Clinical Outcomes in 3343 Children and Adults with Rheumatic Heart Disease from 14 Low and Middle Income Countries: 2-Year Follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY study)

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Zühlke. Clinical Outcomes of Rheumatic Heart Disease

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Abstract

Background

There are few contemporary data on the mortality and morbidity associated with rheumatic heart disease (RHD) or information on their predictors. We report the two year follow-up of individuals with RHD from 14 low and middle income countries in Africa and Asia..

Methods

Between January 2010 and November 2012, we enrolled 3343 patients from 25 centers in 14 countries and followed them for two years to assess mortality, congestive heart failure (CHF), stroke or transient ischemic attack (TIA), recurrent acute rheumatic fever (ARF), and infective endocarditis (IE).

Results

Vital status at 24 months was known for 2960 (88.5%) patients. Two thirds were female. Although patients were young (median age 28 years, interquartile range 18 to 40), the two year case fatality rate was high (500 deaths, 16.9%). Mortality rate was 116.3/1000 patient-years in the first year and 65.4/1000 patient-years in the second year. Median age at death was 28.7 years. Independent predictors of death were severe valve disease (hazard ratio (HR) 2.36, 95% confidence interval (CI) 1.80-3.11), CHF (HR 2.16, 95% CI 1.70-2.72), New York Heart Association functional class III/IV (HR 1.67, 95% CI 1.32-2.10), atrial fibrillation (AF) (HR 1.40, 95% CI 1.10-1.78) and older age (HR 1.02, 95% CI 1.01-1.02 per year increase) at enrolment. Post-primary education (HR 0.67, 95% CI 0.54-0.85) and female sex (HR 0.65, 95%CI 0.52-0.80) were

associated with lower risk of death. 204 (6.9%) had new CHF (incidence, 38.42/1000 patient-years), 46 (1.6%) had a stroke or TIA (8.45/1000 patient-years), 19 (0.6%) had ARF (3.49/1000 patient-years), and 20 (0.7%) had IE (3.65/1000 patient-years). Previous stroke and older age were independent predictors of stroke/TIA or systemic embolism. Patients from low and lower-middle income countries had significantly higher age- and sex-adjusted mortality compared to patients from upper-middle income countries. Valve surgery was significantly more common in upper-middle income than in lower-middle- or low-income countries.

Conclusions

Patients with clinical RHD have high mortality and morbidity despite being young; those from low and lower-middle income countries had a poorer prognosis associated with advanced disease and low education. Programmes of early detection and treatment of clinical RHD are required to improve outcomes.

Keywords: rheumatic heart disease, outcomes, mortality, morbidity, developing countries

Clinical Perspective

1) What is new?

To our knowledge, this is the first prospective multi-center study of mortality and morbidity in rheumatic heart disease (RHD) patients from low and middle income countries (LMICs). Clinical RHD was associated with high mortality at a median age of 28 years. Complications such as congestive heart failure (CHF) and stroke affect a fifth of patients over a two years. Mortality was higher in low income, and low-middle income, compared to upper-middle income countries. Apart from age and gender, the independent risk factors for mortality (i.e., severe valve disease, CHF, dyspnoea, atrial fibrillation, and low education) were modifiable.

2) What are the clinical implications?

Clinical guidelines recommend the use of percutaneous or surgical valve interventions for RHD with CHF. However, these interventions are not available to the majority of affected patients. Strategies to make proven percutaneous and surgical valve interventions more accessible are needed to improve the outcome of patients with RHD living in LMICs. Patients with RHD seeking tertiary care present with advanced disease, and the markers of severity are the greatest determinants of poor outcome. Additional research to identify symptomatic patients with early RHD in the whole population (in addition to screening studies of asymptomatic schoolchildren) is required in this field.

Introduction

Rheumatic heart disease (RHD) is a major public health problem in low and middle income countries (LMICs).[1] According to the most recent estimates, there are nearly 33 million people with RHD globally, contributing to about 275,000 deaths every year.[2] However, there are sparse data on RHD demographics, morbidity and mortality and information on factors which affect outcomes, from the countries most affected by the disease.[3] In most high income countries, RHD ceased to be a public health problem several decades ago. Prospective studies describing outcomes and progression of RHD from these countries are over 50 years old. Therefore their results may not be applicable to current patients in LMICs.[4, 5] Moreover, many of these studies were performed before the availability of echocardiography for diagnosis, or the use of penicillin prophylaxis, drugs for heart failure or surgical and percutaneous valve interventions became part of standard care. Therefore, their findings may not be applicable to contemporary patient populations. Furthermore, much of the currently available prospective data are from small pockets of highly susceptible indigenous groups in New Zealand and Australia.[6-8] The incidence of acute rheumatic fever (ARF), and RHD-related morbidity and mortality are thought to be unusually high in these groups.[7] These data may not be generalizable to the majority of those with RHD in LMICs because of differences in access to medical care and other socio-economic factors.

