Infective endocarditis in patients with rheumatic heart disease: a single-centre retrospective comparative study

Ammar Alsamarrai, Cathlyna Saavedra, Aliya Bryce, Eliazar Dimalapang, Alison Leversha, Simon Briggs, Nigel Wilson, Miriam Wheeler

ABSTRACT

AIMS: We reviewed the baseline characteristics and outcomes of patients with infective endocarditis (IE) and compared those with and without rheumatic heart disease (RHD).

METHODS: We retrospectively reviewed patients ≥15 years with IE treated at Auckland City Hospital between January 2016 and December 2018 and excluded device-related IE and complex congenital heart disease. RHD status was based on echocardiographic features or previous history of rheumatic fever with valvular disease. Microbiologic and echocardiographic results, treatment modalities and complications were recorded. Demographics and outcomes were compared based on RHD status.

RESULTS: There were 155 patients with IE. Twenty-two had RHD. The mean age at admission was 45 years for RHD patients, which was 19 years younger than for non-RHD patients. There were significantly more Pacific patients with RHD (55% vs 14%). Previous IE and prosthetic valve endocarditis (PVE) were more common in RHD patients (27% vs 5%, and 77% vs 29%, respectively). After a median follow-up of 29 months, there was no significant difference in all-cause mortality between the two groups. However, 25/155 patients (16%) had died from IE-related causes (septic or cardiogenic shock post cardiac surgery, or embolic complications), with a significantly higher mortality in patients with RHD (7/22 (32%) patients, HR: 2.5) on univariate analysis. On multivariable analysis, PVE, heart failure, *Staphylococcus aureus* infection, diabetes, stroke and cardiac abscess were all associated with increased mortality, whereas RHD was not independently associated with increased mortality.

CONCLUSIONS: In this retrospective single-centre audit, patients with RHD experienced IE at a younger age, had a higher incidence of prosthetic valve endocarditis and a prior history of IE. Although there was no difference in all-cause mortality, mortality in patients with RHD was almost exclusively secondary to complications of IE. This highlights the need for prevention strategies against endocarditis in the RHD population, including use of antibiotic prophylaxis, accessible dental health care and a high clinical suspicion for IE in RHD by healthcare providers.

Infective endocarditis (IE) remains a challenging clinical entity and carries a significant risk of morbidity and mortality. In developed countries, IE now affects increasingly older populations, with higher rates of nosocomial infection than seen in earlier studies. In developing countries, IE continues to affect younger populations, which is more consistent with epidemiological reports from developed countries last century. This is in part due to the persistent burden of rheumatic heart disease (RHD) in developing countries, which is now rare in most developed countries with improved access to healthcare and improved living conditions.[1]

Historically, RHD was the most common risk factor for IE. [2] Although for many years the burden of Group A streptococcal disease and RHD has been diminishing in most developed countries due to access to healthcare, the increasing use of penicillin to treat streptococcal pharyngitis and improved living conditions.[3] RHD remains prevalent at significant rates in the developing world, in the Pacific and in populations in New Zealand and Australia, where RHD almost exclusively affects Māori, Pacific and Aboriginal populations and those from a low socioeconomic backgrounds.[3,4] The true burden of RHD in New Zealand is difficult to establish, due to the lack of population

screening and because, unlike acute rheumatic fever (ARF), RHD is not a notifiable condition. Although a documented history of ARF is helpful in confirming rheumatic valvular changes seen on echocardiography, some patients with RHD have no known history of ARF, and the diagnosis is made on echocardiography alone, or occasionally at the time of cardiac surgery, when typical findings of leaflet thickening and retraction, and mitral chordal thickening, are seen. The World Heart Federation published a guideline in 2012 defining possible and definite echocardiographic findings of RHD to improve standardisation in reporting.[5]

There are few studies that have assessed the burden and outcome of IE complicating RHD in the modern era of improved diagnostics and surgical treatment.[6] Therefore, the aim of this study was to compare the clinical features of IE in rheumatic versus non-rheumatic heart disease, and to compare demographics and outcomes between these two groups.

