Long-Term Outcomes From Acute Rheumatic Fever and Rheumatic Heart Disease

A Data-Linkage and Survival Analysis Approach

BACKGROUND: We investigated adverse outcomes for people with acute rheumatic fever (ARF) and rheumatic heart disease (RHD) and the effect of comorbidities and demographic factors on these outcomes.

METHODS: Using linked data (RHD register, hospital, and mortality data) for residents of the Northern Territory of Australia, we calculated ARF recurrence rates, rates of progression from ARF to RHD to severe RHD, RHD complication rates (heart failure, endocarditis, stroke, and atrial fibrillation), and mortality rates for 572 individuals diagnosed with ARF and 1248 with RHD in 1997 to 2013 (94.9% Indigenous).

RESULTS: ARF recurrence was highest (incidence, 3.7 per 100 person-years) in the first year after the initial ARF episode, but low-level risk persisted for >10 years. Progression to RHD was also highest (incidence, 35.9) in the first year, almost 10 times higher than ARF recurrence. The median age at RHD diagnosis in Indigenous people was young, especially among males (17 years). The development of complications was highest in the first year after RHD diagnosis: heart failure incidence rate per 100 person-years, 9.09; atrial fibrillation, 4.70; endocarditis, 1.00; and stroke, 0.58. Mortality was higher among Indigenous than non-Indigenous RHD patients (hazard ratio, 6.55; 95% confidence interval, 2.45–17.51), of which 28% was explained by comorbid renal failure and hazardous alcohol use. RHD complications and mortality rates were higher for urban than for remote residents.

CONCLUSIONS: This study provides important new prognostic information for ARF/RHD. The residual Indigenous survival disparity in RHD patients, which persisted after accounting for comorbidities, suggests that other factors contribute to mortality, warranting further research.

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Key Words: alcohol drinking ■ comorbidity ■ complications ■ heart failure ■ rheumatic heart disease ■ survival analysis

Clinical Perspective

What Is New?

- Data linkage between an rheumatic heart disease (RHD) register, hospital data, and death register was used to investigate RHD disease progression, complication development, and survival and to examine the impact of comorbidities.
- In the first year after an acute rheumatic fever (ARF) episode, the incidence of progression to RHD was 10 times higher than ARF recurrence.
- Ten percent of RHD patients had severe disease at RHD diagnosis.
- The presence of comorbidities was associated with a higher incidence of RHD complications and mortality.
- Among the RHD patients, comorbid renal failure and hazardous alcohol use accounted for 28% of the excess Indigenous mortality.

What Are the Clinical Implications?

- To emphasize the need for integrated chronic disease management strategies for patients with ARF/RHD. This recommendation has relevance globally for settings with high ARF/RHD rates.
- To raise the question of what factors, other than higher comorbidity burden, account for remaining gaps in Indigenous mortality and complication rates.
- To show that although secondary penicillin prophylaxis is an important strategy to reduce ARF recurrence and RHD development, the persisting high progression rate from ARF to RHD reinforces the need for new ARF treatments and broader health policies focusing on primary and primordial prevention strategies.

Rheumatic heart disease (RHD) involves damage to the heart valves during episodes of acute rheumatic fever (ARF) after group A streptococcal infection. It is a disease overwhelmingly acquired in childhood among children living in poverty and overcrowded conditions. In the Australian general population and other developed countries, new cases of RHD have been rare for many decades; it is now almost entirely a disease of the elderly who acquired it as children ≥60 years ago.

However, RHD remains very common among Indigenous (Aboriginal and Torres Strait Islander) Australians,[1] many of whom live in conditions of poverty and overcrowding. Such conditions are particularly common in the Northern Territory (NT), a large, sparsely populated area of northern Australia where Indigenous Australians make up 30% of the population and live mostly in remote, isolated communities.[2] ARF and RHD incidence rates among the NT Indigenous population are among the highest rates reported worldwide. A recent study reported that the ARF incidence and RHD incidence were both >60 times higher for Indigenous compared with non-Indigenous NT residents, with significantly higher excess mortality.[1] Another recent study reported that Indigenous Australians living in the NT are 54.8 times more likely to die of RHD than non-Indigenous Australians and have higher RHD mortality than Indigenous people elsewhere in Australia.[3]

In 1997, an RHD control program began in the NT. A register of all people diagnosed with ARF or RHD in the NT is a central component of this control program. The RHD Register is a recording and reminder system for regular penicillin prophylaxis (to prevent recurrent ARF episodes that cause cumulative damage to heart valves) and to coordinate specialist monitoring and management for those with heart valve damage. The RHD Register has also enabled comprehensive epidemiological analysis of ARF and RHD incidence, prevalence, and disease progression.[1]

Limited evidence is available on the development of complications of RHD[4,5] or on the impact of chronic disease comorbidities on outcomes for RHD patients, despite the high prevalence of many chronic diseases among Indigenous Australians.[6] Expanding on previous research,[1] this study incorporated a data-linkage approach using the RHD Register, hospital inpatient data, and death register data to investigate adverse outcomes (eg, RHD complications and mortality) for people with ARF and RHD and the effect of chronic disease comorbidities and other factors (eg, hazardous alcohol use, exposure to violence, and trauma) on these outcomes.

METHODS

Data Sources

The NT RHD Register was used to identify NT residents with a first episode of ARF or diagnosed with RHD between January 1, 1997, and June 30, 2013. Data obtained from the register included demographic (sex, date of birth, Indigenous status, place of residence), diagnostic (date of first ARF episode, date of RHD diagnosis), and clinical information. The register also includes the NT's unique health client identifier (the Hospital Registration Number) that is used by all public health services (hospitals, primary health care, etc) in the NT.