Data on morbidity and mortality among RHD patients are needed to inform patient management, develop healthcare policy and to guide resource allocation for control of RHD in LMICs. Suboptimal use of inexpensive interventions such as secondary penicillin prophylaxis and oral anticoagulation is well recognized,[9, 10] and contemporary data are needed to

document the impact of their underuse on important clinical outcomes. In addition, there is limited information on the determinants of disease progression and on clinical outcomes in contemporary patients with RHD living in LMICs.[7] The Global Rheumatic Heart Disease Registry (REMEDY) was designed to help fill this knowledge gap.[3] We have previously reported the baseline characteristics of the 3343 patients recruited from 14 LMICs in REMEDY.[9] This report describes the major clinical outcomes at two years of follow-up among these patients.

Methods

Study design and setting

The design of the REMEDY study has been published previously.[3] Briefly, REMEDY is a prospective, multicenter, international, hospital-based registry of patients with symptomatic RHD. We enrolled patients with a clinical and echocardiographic diagnosis of RHD, who were seen in outpatient clinics, emergency departments or inpatient facilities of 25 participating hospitals in 14 countries (12 African countries, Yemen and India).[11] We did not include asymptomatic patients in whom RHD was detected solely by clinical or echocardiographic screening. The study was approved by the institutional review board at each site and the subjects gave informed consent.

Follow-up and outcomes

Clinical, demographic and echocardiographic data were collected at baseline and patients were followed up annually for two years. At each visit patients were assessed for occurrence of adverse outcomes, use of secondary antibiotic prophylaxis and oral anticoagulation medication, and need for valve intervention or surgery. The principal outcomes of interest were death,

congestive heart failure (CHF), stroke or transient ischemic attack (TIA), recurrence of acute rheumatic fever (ARF), and infective endocarditis (IE). Other outcomes that were monitored included non-central nervous system (CNS) systemic embolism, major bleeding, atrial fibrillation or flutter (AF), prosthetic heart valve thrombosis, and use of percutaneous or surgical valve procedures.

CHF was diagnosed if any two of the following three criteria were present: (i) symptoms (dyspnea on exertion or at rest, orthopnea, nocturnal paroxysmal dyspnea, or ankle edema) or signs (rales, increased jugular venous pressure or ankle edema) of CHF, (ii) radiologic signs of pulmonary congestion, and (iii) treatment with diuretics. Stroke was diagnosed on the basis of physician-confirmed sudden onset of neurologic deficit consistent with ischemia/infarction of a vascular territory, lasting ≥24 hours, with or without neuroimaging evidence. A similar deficit lasting <24 hours was recorded as a transient ischemic attack (TIA). A systemic embolic episode was diagnosed clinically in a patient with loss of arterial pulse and/or evidence of end-organ ischemia (e.g., ischemic limb pain or gangrene). We used the WHO criteria for diagnosing recurrence of ARF[11] and the modified Duke's criteria for diagnosing IE during follow-up.[12] We determined the severity of valve lesions based on American College of Cardiology/American Heart Association recommendations.[13] The definitions of all outcome measures have been reported previously.[3]

Statistical analysis

Continuous variables were expressed as means with standard deviations or as medians with interquartile ranges as appropriate, and categorical variables as frequencies and percentages. Comparisons between categorical variables were assessed for statistical significance using the Chi-squared test, and the unpaired t-test was used to determine group differences for continuous variables. Linear regression was utilized to explore relationships between variables. Test results were adjusted by age and by specifying study centres as clusters.[9]

We anticipated that mortality among patients with RHD would be about 3.3% per year based on a community-based study in India.[14] We expected that with 3000 patients followed up for two years, we would be able to determine the rates of all the principal outcomes of interest (i.e., death, CHF and stroke) individually, with 95% confidence and a precision of ±1%.