Methods

Study design

A retrospective case series of adult patients admitted to Auckland City Hospital who received a discharge diagnosis of IE (using International Classification of Disease coding) between 1 January 2016 and 31 December 2018. Exclusion criteria included patients <15 years of age, those with a history of complex congenital heart disease (patients with isolated lesions such as bicuspid aortic valve or small ventricular septal defect were not excluded), and cases of cardiac implantable electronic device endocarditis (patients with valvular endocarditis and concurrent, non-infected devices were not excluded). Follow-up was for a median of 29 months (range 0–41 months). For patients referred from outside New Zealand, follow-up was censored to the date of the last documented healthcare encounter.

Our institution (Auckland District Health Board, Auckland, New Zealand) serves a population of 545,640 people that reside within the locality. Tertiary cardiac surgical services are provided to patients from a larger total population (children and adults) of >2 million people (all patients within the wider Auckland and Northland regions and patients from neighbouring Pacific Islands). We expected IE patients requiring cardiac surgery to be over-represented in this study, with adult patients managed medically in the larger total population not being captured. All cases of cardiac surgery are managed by a multidisciplinary heart team, and the decision regarding surgery is by way of consensus between cardiologists, cardiac surgeons, cardiac anaesthetists and cardiac intensive care specialists, in keeping with international recommendations.[7,8]

Data collection and definitions

Patients were classified as having definite or possible IE according to the Modified Duke Criteria.[9] Regarding major criteria, transthoracic and transoesophageal echocardiography reports for each patient were reviewed and pertinent findings recorded including presence of vegetation, valve involvement, cardiac abscess and left ventricular ejection fraction. Electrocardiography was performed on all patients during admission, and significant findings were recorded. Peripheral blood cultures were reviewed and considered significant if the microbiology was consistent with IE or if an organism was persistently cultured with no other focus found. Peripheral blood cultures were obtained within our institution and cultured at an onsite microbiological laboratory using standard microbiological techniques (n=71), or they were obtained within other localities (n=84). Prosthetic valve endocarditis (PVE) was defined as IE affecting a bioprosthetic or metallic heart valve. Patients were classified as having nosocomial IE if symptoms/signs of IE started more than 48 hours after hospitalisation. The diagnosis of RHD was based on echocardiographic features consistent with the World Heart Federation criteria for definite RHD[5] or a previous history of ARF with valvular disease. Patients with prosthetic valves with no documentation of prior rheumatic valvular disease were not included in the RHD group.

Baseline clinical data including demographics and medical comorbidities were retrospectively retrieved from electronic medical records. Ethnicity was self-defined and categorised as New Zealand European, Māori, Pacific, Asian or Other. Pacific ethnicity included people from the Cook Islands, Fiji, Niue, Norfolk Island, Samoa, Tahiti, Tonga and Tuvalu. Chronic kidney disease was defined as a documented estimated glomerular filtration rate of <60 mL/min/1.73m^2 prior to the index admission. Recent invasive procedure was defined as any invasive procedure that occurred within 60 days prior to onset of symptoms. The outcomes of interest were the occurrence of valve vegetation, intracardiac abscess (aortic root abscess or other site), stroke, non-stroke systemic

embolisation (screening for asymptomatic systemic embolism was at the discretion of the treating clinician), conduction abnormality, cardiac surgery and death. IE-related death was defined as death that occurred due to embolic stroke or intracranial haemorrhage from a mycotic aneurysm, sepsis, heart failure, cardiogenic shock, or death secondary to multi-organ failure or shock post cardiac surgery.

Ethics

Institutional ethical approval was gained from the Auckland District Health Board Research Review Committee for a low-risk audit with research methodologies not meeting criteria for formal independent ethics approval.

