54 (0.25 to 1.14)	0.10
Sex (male)	0.82 (0.47 to 1.45)	0.50
Melanesian	1.07 (0.54 to 2.13)	0.84
Age group		
5–20 years	1	0.31
21–40 years	1.97 (0.79 to 4.92)	
>40 years	2.10 (0.72 to 6.10)	
Ongoing secondary prophylaxis at FU	0.33 (0.14 to 0.79)	0.013

ARF, acute rheumatic fever; FU, follow-up; RHD, rheumatic heart disease.

inclusion of children and adolescents with ARF. Patients presenting with ARF were younger, with milder heart valve disease, less LV impairment and pulmonary hypertension compared with those with no ARF.

RHD is still diagnosed at an advanced stage in many cases, revealed by the onset of complications mainly in young adults. Almost one-third present with major cardiovascular complications including heart failure, stroke, non-neurological embolism or cardiovascular death. Furthermore, the incidence of heart failure was high in patients admitted with initially uncomplicated RHD (~30% per year), followed by stroke. Other complications included atrial fibrillation and haemorrhagic events. Maternal morbidity was also notable, in keeping with previous reports.^{18–19} Patients were at considerable risk of developing infective endocarditis, as suggested in a previous report focusing on Oceanic populations.²⁰

When focusing on patients with uncomplicated RHD at entry, we report mortality rates of 2.4% at median 4 years follow-up. Lawrence and colleagues recently reported crude all-cause mortality rates of 3.9% at 5 years.² Our results are, therefore, consistent with those from neighbouring Australia. However, mortality rates from New Caledonia and Australia, two high-income countries where patients have access to treatment, may not be transposable to resource-poor settings and could underestimate the global burden of the disease.

Patients with uncomplicated RHD remain at high risk of heart failure, thromboembolic events and infective endocarditis. When combining all MACEs, the annual incidence is high (~59%), considering the young age of our population. Our data may, however, help refining global burden of disease estimates in the near future.

One-fifth of our study population needed heart valve interventions during the study period. Of note, over one-third of patients had severe valve disease and heart valve interventions may have been underused, as previously described in other settings.²¹ Heart valve interventions are, however, not accessible in many countries where RHD remains endemic, especially in low-income countries.^{22–24}

Approximately 55% of our patients were under secondary prophylaxis at follow-up. All our patients had been diagnosed

with RHD <10 years before.²⁵ One-fourth of our patients were, however, ≥40 years old in whom secondary prophylaxis was usually stopped. The majority of children and adolescents were on secondary prophylaxis at the time of interview. However, as in other hospital-based or population-based registers, there is room for improvement in terms of adherence to guidelines.^{11 25 26}

We identified two factors associated with poor outcomes. The severity of valve disease at diagnosis is understandably associated with adverse events, such as heart failure² or need of heart valve interventions.¹⁰ Continuation of secondary prophylaxis was associated with better outcomes. Patients diagnosed with RHD during an ARF attack presented better outcomes, but this was not confirmed when adjusting for secondary prophylaxis. Our results, therefore, stress the importance of early diagnosis, when heart valve disease is still mild, which bears excellent prognosis. Identifying children with ARF is an opportunity to limit the burden of disease. Our results may also suggest that screening for these mild but definite lesions could be of interest in order to avoid disease progression and future complications.^{27 28 30}

Strengths and limitations

We provide the longest follow-up data from a hospital-based RHD register including precise clinical features of the condition such as echocardiographic baseline characteristics. We used standardised criteria for RHD diagnosis¹⁵ and heart valve disease quantification.¹⁶ The study settings allowed accurate assessment of outcomes, the population being captive in a country with national mortality, overseas referrals for heart surgery and secondary prophylaxis registers. This study consistently adds to the knowledge on the burden of RHD and highlights the relatively low mortality but high morbidity of the condition in a country where medical and surgical interventions are accessible. We acknowledge, however, a series of limitations. We describe here outcomes of patients admitted to a tertiary centre with potential referral bias of most severe cases. However, many children with ARF and mild mitral regurgitation were admitted to our institution given that it is the only centre providing paediatric

Key messages

What is already known on this subject?

Rheumatic heart disease remains the leading acquired heart disease in the young worldwide, affecting patients in developing countries and among indigenous populations. Studies have mainly focused on population-based prevalence and mortality estimates. There is little knowledge on the morbidity related to rheumatic heart disease.

What might this study add?

We provide contemporary data supporting low mortality but high morbidity among indigenous populations affected by rheumatic heart disease in high-income settings. We identified two factors associated with cardiovascular outcomes: diagnosis at an early stage and continuation of secondary prophylaxis.

How might this impact on clinical practice?

This study provides further demonstration that rheumatic heart disease is a burden among young indigenous populations. Early diagnosis and secondary prophylaxis is cornerstone to limit the advent of complications and need for cardiac surgery, and should promote prevention policies.

specialist care. We collected part of the data retrospectively, and missing data have contributed to diminishing the sample study. Diagnosis of ARF was at the discretion of the physician and did not necessarily fulfil modified Jones²⁹ or Australasian criteria.²⁵ However, all presented with definite RHD according to standardised WHF criteria, which implies at least one major criterion for ARF.¹⁵ Restricting our study population to patients with strict echocardiographic criteria further reduced our sample size. We focused our analysis on patients admitted with uncomplicated RHD, which underestimates the burden of the disease, but allows the identification of factors associated with the advent of adverse outcomes.

CONCLUSIONS

Newly diagnosed RHD is often revealed by complications, and outcomes are poor at follow-up especially when heart valve disease is moderate or severe and in the absence of secondary prophylaxis. Our results add to the limited data on the burden of RHD and should warrant early diagnosis when heart valve disease is still mild to introduce and continue secondary prophylaxis.

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Competing interests None declared.

Patient consent Institut National de la Santé et de la Recherche Médicale waived written consent.

Ethics approval IRB Ethical Review Committee of the Institut National de la Santé et de la Recherche Médicale (French Institute of Health and Medical Research), Paris, France.

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Data sharing statement All data are available upon request from the corresponding author.

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