The incidence rates of the principal outcomes were calculated as number of events per 1000 patient-years of follow-up, and countries were stratified by the 2011 World Bank country income groups (low income, lower-middle income, and upper-middle income groups).[15] We used the Stata stptime command to calculate incidence rates, which allowed for variable follow-up time for each patient and provided the 95% confidence intervals for the estimate. The Stata sts list command was used to determine the risks of the adverse events at interval time points. For mortality, CHF, stroke and thromboembolism, we computed Kaplan-Meier survival probabilities and determined predictors of death using a Cox multivariable regression model. Comparisons between unadjusted events and baseline variables were cross-tabulated

and assessed for statistical significance using the Chi-squared test, unpaired t-test or univariate linear regression.

The variables included in the multivariable model were decided *a priori* based on prior information relating them to prognosis. They were: age, sex, presence of AF, New York Heart Association (NYHA) functional class, CHF at enrolment, previous heart valve surgery or intervention, a history of stroke or IE, severe disease (severe valve disease of at least one affected valve), multivalve involvement and use of secondary penicillin prophylaxis. We also determined the association of non-adherence to secondary prophylaxis with the occurrence of episodes of ARF, CHF and death. Among patients with an accepted indication for oral anticoagulation, we determined the association of adherence to vitamin K antagonists (VKA) with the occurrence of stroke/TIA or other systemic embolism, and death. We computed hazard ratios (HR) and their 95% confidence intervals (CIs). A p value of 0.05 or less was considered statistically significant. All analyses were performed using Stata version 14 (StataCorp LP, College Station, Texas).

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Results

Between January 2010 and November 2012, 3343 patients were enrolled at 25 participating sites. A third of the patients were from low income, 41% from lower-middle and a quarter from upper middle income countries. The baseline characteristics of enrolled patients are summarized in Table 1.[9] Briefly, patients were relatively young (median age 28 years) and predominantly female (66.2%). Over a quarter of patients were below the age of 18 years (921 patients, 27.9%). Mixed mitral and aortic valve disease was the most common pattern of valve involvement, except in children <10 years old, in whom isolated mitral regurgitation was the predominant lesion. A fifth of the patients were in AF. A substantial proportion had clinical signs of CHF (13.2%) or poor functional class (NYHA class III/IV) at presentation (24.2%), particularly in low and lower-middle income countries. The use of secondary penicillin prophylaxis and oral anticoagulation were generally poor.[9]

Vital status at 24 months was known for 2960 (88.5%) patients. At two years 55% of patients completed a follow-up visit,20% were interviewed by telephone, and in the remaining, follow-up information was obtained through relatives or the patient's physician. Overall, patients were followed up for a median of 24 months (interquartile range (IQR), 22.9-26.6), for a total of 5482.99 person-years of follow-up.

Mortality

500 patients (16.9%) died (Table 2, Fig. 1). The median age at the time of death was 28.7 (IQR 17.4-46.6) years. The majority of deaths (n=323, 64.6%) occurred within 12 months of

enrolment. The mortality rate was 116.3/1000 patient-years in the first year and 65.4/1000 patient-years in the second year. There were seven risk factors that were independently associated with mortality (Table 4). Severe valve disease (HR 2.36, 95% CI 1.80-3.11), CHF at enrolment (HR 2.16, 95% CI 1.70-2.72), AF at enrolment (HR1.40, 95%CI 1.10-1.78), and poor NYHA functional class (i.e., III or IV) at presentation (HR 1.67, 95% CI 1.32-2.10) were the strongest independent predictors of mortality. There was also a significant increase in mortality with increasing age, with adults having a 50% higher risk of death than those less than 18 years of age (HR 1.50, 95% CI 1.11-1.95). Education beyond primary school was associated with a 33% lower risk of death (HR 0.67, 95% CI 0.54-0.85). Mortality was also lower among female patients (HR 0.65, 95% CI 0.52-0.80).

Congestive heart failure and valve procedures

A third of the patients (1110, 33.4%) had a history of CHF at the time of enrolment. CHF occurred in 204 patients (6.9%) over the follow-up period (38.42/1000 patient-years;Table 3). Most of the variables which were associated with death were also independently associated with the occurrence of CHF (Supplementary Table 1). The presence of CHF at baseline conferred the greatest hazard for the recurrence of CHF on follow-up (HR 2.43, 95% CI 1.64-3.62).

Two hundred and twenty three patients (6.7%) underwent valve surgery and 57 (1.7%) underwent percutaneous intervention.