Statistical analysis

Continuous variables were reported as mean with standard deviation (SD) or median with interquartile range (IQR), and categorical variables were reported as absolute values with percentages. Comparison between RHD and non-RHD groups was performed by Mann-Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables where appropriate. Kaplan-Meier curves were plotted to demonstrate survival from IE-related death and all-cause death. Multivariate analysis using Cox proportional hazards model (stepwise method) was undertaken to calculate the hazard ratio (HR) with 95% confidence interval (95% CI) and included factors that had a $p<0.10$ in the univariate analysis. Statistical analysis was undertaken using IBM SPSS Version 24 and SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Demographic characteristics

Over the three-year study period, a total of 155 patients with a discharge diagnosis of IE were identified, of which 22 (14%) had RHD (Table 1). The mean age at presentation was younger in those with RHD: 45.2 years (SD 15.3) in the RHD group compared with 63.9 years (SD 15.8) in the non-RHD group ($p<0.01$). There was a significant difference in ethnicity, where the largest self-reported ethnic group was Pacific (55%) in the RHD group and New Zealand European (48%) in the non-RHD group. Māori made up five (23%) of the RHD group and 16 (12%) of the non-RHD group. Most of the cohort were New Zealand residents (142 patients (92%)).

Clinical characteristics

Patients with RHD had a significantly higher rate of previous IE (six patients, 27%) compared with the non-RHD group (six patients, 5%) ($p<0.01$), as well as higher rates of PVE (17 patients, 77%) compared with the non-RHD group (39 patients, 29%) ($p<0.01$). Nineteen patients (12%) had a recent (<60 days prior) invasive procedure, of which there were eight surgical operations or procedures, five dental procedures, four cardiac valve operations (representing early PVE) and two cardiac catheterisations. According to Modified Duke criteria, 123 (79%) patients were classified as having definite IE and the remainder as having possible IE.

Microbiology

Staphylococcus aureus was the most common causative organism in both groups, followed by viridans group streptococci and *Enterococcus* species (Table 2). There was no significant difference in causative organisms between the two groups.

Clinical outcomes and survival analysis

Stroke occurred in eight patients (36%) in the RHD group compared with 24 (18%) in the non-RHD group, although this difference was not statistically significant (Table 3). Non-stroke systemic embolisation was common in both RHD and non-RHD groups (27% and 40% respectively). The rates of heart failure, conduction abnormalities and cardiac abscess were not significantly different between the two groups. Surgical treatment was undertaken in 14 patients (64%) in the RHD group (with the majority requiring multi-valve surgery) compared with 71 patients (53%) in the non-RHD group.

After a median follow-up duration of 29.4 (IQR 7.4–40) months, 41 patients died: eight (36%) in the RHD group and 33 (25%) in the non-RHD group. Kaplan-Meier survival demonstrated no significant difference in overall mortality between the two groups (Figure 1). During the same follow-up period, 25 patients met the definition for an IE-related death: seven (32%) in the RHD group and 18 (14%) in the non-RHD group. In the RHD group, three deaths were from multi-organ failure following cardiac surgery, three deaths were from intracranial haemorrhage secondary to embolic complications, and one death was from a stroke while awaiting cardiac surgery. In the non-RHD group, nine deaths were from multi-organ failure post cardiac surgery, six deaths from sepsis, two deaths from intracranial haemorrhage

Table 1: Baseline clinical characteristics and disease factors of patients with infective endocarditis.

Characteristics	Total (n=155)	Non-rheumatic heart disease (n=133)	Rheumatic heart disease (n=22)	P-value
Demographics				
Age				
Mean age	61.3 (17.0)	63.9 (15.8)	45.2 (15.3)	<0.01
Under 18 years	0	0	0	
18–30 years	11 (7%)	5 (4%)	6 (27%)	
31–45 years	16 (10%)	11 (8%)	4 (18%)	
46–60 years	41 (26%)	33 (25%)	9 (41%)	
Over 60 years	87 (56%)	84 (63%)	3 (14%)	
Male	105 (68%)	93 (70%)	12 (55%)	0.15
Ethnicity				
New Zealand European	67 (43%)	64 (48%)	3 (14%)	<0.01
Māori	21 (14%)	16 (12%)	5 (23%)	
Pacific	31 (20%)	19 (14%)	12 (55%)	
Asian	14 (9%)	13 (10%)	1 (5%)	
Other	22 (14%)	21 (16%)	1 (5%)	
New Zealand residency	142 (92%)	124 (93%)	18 (82%)	0.09
Medical history				
Diabetes	31 (20%)	30 (23%)	1 (5%)	0.08
Chronic kidney disease	28 (18%)	23 (17%)	5 (23%)	0.55
Dialysis dependent	6 (4%)	5 (4%)	1 (5%)	1.00
Cancer	17 (11%)	15 (11%)	2 (9%)	1.00
Current intravenous drug use	3 (2%)	3 (2%)	0	1.00
Previous infective endocarditis	12 (8%)	6 (5%)	6 (27%)	<0.01
Invasive procedure within 60 days	19 (12%)	15 (11%)	4 (18%)	0.49
Implanted cardiac device [a]	9 (6%)	7 (5%)	2 (9%)	0.62
Immunosuppression	7 (5%)	7 (5%)	0	0.59

Table 1 (continued): Baseline clinical characteristics and disease factors of patients with infective endocarditis.