An extract of all NT residents on the RHD Register was linked to the NT public hospitals inpatient data set (matched on Hospital Registration Number) to obtain data on all hospital inpatient episodes for individuals on the register. Date of birth and sex were used to verify the match. Data were obtained from the inpatient data set for each inpatient episode: dates of admission and discharge and principal and additional diagnoses. Diagnosis data were used to identify inpatient episodes with ARF or RHD as a principal or secondary diagnosis and those with chronic disease comorbidities and, for RHD patients only, those who had been hospitalized for serious RHD complications (heart failure, stroke, atrial fibrillation, and endocarditis) or indicators of high-risk behaviors and environments (hazardous alcohol use, assault, and transportation accidents; Table 1). The Charlson Comorbidity Index (CCI) was used to

Table 1. Diagnosis Codes for Adverse Outcomes and Health Behavior–Related Hospitalization

Hospitalization	*ICD-9* Codes*	*ICD-10* Codes*
ARF	390–392	I00–I02
RHD	393–398	I05–I09
Complications		
Atrial fibrillation	427.31	I48
Endocarditis	421.0, 421.9, 424.9	I33.0, I33.9, I38
Heart failure	428	I50
Stroke	430–436	I60–I64
Hospitalizations that indicate high-risk behavior or environment		
Assault	E96	X85–Y09, Y87.1
Hazardous alcohol use†	265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5,535.3, 571.0–571.3, 980, V11.3	F10, E52, G62.1, I42.6,K29.2, K70.0, K70.3, K70.9,T51, Z50.2, Z71.4, Z72.1
Transportation accident	E800–E848, E929.0–E929.1	V00–V99, Y85

ARF indicates acute rheumatic fever; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, 10th Revision*; and RHD, rheumatic heart disease.

*Diagnosis code in the hospital inpatient data set was classified with the *ICD-9* (January 1991–June 1998) and *ICD-10* (July 1998 onward).

†Hazardous alcohol use (alcohol abuse) was one of the comorbidities in the Elixhauser Comorbidities Index.[7]

measure chronic disease comorbidity. The CCI is a widely used summary measure of 19 comorbid conditions that has been adapted for use with health administrative data.[7,8] In the CCI, each comorbidity was assigned a weight, and the sum of all the weights results in the total CCI score[7]: CCI score=0 indicates no comorbidities; CCI score=1 indicates presence of only 1 comorbidity; and CCI score ≥2 indicates multiple comorbidities or serious comorbidities. Comorbidities and high-risk indicators were identified from principal and secondary diagnoses for inpatient episodes in the 5 years preceding the first ARF episode or RHD diagnosis.

The RHD Register extract was also linked (using the Hospital Registration Number) to the NT Department of Health's Client Master Index to obtain information on vital status and date of death. All deaths registered in the NT are recorded in the Client Master Index, although deaths of NT residents that occur interstate are not recorded.

The first ARF episode was defined as the first ARF episode recorded in the register. Patients with a diagnosis of RHD before or on the same day as their first ARF episode were excluded from the ARF analysis because they may have had a prior ARF episode that had not been diagnosed or recorded. Patients with a first ARF episode before January 1, 1997 or after June 30, 2013, were excluded.

The date of RHD incidence was defined as the earliest of the RHD diagnosis date recorded in the register, the date of first clinical review for RHD recorded in the register, or the admission date of the first inpatient episode with a diagnosis of RHD. Patients with a diagnosis date before January 1, 1997, or after June 30, 2013, were excluded, as were those with an inpatient episode that included a diagnosis of heart failure, endocarditis, stroke, or atrial fibrillation before the RHD diagnosis date (because these were likely to be complications of previously undiagnosed RHD).

Patients living in the cities of Darwin and Alice Springs and their hinterlands were classified as urban residents; all others were classified as remote residents.

Study Outcomes

The primary outcomes for patients with a first ARF episode were recurrent ARF and progression to RHD. The RHD Register was used to identify recurrent ARF episodes. The primary outcomes for patients with RHD were progression to severe RHD, diagnosis of a serious complication (heart failure, endocarditis, stroke, or atrial fibrillation), or death. Data from the RHD Register about clinical reviews by medical specialists were used to identify progression to severe RHD. Since 2004, the NT RHD control program has classified the patient's cardiac status into 4 categories (no, mild, moderate, or severe RHD) based on Australian national guidelines.[9] Hospital inpatient data were used to identify the occurrences of RHD complications (atrial fibrillation, endocarditis, heart failure, or stroke). All 4 are almost always investigated and treated in hospital at their first occurrence. The secondary outcomes were hospitalization for treatment of ARF or RHD after the first ARF episode or RHD diagnosis.

Statistical Analysis

Statistical analyses were conducted with Stata, version 13 (StataCorp, College Station, TX). The χ^2 test was used to compare prevalence of comorbidities, high-risk indicators, and RHD hospitalization (within 1 year) between Indigenous and non-Indigenous patients and other population subgroups.

Survival analysis was used to analyze the following adverse outcomes for ARF patients: ARF recurrence and progression to RHD. For RHD patients, the following adverse outcomes were analyzed: progression to severe RHD, the occurrence of RHD complications, and death. For each of the adverse events except death, the follow-up time was censored at the earliest of the following: date of diagnosis of each adverse event, date of death, or June 30, 2013. For the analysis of death, follow-up time was censored at June 30, 2013. The incidence rate (per 100 person-years) of adverse outcomes was calculated for years 0, 1 to 4, 5 to 9, and 10 to 14 after diagnosis. The Stata stptime command was used to calculate incidence rates, which allowed variable follow-up time for each patient. The risks of the adverse outcomes at each time point (1, 5, and 10 years) were calculated from the Kaplan-Meier failure function as the cumulative probability of each event using the Stata sts list command.