Stroke and thromboembolism

Overall, 46 (1.7%) patients had a stroke or TIA at the end of two years (8.45 per 1000 patient-years; Table 3) and three patients had non-CNS systemic embolism. Patients who were in AF at enrolment were twice as likely to have a stroke as those who were in sinus rhythm (2.4% vs. 1.2%, p=0.04). Stroke also occurred more commonly among patients with prosthetic heart valves than in those with native valves (2.6% vs. 1.1%, p=0.01). However, after adjustment for other variables, previous stroke (HR 2.71, 95% CI 1.18-6.39), and older age remained the only significant predictors of stroke, TIA or systemic embolism. Prosthetic heart valve thrombosis occurred in 9 of 547 patients (1.64%) with mechanical valves (There were 588 patients with prosthetic valves, 547 of whom had mechanical valves).

At baseline, there were 1362 (40.7%) patients with indications for oral anticoagulation.[9] VKAs were prescribed in 69.5% (946) of such patients. VKA use was high in patients with mechanical heart valves (91.6%) and AF (68.6%), but low in those with mitral stenosis in sinus rhythm (20.3%) with other markers of high embolic risk (such as dilated left atrium or left atrial thrombus). Among patients prescribed VKAs, just over a quarter (27.4%) had an International Normalised Ratio (INR) in therapeutic range.

Among patients with native valves and AF or those with mitral stenosis and concomitant high risk features, the likelihood of suffering a stroke was lower among patients who had an INR in the therapeutic range (i.e., 2-3) at baseline (1.4% vs. 4.3%, p=0.031). For patients with mechanical valves (n=547), the risk of stroke was not statistically different between those with

INR in therapeutic range or otherwise (3.0 vs. 3.6%, p=0.69). There were 23 major bleeding events (0.8%) in all. The incidence of bleeding did not differ significantly by INR at baseline.

Acute rheumatic fever, infective endocarditis and secondary prophylaxis

Nineteen patients (0.6%) had ARF, and 20 (0.7%) had IE. At enrollment, just over half the patients (1761, 54.8%) were on secondary prophylaxis and of these 78% were adherent to therapy (i.e., had received ≥80% of the prescribed number of doses in the preceding 12 months).[9] Patients who were prescribed secondary prophylaxis were less likely to have ARF, new onset of CHF or die at two years (16.2% vs. 20.7% p=0.001). However, this association did not remain statistically significant after adjustment for other prognostic variables.

The incidence rates of all morbid events are summarized in Table 3.

Country income group

Patients from upper middle income countries were older, and more often had a history of complications due to valve disease (such as stroke or IE), or were in CHF at baseline (Table 1).[9] A larger proportion of patients from upper middle income countries (UMIC) had valve surgery or intervention prior to entry into the study. Consequently, the risk of valve-related and anticoagulation related problems (such as stroke) were significantly higher among these patients. However, they were significantly less likely to die at the end of two years compared to patients from low (LIC) and lower-middle income (LMIC) countries (12.7% UMIC, 14.2% LMIC and 18.0% (LIC), respectively; p=0.001) (Fig. 2). The hazard for mortality remained higher for low-income (HR 1.95, 95% CI 1.51-2.50) and low-middle income countries (HR 1.51, 95% CI

1.17-1.92), when compared to upper middle income countries, after adjustment for patient age and sex. Adjustment for all other prognostic variables resulted in attenuation of risk for low income countries (HR 1.53, 95% CI 1.12-2.14), and low-middle income countries (HR 1.34, 95% CI 1.02-1.87).

Discussion

In this contemporary registry, the rates of death, CHF and stroke are high among patients with clinical RHD living in LMICs despite their relatively young age (mean 28 years). Nearly a fifth of patients developed one of these complications over two years. This was largely attributable to advanced disease at the time of presentation. Mortality was significantly higher among patients living in low income countries and among the less educated. The use of secondary antibiotic prophylaxis was suboptimal. Oral anticoagulation was underutilized and the quality of oral anticoagulation was poor, contributing to an increased risk of stroke. These indicate that patients with RHD are managed suboptimally despite the availability of simple and effective preventive and management strategies.