Characteristics	Total (n=155)	Non-rheumatic heart disease (n=133)	Rheumatic heart disease (n=22)	P-value
Disease characteristics				
Duke's definite	123 (79%)	103 (77%)	20 (91%)	0.25
Duke's possible	32 (21%)	30 (23%)	2 (9%)	0.25
Prosthetic valve endocarditis	56 (36%)	39 (29%)	17 (77%)	<0.01
Duration of symptoms [b]				
<1 week	72 (46%)	59 (44%)	13 (59%)	0.19
1–4 weeks	26 (17%)	25 (19%)	1 (5%)	0.13
>4 weeks	35 (23%)	31 (23%)	4 (18%)	0.78
Community acquired	150 (97%)	128 (96%)	22 (100%)	1.00
Nosocomial	5 (3%)	5 (4%)	0	1.00

[a] Patients had valvular endocarditis and not device-related endocarditis.
[b] Data not available in 22 patients.

Table 2: Causative organisms of infective endocarditis.

Causative organism	Total (n = 155) [a]	Non-rheumatic heart disease (n=133)	Rheumatic heart disease (n=22)
Staphylococcus aureus	51 (33%)	42 (32%)	9 (41%)
Coagulase-negative staphylococci	6 (4%)	6 (5%)	0
Viridans group streptococci	26 (17%)	24 (18%)	2 (9%)
Streptococcus gallolyticus	4 (3%)	4 (3%)	0
Other *Streptococcus* species	13 (8%)	10 (8%)	3 (14%)
Enterococcus species	21 (14%)	20 (15%)	1 (5%)
HACEK group [b]	12 (8%)	7 (5%)	5 (23%)
Polymicrobial	3 (2%)	3 (2%)	0
Other organisms	14 (9%)	13 (10%)	1 (5%)
Culture negative	5 (3%)	4 (3%)	1 (5%)

[a] There was no statistically significant difference between the distribution of causative organisms between the two groups.
[b] HACEK: *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae*.

and one death from ischaemic bowel. Kaplan-Meier survival demonstrated a significantly higher IE-related death rate in patients with RHD (p=0.03) (Figure 2). On multivariate analysis, factors associated with increased risk of IE- related death included PVE, heart failure, *Staphylococcus aureus* endocarditis, diabetes, stroke and cardiac abscess (Table 4).

Discussion

One in three RHD patients with IE in this study had an IE-related death within 20 months of diagnosis, which was twice the IE-related death rate of non-RHD patients at the same duration of follow-up. This high IE-related death rate in the RHD group is comparable to the reported IE-related death rate in low- and middle-income countries.[10] Overall, the outcomes in our study are similar to contemporary series. The European Infective Endocarditis study (2019) prospectively enrolled 3,116 patients across 40 countries. In-hospital outcomes included heart failure in 14% and surgical treatment in 51%, and the overall in-hospital death rate was 17%. Underlying rheumatic heart disease incidence was not specified.[11]

In addition to the higher mortality rate in the RHD group, the near 20-year age difference between the two groups implies a very significant reduction in life expectancy in the RHD group. The increased IE-related death rate in patients with RHD may have been contributed to by the higher rate of PVE, which was also the strongest predictor of death.