For the multivariable analysis, separate Cox proportional hazards regression analysis was used to identify factors associated with each adverse outcome. The same independent variables were included in all final regression models: Indigenous status (Indigenous compared with non-Indigenous); remoteness of residence (remote compared with urban); sex (male compared with female); age at diagnosis (per year); year of diagnosis (per year);

Circulation. 2016;134:222–232. DOI: 10.1161/CIRCULATIONAHA.115.020966

and comorbidity (CCI scores of 1 and 2 or more compared with 0). Cox regression and logistic regression were used to identify the factors associated with higher hospitalization for ARF/RHD treatment of ARF patients and higher hospitalization for RHD treatment (within 1 year) of RHD patients.

Ethics

The study was approved by the Human Research Ethics Committee of the NT Department of Health and the Menzies School of Health Research (HREC-2011-1680). Approval to access RHD Register data was obtained from the NT RHD Steering Committee and the Register's data custodian. Approval to access the NT hospital inpatient data and Client Master Index data was obtained from the NT hospital inpatients data custodian.

RESULTS

After the exclusion of those who died before 1997 or had their first ARF episode or RHD diagnosis after June 30, 2013, there were 2660 potentially eligible individuals in the RHD Register.

To derive the ARF cohort, we excluded 926 patients with first ARF episode or RHD diagnosis before 1997, 193 with unconfirmed ARF, and 969 patients in whom we were unable to identify the first ARF episode, leaving 572 individuals with a first ARF episode in the study period. To derive the RHD cohort, we excluded 746 with no RHD diagnosis, 561 patients diagnosed before 1997, and 105 patients who had prior hospitalization for heart failure (n=62), endocarditis (n=11), stroke (n=10), or atrial fibrillation (n=22), leaving 1248 patients diagnosed with RHD during the study period. There were 152 RHD patients who had a clinical review for RHD before their RHD diagnosis date was recorded in the RHD Register; the diagnosis date was replaced with the first review date. Similarly, the RHD diagnosis date was replaced for 330 patients who had a prior inpatient episode with a diagnosis of RHD. For the analysis of ARF and RHD patients, there were no missing data for Indigenous status, sex, age, and remoteness.

ARF Patient Cohort

ARF Patients' Characteristics

Of the 572 confirmed first ARF episodes, 97.0% patients were Indigenous, 43.5% were male, and 5.1% had comorbidities (CCI score ≥1; Table 2). The median age of

Table 2. Demographic Characteristics of ARF and RHD Patients, NT, 1997 to 2013

	ARF, %		RHD, %	
	Indigenous (n=555)	Non-Indigenous (n=17)	Indigenous (n=1173)	Non-Indigenous (n=75)
Male	43.2	52.9	35.2	28.0
Remote resident	85.4	29.4	84.1	20.0
Age group, y				
0–4	0.9	0.0	0.3	0.0
5–9	21.1	5.9	10.3	0.0
10–14	39.5	23.5	20.0	6.7
15–24	25.4	23.5	26.0	9.3
25–34	7.9	17.7	17.8	10.7
35–44	4.3	29.4	13.1	18.7
≥45	0.9	0.0	12.4	54.7
Median age, y	12	19	21	46
Year of diagnosis				
1997–2000	16.8	41.2	18.2	17.3
2001–2005	33.7	17.7	38.3	56.0
2006–2010	28.7	11.8	31.5	18.7
2011–2013	20.9	29.4	11.9	8.0
CCI score				
0	94.8	100.0	78.9	73.3
1	4.0	0.0	13.0	14.7
≥2	1.3	0.0	8.0	12.0

ARF indicates acute rheumatic fever; CCI, Charlson Comorbidity Index; NT, Northern Territory; and RHD, rheumatic heart disease.

first presentation was 12 years for Indigenous subjects regardless of sex. Eleven ARF patients died in the 16-year study period.

ARF Recurrence

The incidence of recurrent ARF was greatest in the first year after the first ARF episode (Table 3); recurrences continued to be seen >10 years after the first episode (incidence rate, 1.41 per 100 person-years 10–14 years after first ARF episodes). Among the ARF patients who were ≤12 years of age, the incidence rate was 2.52 per 100 person-years (95% confidence interval, 1.05–6.04) in years 10 to 14.

The cumulative incidence of ARF recurrence at 10 years was 19.8% (Table 3). Among Indigenous people, the cumulative incidence of ARF recurrence was 3.8% at 1 year, 14.9% at 5 years, and 20.1% at 10 years. In multivariable analysis, the only factor associated with time to ARF recurrence was age at first ARF episode (incidence decreased by 9% per year of age; Table 4).

Progression to RHD

The risk of progression to RHD was higher than ARF recurrence, was very high in the first year after the first ARF episode, and decreased thereafter (Table 3). The cumulative incidence of progression to RHD was 27.1% at 1 year, 44.0% at 5 years, and 51.9% at 10 years. In multivariable analysis, the rate of progression to RHD decreased with age at first ARF episode (by 3% per year of age). The risk of developing RHD was higher for remote residents and those with CCI score ≥2 (Table 4).