There are few contemporary prospective studies reporting on mortality among patients with echocardiographically confirmed RHD. In a small community-based cohort of 257 patients with RHD who were followed up for 12 years, Kumar and colleagues reported a death rate of 32.5/1000 patient-years. In a report from a register from the Northern Territory of Australia, Lawrence and colleagues showed a survival of 96.1% at 5 years, and 88.4% at 10 years.[7] The mortality rates reported in these studies are those of unselected patients with ARF and RHD

recruited from the community and not surprisingly are substantially lower than our estimates. Moreover, nearly all patients were on secondary prophylaxis and had access to high quality care through outreach services by expert clinicians.[7] By contrast, Gunther and colleagues reported a very high mortality rate of 125·3 per 1000 person-years in a small cohort of 47 patients in a community from Ethiopia, but there was an excessively high loss to follow-up rate of 44%.[16]

Several of the factors which we found to be strongly associated with mortality and other major adverse outcomes are potentially amenable to intervention. The majority of our patients had moderate to severe disease and nearly a third were in NYHA class III/IV at enrolment,[9] and the severity of valve disease was the strongest predictor of mortality. While most of these patients were likely to require intervention, only 10.3 % (n=175) of those with severe valve disease had surgery or percutaneous intervention. In a study of newly diagnosed RHD with a similar profile, seen at a well-equipped tertiary care center in South Africa, 22% of patients underwent surgery at 30 months of follow-up.[17] Timely surgery or percutaneous intervention may improve outcomes in patients with severe disease.[13, 18] However, facilities for cardiac surgery are scarce in poor countries and waiting periods are long.[19, 20] Gaps in the use of effective therapies may be due to difficulties in access to care, and may explain some of the observed difference in mortality between middle income and low income countries (Fig. 2). Strategies to provide high-quality tertiary care for patients with RHD have been proposed in Africa. [21]

Despite a substantial proportion of patients being in AF, oral anticoagulation was used in only 70% of these individuals. Even among patients with mechanical valves, about 9% of patients were not on any oral anticoagulation. Among those on VKAs, INR monitoring was infrequent and less than a third of patients were in therapeutic range. Predictably, patients with INRs out of therapeutic range had a 3-fold higher risk of stroke. Underuse of oral anticoagulation is widespread,[22] but the level of INR control is poorer in developing countries. In a worldwide registry of AF, the time in therapeutic range for patients from Africa, China and India was below 40%.[23] This may be due to poor awareness by both physicians and patients on their importance, poor patient education and limited access to INR testing.[24, 25] Strategies targeting these factors are needed to improve clinical outcomes with oral anticoagulation. While self-monitoring using point-of-care devices may be theoretically appealing, they are currently not affordable for the majority of patients in Africa and Asia.[26, 27] Moreover it is unknown if patients in LMICs can effectively self-monitor and adjust their VKA doses. Perhaps novel approaches need to be tested, such as the recruitment of educated and motivated individuals from the community (e.g., local school teachers), and may be useful surrogate healthcare providers to perform home monitoring.[14] While newer oral anticoagulants overcome the need for monitoring, their efficacy and safety in RHD is unknown and they are at present unaffordable to the majority of patients living in poor countries. However, it is possible that in future these drugs may become more affordable and widely used (as has happened with antiretroviral therapy for HIV), and therefore trials evaluating these agents in RHD are needed.[9, 28]

Although there was a significant association of non-use of secondary prophylaxis with the occurrence of ARF, CHF or death, this was attenuated after adjustment for other prognostic variables. The effect of secondary prophylaxis on the occurrence of CHF or death is likely to be greatest among patients in the early stages of disease. Patients in poor countries are likely to have suffered substantial valve damage from multiple, unrecognized episodes of ARF before they first come to clinical attention, at which point the hemodynamic consequences of severe valve disease may be the overwhelming determinants of prognosis.[29] A similar lack of impact of secondary prophylaxis on mortality was observed in the Australian Northern Territory register which relied on clinical diagnosis of RHD at the point of entry.[7] These findings highlight the need for studying the efficacy of earlier institution of secondary prophylaxis in patients detected through screening programmes,[30, 31] combined with approaches to prevent the first episode of ARF.[29] In patients with advanced disease, given its documented effect of reducing recurrences of ARF, secondary prophylaxis should continue to be administered in addition to definitive therapy for valve disease.[32]

Finally, education beyond primary school was associated with a significant reduction in mortality. Patient education is an indicator of socioeconomic status in resource-poor countries. A multi-national retrospective study of African patients with rheumatic heart disease showed that the ratio of patients with severe disease to any RHD valvular lesion was higher in countries with the lowest gross domestic product.[33] This observation is consistent with the mortality gradient observed with respect to the country income group in this study. These findings point

to the inextricable link between socioeconomic development and RHD, and emphasize the need for overall societal development as a key prerequisite for RHD control.[34]