In the present study, 14% of patients with IE had a diagnosis of RHD, which contrasts with estimates for the community prevalence of RHD; echocardiography screening studies in high-risk groups in Auckland have shown approximately 5% of young Pacific adults and 2.5% of Māori and Pacific children have RHD changes on echocardiography.[12,13] The over-representation of RHD patients in the total number of patients with IE is still apparent even when compared to a publication from the 1980s for the same region (where 45% of the cohort had RHD), despite clear evidence for modifiable risk factors for ARF and national guidelines for management of sore throats.[14]

We observed a significant difference in the rate of previous IE between the RHD and the non-RHD groups; a quarter of the RHD group had a previous episode of IE, compared with only 5% of the non-RHD group. A significantly higher incidence of PVE was seen in the RHD group compared to the non-RHD group. Heart valve surgery early in life in patients with RHD, a condition often affecting multiple valves, exposes them to high cumulative risk of developing PVE over their lifetime. This supports a notion of a vicious cycle which can emerge from the combination of RHD, prosthetic heart valves and episodes of IE, which create a host that is at an exceedingly high risk of recurrent IE and complications thereof. In this regard, New Zealand and Australian IE prophylaxis guidelines recommend several measures to prevent the occurrence of IE, including continued recognition of the role of prophylactic antibiotics prior to invasive procedures in patients with RHD.[15–17] This contrasts with the guidelines of the European Society of Cardiology and the American Heart Association,[8,18] which do not specifically list people with RHD as part of the high-risk populations that require antibiotic prophylaxis. The specific recognition of RHD in New Zealand and Australian guidelines reflects the higher prevalence of this condition in these regions. Our finding that PVE and previous IE were common in the RHD group supports the recommendation to include these patients in the high-risk populations that require antibiotic prophylaxis. In the present study, PVE was associated with a near tenfold increase in the hazard of death compared to native valve IE. This increased risk of death may be because the management of PVE is characterised by high rates of surgical intervention and technically challenging operations and that there are significant rates of recurrent IE with the need for future redo surgery in this patient group.[19]

Given the mortality risk and complications of IE, high-risk patients with valvular heart disease (in particular, patients with a prosthetic valve replacement, patients with previous IE and patients with RHD) should have regular dental reviews. Funded dental treatment options should be available for those who are unable to have regular dental reviews due to financial reasons. Patients should also be provided with "Infective Endocarditis" wallet cards, such as those produced by the New Zealand Heart Foundation,[20] and advised of symptoms that should prompt urgent medical review. Experience from most of the developed world indicates that the eradication of ARF and RHD is possible, and therefore ongoing efforts to reduce the incidence of ARF within Indigenous populations are essential. A focus on adequate provision of safe, healthy housing and funded access to healthcare, including dental services for high-risk populations, is required.

Table 3: Complications, surgical treatment and outcomes of patients with infective endocarditis.

	Total (n=155)	**Non-rheumatic heart disease (n=133)**	**Rheumatic heart disease (n=22)**	**P-value**
Complications				
Vegetation [a]	118 (76%)	98 (74%)	20 (91%)	0.11
Aortic valve	42 (27%)	38 (29%)	4 (18%)	
Mitral valve	77 (50%)	60 (45%)	17 (77%)	
Tricuspid valve	15 (10%)	14 (11%)	1 (5%)	
Intra-cardiac abscess	23 (15%)	20 (15%)	3 (14%)	0.86
Aortic root	18 (12%)	15 (11%)	3 (14%)	
Other site [b]	5 (3%)	5 (4%)	0	
Stroke	32 (21%)	24 (18%)	8 (36%)	0.08
Non-stroke systemic embolisation [c]	59 (38%)	53 (40%)	6 (27%)	0.26
Conduction abnormality or arrhythmia [d]	34 (22%)	29 (22%)	5 (23%)	0.67
Heart failure	17 (11%)	16 (12%)	1 (5%)	0.47
Surgery	85 (55%)	71 (53%)	14 (64%)	0.37
Aortic valve repair or replacement [e]	42 (27%)	33 (25%)	9 (41%)	
Mitral valve repair or replacement [e]	47 (30%)	36 (27%)	11 (50%)	
Tricuspid valve repair or replacement [e]	11 (7%)	6 (5%)	5 (23%)	
Multi-valve surgery	16 (10%)	8 (6%)	8 (36%)	
Outcomes				
Median follow-up in months	29 (7.4–40)	32 (16–41)	20 (0.07–36)	0.11
IE-related in-hospital death	20 (13%)	15 (11%)	5 (23%)	0.16
IE-related death at 30 days	22 (14%)	16 (12%)	6 (27%)	0.06
IE-related death during follow-up	25 (16%)	18 (14%)	7 (32%)	0.05
All-cause death during follow-up	41 (26%)	33 (25%)	8 (36%)	0.26
Recurrent IE	7 (5%)	7 (5%)	0	0.59