Hospitalization for ARF or RHD Treatment

Among the 572 ARF patients, the date of hospital admission corresponded with the date of first ARF notification in 163 patients (28.5%), and 323 (56.5%) were hospitalized for ARF or RHD treatment within 14 days of notification. After adjustment for age, sex, remoteness of residence, and diagnosis year but not comorbidities, Indigenous people had higher hospitalization for ARF/RHD treatment than non-Indigenous people (hazard ratio [HR], 2.18; P=0.047); after further adjustment for comorbidities, the association of being Indigenous and higher hospitalization for ARF/RHD treatment became statistically insignificant (HR, 2.14; P=0.053; Table 5). In the multivariable analysis adjusting for comorbidities, the hospitalization for ARF/RHD treatment was higher for ARF patients who were younger and with later diagnosis years (Table 5).

Table 3. Incidence Rate and Cumulative Incidence Rate (95% Confidence Interval) of Adverse Outcomes for ARF Patients (n=572) at Different Years After the First ARF Diagnosis

	Year	ARF Recurrence	Progression to RHD
Incidence rate (per 100 person-years)	0–1	3.72 (2.40–5.77)	35.92 (30.66–42.09)
	1–5	3.01 (2.27–3.99)	6.66 (5.31–8.35)
	5–10	1.31 (0.80–2.14)	2.99 (1.99–4.50)
	>10	1.41 (0.63–3.14)	1.47 (0.55–3.92)
	Total	2.38 (1.94–2.93)	9.84 (8.70–11.12)
Cumulative incidence (%)	1	3.66 (2.38–5.61)	27.09 (23.61–30.96)
	5	14.43 (11.53–17.98)	43.95 (39.67–48.47)
	10	19.82 (16.18–24.16)	51.89 (47.12–56.84)

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

RHD Patient Cohort

RHD Patients' Characteristics

Of the 1248 people diagnosed with RHD, 94.0% were Indigenous and 34.8% were male (Table 2). Age at RHD diagnosis was younger for male than female patients and for Indigenous than non-Indigenous patients (median age at diagnosis: Indigenous: male patients, 17 years; female patients, 23 years; non-Indigenous: male patients, 42 years; female patients, 49 years). Of RHD patients, 13.1% had a CCI score of 1 and 8.25% had a CCI score ≥2. Urban residents had more comorbidities (19.8% with CCI score of 1 and 13.8% with a CCI score ≥2) than remote residents (11.5% with a CCI score of 1 and 6.9% with a CCI score ≥2; P<0.001). After adjustment for age, Indigenous RHD patients were more likely to have comorbidities (CCI score ≥1) than non-Indigenous patients (odds ratio, 2.50; 95% confidence interval, 1.34–4.64).

Table 4. Multivariable Cox regression for ARF Adverse Outcomes, NT, 1997 to 2013

	ARF Recurrence	Progression to RHD
Variable	HR (95% CI)	HR (95% CI)
Indigenous vs non-Indigenous	2.00 (0.26–15.27)	0.97 (0.38–2.43)
Remote vs urban	1.02 (0.55–1.91)	1.70 (1.14–2.55)*
Male vs female	0.97 (0.64–1.48)	0.84 (0.65–1.08)
Age at diagnosis (per year of age)	0.91 (0.87–0.95)	0.97 (0.96–0.99)*
Diagnosis year (per year)	1.03 (0.97–1.09)	1.02 (0.99–1.05)
CCI score		
1	1.21 (0.44–3.31)	0.88 (0.43–1.80)
≥2	1.71 (0.24–12.44)	5.63 (2.17–14.61)*

ARF indicates acute rheumatic fever; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NT, Northern Territory; and RHD, rheumatic heart disease.

*P<0.05.

Circulation. 2016;134:222–232. DOI: 10.1161/CIRCULATIONAHA.115.020966

Table 5. Hospitalization for ARF/RHD Treatment of ARF Patients (n=572) and Hospitalization (Within 1 Year of RHD diagnosis) for RHD Treatment of RHD Patients (n=1248), NT, 1997 to 2013

	Hospitalization for ARF/RHD Treatment		Hospitalization for RHD Treatment	
	Baseline	Plus CCI	Baseline	Plus CCI
Exposure Variables	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Indigenous	2.18 (1.01–4.71)*	2.14 (0.99–4.63)	2.08 (1.18–3.67)*	1.61 (0.89–2.90)
Urban vs remote	0.98 (0.75–1.28)	0.97 (0.74–1.27)	0.79 (0.58–1.08)	0.92 (0.66–1.27)
Female vs male	1.12 (0.92–1.36)	1.12 (0.93–1.36)	1.47 (1.15–1.88)*	1.56 (1.21–2.01)*
Age (per year of age)	0.98 (0.97–0.99)*	0.98 (0.97–0.99)*	1.00 (1.00–1.01)	0.99 (0.98–1.00)*
Diagnosis year (per year)	1.04 (1.02–1.06)*	1.04 (1.02–1.06)*	1.00 (0.97–1.03)	1.00 (0.97–1.03)
CCI score 1 vs 0		0.93 (0.54–1.59)		4.95 (3.41–7.19)*
CCI score ≥2 vs 0		1.81 (0.72–4.54)		3.88 (2.45–6.13)*

ARF indicates acute rheumatic fever; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NT, Northern Territory; OR, odds ratio; and RHD, rheumatic heart disease.

*$P<0.05$.