Our study has several strengths. First, it is the largest prospective study of patients with RHD in LMICs allowing for precise estimates of patient-important clinical outcomes. Second, the diagnosis of RHD was confirmed by echocardiography, and disease severity and clinical outcomes were measured using pre-specified, objective criteria, thereby reducing bias. Third, because we collected data from various countries in different stages of economic development, we were able to explore some of the socioeconomic factors that influence outcomes. The most important limitation of this study is that despite extensive efforts to track patients, 11.7% of our patients were lost to follow-up. Though this proportion was lower than initially projected (20%), it reflects the challenging and resource constrained settings in which the study was conducted.[16, 35] Moreover, significantly greater proportions of those lost to follow-up had severe disease, were in CHF or worse functional class at enrolment, or were less educated (Supplementary Table 2) and so our data may be an underestimate of the poor prognosis in this condition. Finally, this is a hospital-based registry of symptomatic patients and so our results cannot be extrapolated to unselected patients with the disease in the community. Whether those who are asymptomatic when they are initially encountered will have a similar disease trajectory is not known.[36]

Conclusion: Clinical RHD is associated with high morbidity and mortality in young adults. Better access to high-quality tertiary care services, and optimizing the use of proven interventions

such as secondary antibiotic prophylaxis and oral anticoagulation are likely to improve outcomes. Given the scarcity of high quality data (from large international registries and randomized trials), more research is needed to devise effective ways of preventing ARF, detecting early RHD, improving access to essential care, and preventing disease progression.

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Figure legends

Figure 1: Kaplan-Meier estimates of time to death (in months) in the overall group.

Figure 2: Risk of age and sex-adjusted mortality by country-income group.