Abbreviations: IE, infective endocarditis.
[a] Indicates number of patients affected, as some patients had multiple valve vegetations.
[b] mitral annulus, interventricular septum, or left ventricular outflow tract.
[c] Includes cerebral abscess, meningitis, meningoencephalitis, epidural abscess, discitis, transient ischaemic attack, splenic embolism, renal embolism, mesenteric ischaemia, liver abscess or infarcts, osteomyelitis, muscle abscess, septic arthritis, endophthalmitis, septic pulmonary emboli, limb artery embolism and Janeway lesions.
[d] Includes sinus bradycardia, first degree heart block, complete heart block, bundle branch block, atrial fibrillation or flutter, junctional arrhythmia and ventricular tachycardia.
[e] Includes cases of redo valve surgery and multi-valve surgery.

Figure 1: Kaplan-Meier survival free from all-cause death based on rheumatic heart disease (RHD) status.

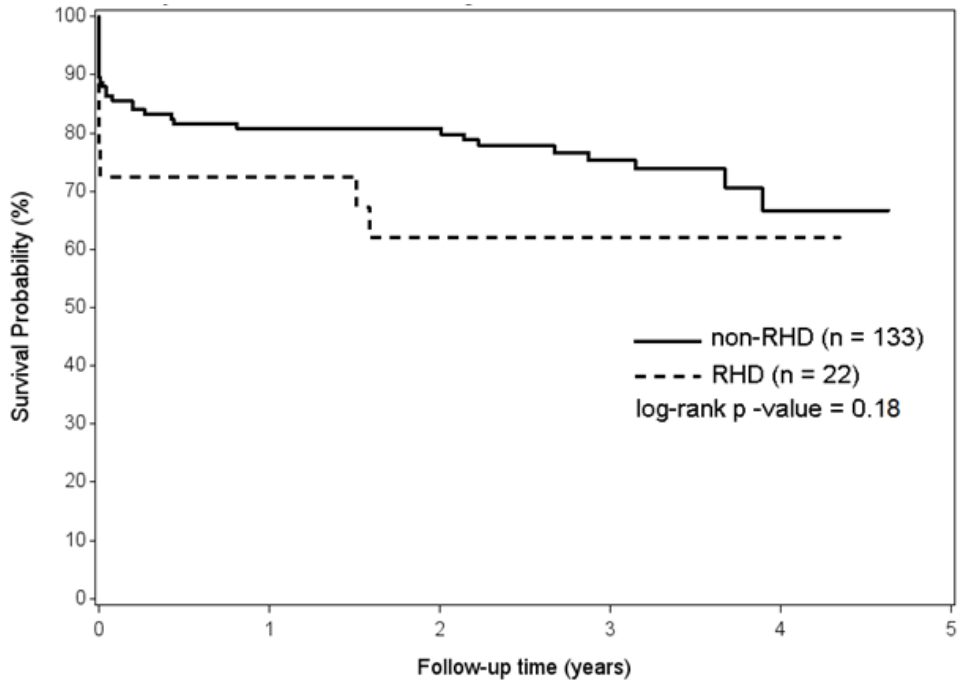

Figure 2: Kaplan-Meier survival free from infective endocarditis-related death based on rheumatic heart disease (RHD) status.