RHD Hospitalization After RHD Diagnosis

Fewer than half of the 1248 RHD patients were hospitalized for RHD treatment within 1 year of diagnosis: 345 (27.6%) on the day the diagnosis was first recorded, 422 (33.8%) within 90 days, and 492 (39.4%) within 1 year. The proportion hospitalized within 1 year for RHD treatment was greater for female than male patients (42.6% compared with 33.1%) and for Indigenous than non-Indigenous patients (40.1% compared with 29.3%) but was similar for remote and urban residents (41.9% compared with 38.8%). After adjusting for age, sex, remoteness of residence, and diagnosis year but not comorbidities, Indigenous people had higher hospitalization within 1 year for RHD treatment than non-Indigenous people (odd ratio, 2.08; $P=0.011$); after further adjustment for comorbidities, the association between Indigenous status and hospitalization within 1 year for RHD treatment become statistically insignificant (odds ratio, 1.61; $P=0.116$; Table 5). In the multivariable logistic regression adjusted for comorbidities, the hospitalization rate within 1 year for RHD treatment was higher for RHD patients who were female, younger, and with comorbidities (Table 5).

Progression to Severe RHD

Seventy-eight of the 772 patients (10.1%) diagnosed with RHD between 2004 and 2013 had severe RHD at diagnosis. The rate of progression to severe RHD was highest in the first year after diagnosis and decreased thereafter (Table 6).

Complications

Heart failure and atrial fibrillation were more common complications than endocarditis or stroke (Table 6). The incidence of development of all 4 complications was highest in the first year after diagnosis and decreased

Table 6. Incidence Rate and Cumulative Incidence Rate (95% Confidence Interval) of Adverse Outcomes for RHD Patients (n=1248) at Different Years After the First RHD Diagnosis

	Year	Severe RHD*	Atrial Fibrillation	Endocarditis	Heart Failure	Stroke	Death
Incidence rate (per 100 person-years)	0–1	25.72 (21.99–30.09)	4.70 (3.61–6.13)	1.00 (0.57–1.76)	9.06 (7.46–11.00)	0.58 (0.28–1.22)	0.50 (0.22–1.10)
	1–5	2.61 (1.96–3.47)	0.77 (0.54–1.10)	0.31 (0.18–0.54)	1.23 (0.92–1.63)	0.24 (0.13–0.44)	0.83 (0.59–1.15)
	5–10	1.95 (1.23–3.10)	1.30 (0.95–1.76)	0.38 (0.22–0.66)	1.44 (1.07–1.94)	0.38 (0.22–0.66)	1.33 (1.00–1.78)
	>10	3.43 (1.11–10.65)	1.41 (0.85–2.33)	0.42 (0.18–1.02)	1.60 (0.98–2.62)	0.77 (0.40–1.48)	1.90 (1.26–2.85)
	Total	6.55 (5.75–7.47)	1.51 (1.28–1.78)	0.43 (0.32–0.58)	2.33 (2.03–2.67)	0.39 (0.29–0.54)	1.09 (0.90–1.31)
Cumulative incidence (%)	1	20.45 (17.75–23.49)	4.46 (3.44–5.77)	0.97 (0.55–1.7)	8.24 (6.84–9.92)	0.58 (0.28–1.21)	0.5 (0.22–1.1)
	5	28.04 (24.87–31.52)	7.42 (6.04–9.1)	2.17 (1.47–3.2)	12.63 (10.85–14.67)	1.51 (0.94–2.42)	3.75 (2.77–5.06)
	10	34.62 (30.4–39.23)	13.35 (11.23–15.84)	4.03 (2.9–5.58)	18.62 (16.25–21.28)	3.63 (2.5–5.28)	10.27 (8.33–12.63)

RHD indicates rheumatic heart disease.

*Only for those with diagnosis year of 2004 or later (n=772).

thereafter (Table 6). In the multivariable analysis, urban residents were more likely than remote residents to develop atrial fibrillation and heart failure; atrial fibrillation and stroke incidence increased with age at diagnosis (by 5% and 4% per year of age, respectively; Table 7). RHD patients with comorbidities (CCI score ≥1) had a higher incidence of atrial fibrillation, endocarditis, and heart failure.

Death

After adjustment for age, sex, remoteness of residence, and diagnosis year but not comorbidities, Indigenous people had higher risk of death after a RHD diagnosis than non-Indigenous people (HR, 6.59; $P<0.01$). Adjustment for comorbidities (Table 7) reduced this disparity somewhat (HR, 5.19; $P<0.01$). In the multivariable analysis (Table 7), the death rate was higher for patients who were Indigenous, male, older, or urban-dwelling or who had comorbidities.

Comorbidities of RHD Patients ≥18 Years Old

The proportion of patients with any comorbidity (CCI score ≥1) was the same for Indigenous and non-Indigenous RHD patients. However, the Indigenous RHD patients had a higher prevalence of hospitalization as a result of hazardous alcohol use (13.2% compared with 0%; $P=0.002$) and assault (12.3% compared with 0%; $P=0.003$) than the non-Indigenous RHD patients (Table 8). RHD patients with hazardous alcohol use also had higher hospitalization resulting from assault (53.4% compared with 5.4%; $P<0.001$; Table 8). Among Indigenous RHD patients, the prevalence of any comorbidity (CCI score ≥1) was higher for urban than for remote residents (43.0% compared with 27.0%; $P=0.001$), as was the prevalence of many individual conditions (Table 8).

In the baseline Cox regression model, death rates were higher for Indigenous, urban, male, and older RHD adult patients (Table 9). The HR for Indigenous status decreased from 6.55 in the baseline model to 4.64 when also adjusted for renal failure, and it decreased further to 3.87 when further adjusted for hazardous alcohol use (Table 9), indicating that the higher prevalence of renal failure and hazardous alcohol use (which are both associated with higher mortality) was part of the reason for the higher mortality of Indigenous RHD patients. Further adjustment for other comorbidities (ie, adding CCI excluding renal failure to the model) did not decrease the HR for Indigenous individuals much further. Adjustment for renal failure and hazardous alcohol use similarly reduced the HR for urban compared with remote residents (Table 9).