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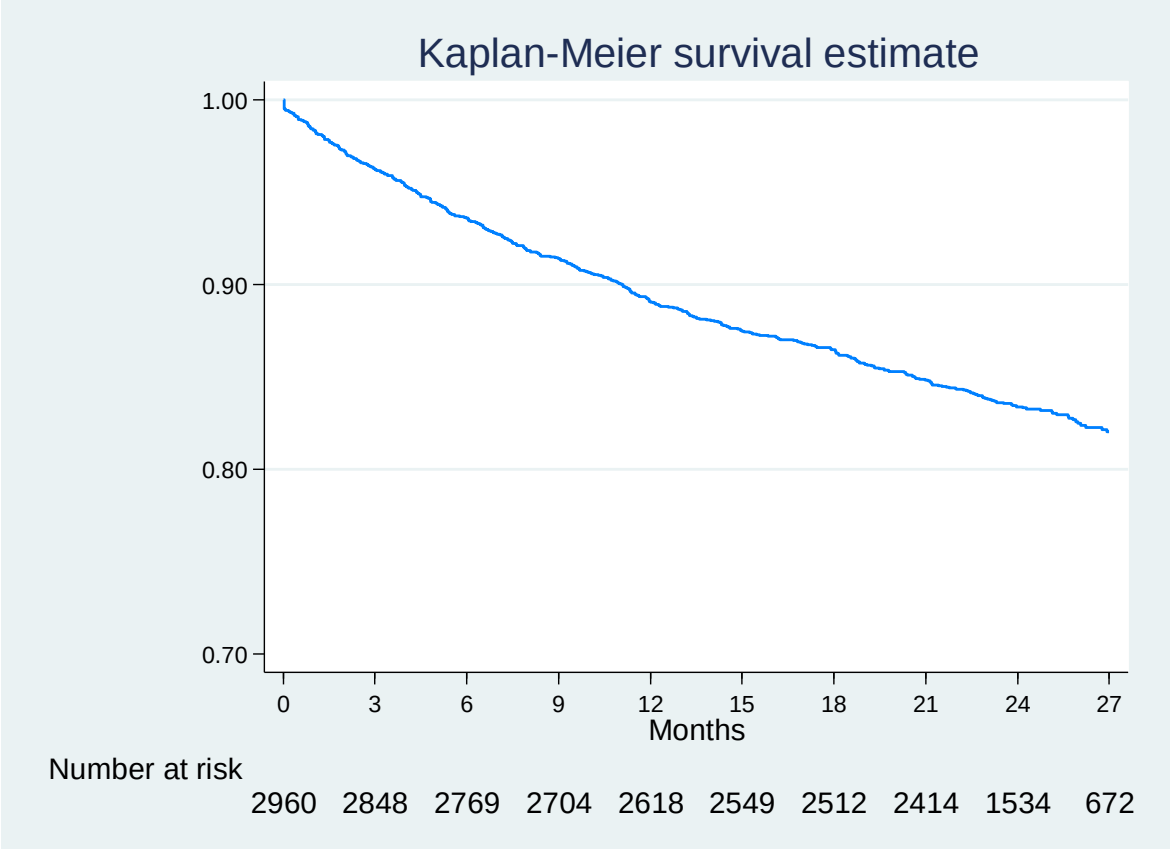
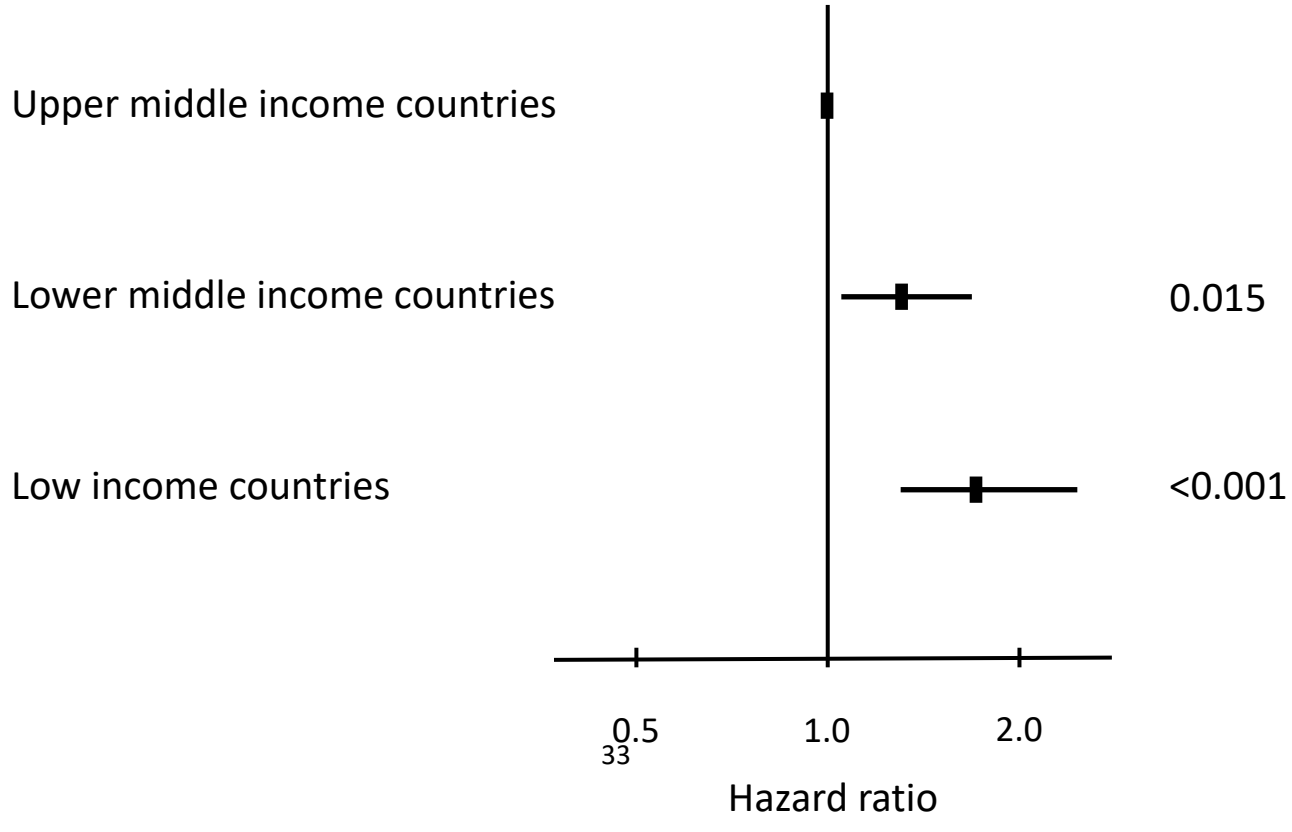


Figure 2: Risk of age and sex-adjusted mortality by country-income group.



Mortality was higher in low income countries (HR 1.95, 95% CI 1.51-2.50, p<0.0001) and low-middle income countries (HR 1.51, 95% CI 1.17-1.92, p=0.001).