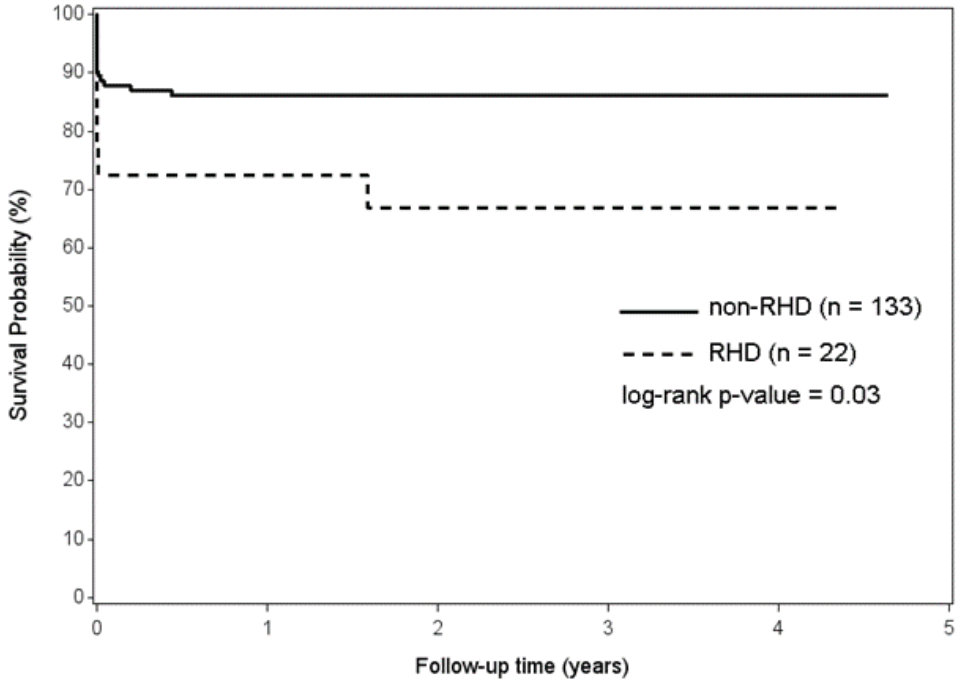

Table 4: Cox univariate and multivariate analyses of factors for association with infective endocarditis-related mortality.

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Prosthetic valve endocarditis	2.8 (1.2–6.2)	0.01	9.5 (3.2–28.5)	<0.01
Heart failure	2.8 (1.1–6.9)	0.03	6.3 (2.0–19.4)	<0.01
Staphylocccus aureus infective endocarditis	3.2 (1.5–7.2)	<0.01	4.1 (1.8–9.7)	<0.01
Diabetes	2.4 (1.1–5.4)	0.04	3.9 (1.6–9.9)	<0.01
Stroke	2.7 (1.2–5.9)	0.02	2.8 (1.2–6.5)	0.02
Cardiac abscess	2.8 (1.2–6.5)	0.02	2.4 (1.0–5.6)	0.049
Rheumatic heart disease	2.5 (1.0–6.0)	0.04	Not significant	
Chronic kidney disease	2.7 (1.2–6.1)	0.02	Not significant	
Age	1.0 (0.9–1.0)	0.68		
Cancer	1.2 (0.3–3.8)	0.82		
Cardiac operation	1.1 (0.5–2.3)	0.90		
Male gender	1.0 (0.4–2.3)	0.99		
Previous infective endocarditis	1.7 (0.5–5.6)	0.51		
Vegetation	1.0 (0.4–2.5)	0.99		
Ethnicity				
New Zealand European	Reference			
Māori	2.7 (1.0–7.1)	0.053		
Pacific	1.3 (0.4–3.8)	0.66		
Asian	1.1 (0.2–4.9)	0.95		
Other	0.7 (0.2–3.2)	0.65		

This study has a number of limitations. It is retrospective and based on a single centre. Further, we were not able to include patients treated non-surgically from the other centres that referred patients for cardiac surgery, and therefore there is a risk that referral bias may have affected the results. A small number of patients were included having been referred from the Pacific, and follow-up data were also limited for these patients, which contributes to the referral bias.

Conclusion

This study has shown that patients with underlying RHD are at risk of developing IE. Patients with RHD experienced IE at a significantly younger age and had higher rates of previous IE and prosthetic valves. Although there was no difference in all-cause mortality, mortality in patients with RHD was almost exclusively secondary to IE- related factors. Prevention strategies to reduce the risk of endocarditis in the RHD population are important, including the use of antibiotic prophylaxis as per the New Zealand Heart Foundation Guidelines, accessible dental healthcare and a high clinical suspicion for IE by healthcare providers. Efforts to eradicate ARF should also continue for this preventable disease.

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COMPETING INTERESTS
Nil.

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