DISCUSSION

The NT RHD Register has previously been used to investigate ARF and RHD occurrence, progression, and survival for a population with a very high RHD burden.[1] This study used a data-linkage approach to refine and expand that work to include adverse outcomes other than death and the influence of chronic disease comorbidity on adverse outcomes. Linking hospital inpatient data to the RHD Register enabled us to more accurately identify the timing of the onset of RHD, to identify the occurrence of serious complications, and to document chronic disease comorbidities in ARF and RHD patients.

Our results confirm the previous findings[1] that the progression from ARF to RHD is rapid and is occurring faster than documented ARF recurrences; RHD incidence was almost 10 times higher than the incidence of ARF recurrence in the year after the first ARF episode. Secondary prophylaxis with penicillin is important for reducing ARF recurrence and the consequent worsening of heart valve

Table 7. Multivariable Cox Regression for RHD Adverse Outcomes, NT, 1997 to 2013

Variable	HR (95% CI)					
	Severe RHD*	Atrial Fibrillation	Endocarditis	Heart Failure	Stroke	Death
Indigenous	0.73 (0.43–1.25)	1.37 (0.76–2.46)	1.18 (0.32–4.37)	1.21 (0.70–2.07)	1.39 (0.44–4.41)	5.19 (1.96–13.77)†
Urban vs remote	1.16 (0.83–1.62)	1.67 (1.12–2.50)†	1.72 (0.84–3.50)	1.78 (1.29–2.45)†	1.67 (0.77–3.64)	1.70 (1.08–2.67)†
Male vs female	0.89 (0.68–1.17)	1.30 (0.92–1.84)	1.19 (0.64–2.23)	1.09 (0.81–1.45)	0.94 (0.46–1.90)	1.67 (1.13–2.47)†
Age (per year)	1.00 (0.99–1.01)	1.05 (1.04–1.06)†	0.99 (0.97–1.02)	1.01 (1.00–1.02)	1.04 (1.02–1.06)†	1.04 (1.03–1.06)†
Diagnosis year	1.05 (1.00–1.11)	1.01 (0.96–1.06)	1.05 (0.96–1.14)	0.99 (0.95–1.03)	0.99 (0.90–1.10)	0.96 (0.90–1.02)
CCI						
1	1.25 (0.85–1.83)	1.85 (1.24–2.78)†	1.68 (0.75–3.80)	2.81 (2.01–3.93)†	1.05(0.44–2.50)	1.28 (0.76–2.15)
≥2	1.19 (0.74–1.91)	1.37 (0.83–2.26)	3.25 (1.33–7.92)†	2.94 (1.95–4.44)†	1.28(0.49–3.38)	2.85 (1.73–4.70)†

CCI indicates Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NT, Northern Territory; and RHD, rheumatic heart disease.
*Only for those with diagnosis year of 2004 or later (n=772).
†$P<0.05$.

Circulation. 2016;134:222–232. DOI: 10.1161/CIRCULATIONAHA.115.020966

Table 8. Prevalence of Selected Comorbidities and Health Behavior–Related Hospitalizations Among Indigenous (Urban and Remote) and Non-Indigenous RHD Patients (≥18 Years Old)

	Indigenous, %		Non-Indigenous (n=66), %
Conditions	Urban (n=128)	Remote (n=541)	
Selected comorbidities			
Chronic obstructive pulmonary disease	14.1*	6.5	6.1
Congestive heart failure	16.4†	9.8	15.2
Diabetes mellitus	13.3†	6.8	12.1
Diabetes mellitus with complications	10.2†	4.4	3.0
Liver disease (mild)	4.7	2.0	0.0
Liver disease (moderate/severe)	0.8	0.9	0.0
Renal failure	7.8	4.3	3.0
Hospitalizations that indicate high-risk behavior or environment			
Assault	21.9*	10.0	0.0‡
Hazardous alcohol use	25.8*	10.2	0.0‡
Transportation accident	7.8†	15.3	9.1

RHD indicates rheumatic heart disease.
*Significant difference between urban- and remote-residing Indigenous RHD patients ($P<0.01$).
†Significant difference between urban- and remote-residing Indigenous RHD patients ($P<0.05$).
‡Significant difference between Indigenous and non-Indigenous RHD patients ($P<0.01$).

damage, but the high proportion of patients with RHD at or shortly after their first diagnosed ARF episode demonstrates the limitations of secondary prevention and the importance of primordial and primary preventive strategies.