Table 1: Baseline characteristics of the 3343 children and adults with rheumatic heart disease by country income group

	Low income countries N=1110	Lower middle income countries N=1370	Upper middle income countries N=863	p value
Age, median (IQR)	24 (15-34)	28 (18-38)	39 (22-52)	0.51
Women, n (%)	728 (65. 8)	867 (63.0)	616 (71.3)	0.33
Schooling below or at primary school, n (%)	312 (44.7)	632 (62.3)	242 (35)	0.23
Atrial fibrillation, n (%)	163 (18.2)	241 (22.6)	182 (27.5)	<0.0001
Severe disease, n (%)*	682 (61.4)	684 (49.9)	343 (39.8)	<0.001
Multi-valve disease, n (%)	719 (64.8)	825 (60.2)	470 (54.7)	<0.001
Congestive heart failure at enrolment, n (%)	173 (15.9)	165 (12.2)	102 (11.9)	0.010
New York Heart	306 (27.6)	384 (29.1)	119 (13.9)	0.24

Association functional class III/IV, n (%)				
Prior infective endocarditis, n (%)	25 (2.3)	59 (4.4)	49 (5.7)	<0.001
Prior stroke or systemic embolism, n (%)	58 (5.2)	52 (3.8)	125 (14.5)	<0.001
Secondary prophylaxis, n (%)	716 (69.8)	794 (59.7)	251 (29.3)	<0.001

IQR, inter-quartile range; *Severe disease includes all patients with severe disease involving at least one valve.

Table 2: Clinical outcomes at two years of follow-up in 2960 children and adults with rheumatic heart disease

	Low income countries (N=964)	Lower middle income countries (N=1158)	Upper middle income countries (N=838)	p
Death, n (%)	200 (20.8)	195 (16.8)	105 (12.5)	<0.001
Congestive heart failure, n (%)	87 (9.0)	66 (5.7)	51 (6.1)	0.006
Stroke or transient ischaemic attack, n (%)	14 (1.5)	12 (1.0)	20 (2.4)	0.053
Recurrence of acute rheumatic fever, n (%)	4 (0.4)	11 (1.0)	4 (0.5)	0.244
Infective endocarditis, n (%)	1 (0.1)	13 (1.1)	6 (0.7)	0.18
Atrial fibrillation	28 (2.9)	14 (1.2)	14 (1.7)	0.013
Prosthetic valve thrombosis	0 (0)	2 (0.1)	7 (1.0)	0.003
Surgery	30 (3.1)	84 (7.3)	109 (13.0)	<0.001
Death, congestive heart failure or acute rheumatic fever, n (%)	251 (26.0)	228 (19.7)	143 (17.1)	<0.001
Death, stroke, systemic embolism or major bleeding, n (%)	209 (21.7)	203 (17.5)	129 (15.4)	0.002

Table 3: Incidence of morbid outcomes in in 2960 children and adults with rheumatic heart disease followed up over two years

Outcome	Number of events over 27 months	Patient-years	Incidence rate per 1000	95% Confidence interval
Congestive cardiac failure	204	5309.1	38.42	33.50-44.10
Stroke or transient ischaemic attack	46	5440.8	8.45	6.33-11.29
Acute rheumatic fever	19	5444.9	3.49	2.23- 5.47
Infective endocarditis	20	5473.8	3.65	2.36-5.66
Atrial fibrillation	56	5431.1	10. 3	7.94-13.40
Major bleeding	23	5455.5	3.51	2.80-6.34
Prosthetic valve thrombosis	9	5478.9	1.64	0.85-3.16
Valvuloplasty	57	5403.8	8.83	8.14-13.67
Surgery	223	5187.7	42.99	37.70-49.01

Table 4: Predictors of mortality in in 2960 children and adults with rheumatic heart disease followed up over two years

Baseline variable	Hazard ratio	95% Confidence interval	p value
Age*	1.02	1.01 - 1.02	<0.0001
Female sex	0.65	0.52 - 0.80	<0.0001
Education beyond primary school	0.67	0.54 - 0.85	0.001
Atrial fibrillation	1.40	1.10 - 1.78	0.008
Severe disease†	2.36	1.80 - 3.11	<0.01
Multi-valve disease	0.97	0.75 - 1.25	0.852
Congestive heart failure at enrolment	2.16	1. - 2.72	<0.001
New York Heart Association functional class III/IV	1.67	1. 32 - 2.10	<0.001
Prior valve intervention or surgery	0.78	0. 57 - 1.07	0.14
Prior infective endocarditis	1.30	0.84 – 2.14	0.22
Prior stroke	1.19	0. 78 - 1.77	0.39
On secondary antibiotic prophylaxis at enrolment	0.86	0. 70 - 1.09	0.17

*Hazard ratio was 1.16 (1.11-1.25) when age was categorized as <18, and 10 year increments thereafter.

†Severe disease refers to patients with severe disease involving at least one valve.