Secondary prophylaxis with penicillin is recommended to continue for 10 years after a diagnosis of ARF or to age 21, whichever comes later, according to Australian and New Zealand guidelines.[9] US guidelines differ slightly, recommending penicillin for only 5 years or to age 21 after ARF without carditis,[10] and Gordon et al[11] indicate that a 5-year duration is commonly used in Canada. In the 10- to 14-year interval after the initial ARF diagnosis, we found an ARF recurrence rate of 1.41 per 100 person-years overall and 2.52 per 100 person-years among patients ≤12 years of age. This contrasts somewhat with our previous study that also confirmed decreasing recur-

Table 9. Multivariable Cox Regression for Mortality of RHD Patients (≥18 Years Old) With Adjustment for Different Comorbidities

	HR (95% CI)			
Exposure Variables	Baseline	Plus Renal Failure	Plus Hazardous Alcohol Use	Plus CCI
Indigenous	6.55 (2.45–17.51)*	4.64 (1.72–12.49)*	3.87 (1.41–10.57)*	3.79 (1.39–10.36)*
Urban vs remote	2.03 (1.26–3.27)*	1.76 (1.09–2.85)*	1.54 (0.94–2.54)	1.52 (0.92–2.50)
Male vs female	1.73 (1.13–2.65)*	1.71 (1.11–2.62)*	1.63 (1.06–2.51)*	1.67 (1.08–2.57)*
Age (per year of age)	1.05 (1.04–1.07)*	1.04 (1.03–1.06)*	1.04 (1.03–1.06)*	1.04 (1.02–1.06)*
Diagnosis year (per year)	0.99 (0.93–1.05)	0.99 (0.92–1.05)	0.97 (0.91–1.04)	0.96 (0.90–1.03)
Renal failure		4.48 (2.58–7.77)*	4.16 (2.38–7.25)*	3.61 (2.01–6.48)*
Hazardous alcohol use			1.94 (1.10–3.40)*	1.78 (1.01–3.15)*
CCI score 1 vs 0				1.37 (0.82–2.29)
CCI score ≥2 vs 0				1.61 (0.89–2.93)

CCI indicates Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; and RHD, rheumatic heart disease.
*$P<0.05$.

rence risk in each year after ARF diagnosis (9%/y) but found that the risk fell to 0 by 10 years.[1] These findings support the longer secondary prophylaxis duration recommended in our national guidelines[9] but indicate that continuing low-level risk may persist thereafter, again emphasizing the fundamental importance of broader control strategies than secondary prophylaxis alone. Recommending penicillin for >10 years would be difficult to justify given the need to balance morbidity related to needle administration against the low risk of further recurrences more than a decade after the last ARF episode.

This study demonstrates that although there are guidelines stating that all patients with suspected ARF should be hospitalized as soon as possible,[9,12,13] only 56.5% of patients were admitted to hospital for the treatment of ARF or RHD within 14 days of the onset of their first ARF episode. Early hospitalization facilitates specialist review, exclusion of differential diagnosis, confirmation of the ARF diagnosis, access to echocardiography, beginning of penicillin and ARF treatments (eg, salicylates for ARF arthritis or arthralgia), and provision of education for the patient and their family about ARF/RHD. Although treatment might have been initiated in primary care, these findings suggest delays in the initiation of treatment for ARF patients that might have contributed to the early onset or progression of heart valve damage. This study demonstrates the importance of the use of routine linkage of RHD Register and hospital data to investigate this missing link, consistent with another study[14] suggesting the effectiveness of using hospitalization data to identify ARF/RHD cases not documented in the RHD Register. Even in a jurisdiction with an effective and long-lasting register, our study has demonstrated that data are incomplete and that a linkage approach can supplement additional data on both outcomes and case ascertainment.

Our finding of higher mortality in older and Indigenous RHD patients is consistent with previous studies.[1,15] In the multivariable analysis, male patients had a higher mortality despite having a similar incidence rate for all of the 4 complications compared with female patients. Although it was previously shown that males have a lower ARF and RHD incidence than females,[1,15] our study found that when they do have RHD, male patients are more likely to die. Other factors may contribute to the higher mortality of male RHD patients, such as lower adherence to secondary prophylaxis, a higher prevalence of comorbidities, or hazardous alcohol use. The findings of a similar hospitalization rate for male and female ARF patients (mainly children) but a lower proportion of male RHD patients (mainly young adults) receiving RHD treatment at hospital suggest different health-related behaviors of the 2 sexes at different phases of their lives.

Our finding that the highest incidence of all 4 complications occurred in the first year after diagnosis highlights the importance of prompt action plans within this time frame to prevent or manage these complications in RHD patients (who were mainly young people with a median age at diagnosis of 21 years) because they contributed to higher death rates. Atrial fibrillation and heart failure were more common among RHD patients (5% and 8%, respectively, in first year; 13% and 19% within 10 years), whereas endocarditis and stroke were less common but still occurred in 4% of RHD patients within 10 years. Unfortunately, the development of complications was not less common in those diagnosed with RHD in more recent years.

Progression from ARF to RHD was more common for remote than for urban residents, but for RHD patients, urban residents had higher rates of atrial fibrillation and heart failure and higher mortality even after adjustment for comorbidities and hazardous alcohol use. Lower identification of atrial fibrillation and heart failure among remote residents could be an artifact of lower access to inpatient care for them, but this seems unlikely because hospitalization rates were similar for remote and urban RHD patients. Alcohol is less accessible or not accessible at all in remote communities; thus, individuals labeled as having hazardous alcohol use, who mostly live in remote locations and drink only when visiting town, would have lower risk than urban-based individuals with hazardous alcohol use. In addition, the death data, being the most reliable source of data (compared with hospital and register data), also showed that remote RHD patients have lower mortality, which is consistent with the findings[16] of lower-than-expected cardiovascular morbidity and all-cause mortality for people residing in remote Aboriginal communities.

Because this is the first study to link hospital data with register data to investigate the incidence of long-term RHD complications, there were no available studies with which to compare our results. This study may have underestimated the incidence of complications and mortality among RHD patients because some who developed a complication might not have been admitted to hospital, either because the complication was very mild or because it was very severe and they died before arriving at hospital. The latter possibility could be investigated by linking RHD Register and hospital inpatient data with the National Death Index (which includes cause of death) to identify RHD patients who died of a complication before hospital admission; this was beyond the scope of the present study.

Our study demonstrated the high prevalence of comorbidities in RHD patients and their role in adverse outcomes. The presence of comorbidities was associated with a higher incidence of atrial fibrillation, endocarditis, and heart failure (but not stroke) and higher mortality. In particular, renal failure and hazardous alcohol use were more common among Indigenous than non-Indigenous patients, which accounted for 28% of the excess mortality of Indigenous patients (HR decreases from 6.55 to 3.87). The finding of the adverse effect of kidney failure

on Indigenous RHD patients is consistent with the finding from another study that kidney failure is the only chronic disease that is associated with 30-day and long-term mortality after RHD-related valve surgery, particularly for Indigenous RHD patients (30-day mortality odds ratio, 14.1; 95% confidence interval, 1.0–200.0).[17] Between 2007 and 2009, renal failure was the main contributor (19%) to deaths of people with RHD.[15] Hazardous alcohol use was the other comorbidity that contributed to Indigenous/non-Indigenous and urban/remote differentials in adverse outcomes. This is particularly relevant to NT, which has the highest alcohol consumption rates in Australia.[18,19] In a 2012–2013 national survey, 30.5% of NT Indigenous adults reported alcohol consumption at risky or high-risk levels (28.4% for remote residents, 35.3% for urban residents)[18] compared with 16.1% of NT non-Indigenous adults in a comparable national survey in 2010. Our finding that 25.8% of urban Indigenous adult RHD patients had been admitted to hospital for a condition related to hazardous alcohol consumption is consistent with these high consumption levels.

Our study suggests that hazardous alcohol use is the greatest contributor (among factors that we could investigate) to the urban/remote differentials in mortality. RHD patients with hazardous alcohol use are almost twice as likely to die even after adjustment for other comorbidities. In this case, hazardous alcohol use should not be seen only as a behavior. Rather, it could be also seen as a proxy for other unmeasured variables that are causing it. To complicate things, hazardous alcohol use could also affect other chronic diseases and other unfavorable health-related behaviors, leading to poorer outcomes.

Even after adjustment for comorbidities and hazardous alcohol use, Indigenous RHD patients are still >3 times more likely to die than non-Indigenous patients, indicating that there are other unmeasured factors contributing to this disparity that need further research. No data were available for this study on socioeconomic conditions, which may be major contributors to this disparity. Indigenous Australians, particularly in the NT, have much poorer socioeconomic conditions, including housing, than other Australians.[2,20] An NT study found that socioeconomic disadvantage accounted for more than one third of the gap between Indigenous and non-Indigenous life expectancy and that >60% of the gap was explained by the combined effects of socioeconomic disadvantage plus smoking, hazardous alcohol use, obesity, pollution, and intimate partner violence.[21]

Unlike in other Australians, ARF is a common childhood disease of Indigenous Australians, and RHD is a dangerous, sometimes fatal disease among their children and young adults. The NT RHD Register, the most comprehensive data on ARF and RHD available in Australia, has previously been used to demonstrate the very high incidence of and mortality from ARF and RHD among the NT Indigenous population. By linking the RHD Register to hospital and death records, this study has demonstrated the high frequency of serious complications in the years after the onset of RHD and the deleterious effect of the higher prevalence of chronic disease comorbidity, particularly chronic kidney disease and hazardous alcohol use, among Indigenous people (including those with RHD) on both the development of complications and survival. ARF incidence and RHD incidence have not declined in recent years. It is not clear whether this is a result of inadequate compliance with secondary prophylaxis or of the limitations of secondary prophylaxis in the absence of improvements in housing and other socioeconomic conditions. The RHD Register includes data on the administration of secondary prophylaxis that could be used to investigate the effectiveness of secondary prophylaxis, which needs to be done urgently. Data are not so readily available to investigate socioeconomic conditions; data on housing also need to be investigated with similar urgency.

ACKNOWLEDGMENTS

We acknowledge the support of the NT Department of Health and thank the staff of the NT Department of Health Data Management and System Reporting Branch for extracting and linking the hospital inpatient data and mortality data; Cath Milne from the NT RHD control program for extracting the RHD Register data; and Shu Qin Li from the Department of Health Health Gains Planning Branch for linking the RHD Register to the hospital inpatient data.

SOURCES OF FUNDING

V.Y.F. He was supported by a University Postgraduate Research Scholarship from Charles Darwin University. Dr Ralph is supported by the National Health and Medical Research Council of Australia (GNT1113638). J.L. de Dassel is supported by an Australian Postgraduate Award scholarship. Dr Zhao, Dr Roberts, Dr Currie, M. Fittock, and Dr Edwards are supported by the NT Department of Health.

DISCLOSURES

None.

AFFILIATIONS

From Menzies School of Health Research, Charles Darwin University, Darwin, Australia (V.Y.F.H., J.R.C., A.P.R., K.R., J.L.d.D., B.J.C.); Royal Darwin Hospital (A.P.R., K.R., B.J.C., K.N.E.) and Health Gains Planning Branch (Y.Z.), Northern Territory Government Department of Health, Darwin, Australia; Northern Territory Rheumatic Heart Disease Control Program, Centre for Disease Control, NT Department of Health, Darwin, Australia (M.F., K.N.E.); Telethon Kids Institute, University of Western Australia, Perth, Australia (J.R.C.); and Princess Margaret Hospital for Children, Perth, Australia (J.R.C.).

FOOTNOTES

Received December 16, 2015; accepted May 27, 2016.
Circulation is available at http://circ.ahajournals.org.

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