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Clinical and geographic patterns of rheumatic heart disease in outpatients attending cardiology clinic in western Kenya

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ABSTRACT

Introduction: Rheumatic heart disease (RHD) remains a leading cause of cardiovascular mortality in sub-Saharan Africa. Identifying high risk populations and geographic patterns of disease is crucial to developing RHD prevention and screening strategies in endemic areas.
Objectives: To identify clinical and geographical trends in RHD throughout western Kenya
Methods: We conducted a retrospective chart review of all patients <50 years old attending adult cardiology clinic at a national referral hospital in western Kenya. Demographic information, residential location and cardiac history were collected. We mapped the spatial distribution of cardiac disease rates and analyzed the effect of distance from the hospital on RHD status.
Results: Two-thirds (64%) of cardiology clinic patients <50 years old ($n = 906$) had RHD. RHD patients were younger (26 vs. 33 years, $p < 0.001$) and more often female (69% vs. 59%, $p = 0.001$) than non-RHD patients. Global clustering of disease rates existed within 200 km of the hospital with significant clustering of the RHD and non-RHD rate difference surrounding the hospital (Moran's I: 0.3, $p = 0.001$). There was an interaction between ethnicity and distance from the hospital such that the odds of RHD decreased with further distance for Nilotes, but the odds of RHD increased with further distance for non-Nilotes
Conclusion: Most adult cardiology patients treated at a national referral hospital in western Kenya have RHD. Young people and females are commonly affected. Ethnicity and distance to the hospital interdependently affect the odds of RHD. Future studies in this area should consider the impact of ethnic predisposition to RHD.

1. Introduction

Rheumatic heart disease (RHD) is a leading cause of cardiovascular morbidity and mortality worldwide, affecting over 15.6 million people throughout the world and accounting for over 233,000 deaths annually [1]. While there has been a radical decline in the incidence of RHD in high-income countries (HIC) over the past fifty years, RHD prevalence remains high in low and middle-income countries (LMIC) [2,3] with a disproportionate number of cases in sub-Saharan Africa (SSA) [4]. A combination of environmental, bacterial and host factors has been thought to influence geographic patterns of disease and contributes to the increased burden of RHD in SSA [5].

RHD is considered a disease of poverty, and increased rates of RHD are associated with low socioeconomic status, urbanization, overcrowding, poor nutrition and lack of access to medical care [3,6,7]. Additionally, an unequal geographic distribution of various strains of Group A Streptococcus (GAS), the bacteria traditionally held responsible for RHD, across certain regions of the world may play a role in global variation of RHD frequency [8]. SSA is one of the poorest regions of the world, comprised of the largest number of LMIC worldwide, and is one of the regions most affected by RHD [9]. The burden of cardiovascular disease attributable to RHD in SSA ranges from 14 to 40%, as evidenced by single and multi-national studies across the continent [4,10,11]. Limited access to specialized cardiovascular care and surgical intervention across SSA leads to high mortality rates among young people with advanced disease [12].

Kenya is a lower-middle-income country in SSA with an ethnically diverse population, where little is known about the current prevalence or distribution of RHD. Prior reports from Kenya are thought to underestimate the actual prevalence due to limitations in sampling methods [13–15]. Our own clinical experience together with epidemiologic evidence of unexpectedly low rates of culture-positive group A streptococcal (GAS) pharyngitis in febrile children presenting to a rural hospital in

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an ethnically homogenous area of western Kenya [16] suggest geographic disparities in RHD distribution in the region.

Identifying geographic trends and demographic characteristics correlating with RHD in western Kenya can inform epidemiologic hypotheses about GAS and RHD for targeted prevention and screening efforts in the future. Our study aimed to better characterize the burden of RHD among patients presenting to an outpatient, cardiology clinic at a national referral hospital in western Kenya. We sought to describe the clinical profile of RHD patients, identify demographic factors associated with RHD, and determine if a pattern of geographic distribution of RHD exists throughout the region.

2. Methods

2.1. Study site & design

We conducted a retrospective, cross-sectional chart review of patients attending adult cardiology clinic at a national referral hospital in western Kenya to determine the demographic, clinical and geographic factors associated with RHD in this region. Our study site, Moi Teaching and Referral Hospital (MTRH), is the clinical care arm of one of the eleven National Heart, Lung and Blood Institute (NHLBI) funded Centers of Excellence in cardiovascular care worldwide and provides highly specialized inpatient and outpatient cardiovascular care through collaborations between Kenyan and American cardiologists [17]. MTRH is located 300 km northwest of Nairobi and is the only public cardiac referral facility outside of the capital city.

This study was approved by the Institutional Review and Ethics Committee (IREC) at the Moi University School of Medicine who waived the need for informed consent.

2.2. Data collection

We used convenience sampling to review the paper medical charts of all patients who attended the adult cardiology clinic at MTRH at least once between January 2012 and August 2014. We collected data only on patients <50 years old who carried a cardiac diagnosis in order to maximize the percentage of RHD patients represented in our sample.

Four individuals reviewed charts (RL, SC, AK, VO). Standardized data collection forms were used to extract information from the chart about age, sex, occupation, ethnicity and place of residence. Ethnicity is not routinely collected in the medical chart. Kenyan tribal affiliation was deduced by Kenyan research assistants based on patient name, place of residence, and next of kin, or recorded as unknown if ethnicity was unclear. The presence of RHD was recorded if RHD was directly listed as a diagnosis in any outpatient or inpatient provider notes or hospital discharge summaries and subsequently confirmed by an MTRH-trained cardiologist. For RHD cases, valvular involvement and lesion type (regurgitant and/or stenotic) were explicitly sought from standardized, MTRH echocardiography reports completed by MTRH-trained echocardiography technicians. History of secondary antibiotic prophylaxis was noted if monthly penicillin was prescribed at least once in the chart.

All non-RHD cardiac diagnoses were recorded if listed in any outpatient or inpatient provider notes, hospital discharge summaries, referral notes, or if reported on echocardiogram and/or electrocardiogram reports by an MTRH cardiologist. Systolic heart failure (defined as reduction in left ventricular ejection fraction <45% on echocardiography report), diastolic dysfunction (assessed by echocardiography technician and reported as class I-IV on echocardiography report), pulmonary hypertension (defined by pulmonary artery systolic pressure >35 mm Hg on echocardiogram report), ischemic heart disease (defined by history of myocardial infarction or positive stress test reported by MTRH cardiologist), pericardial disease (including pericarditis of any etiology or pericardial effusion reported by an MTRH cardiologist), and arrhythmias (atrial or ventricular as recorded by MTRH cardiologist or MTRH electrocardiography technician) were collected. Patients could carry more than one diagnosis. Prescribed medical and surgical therapies and history of diagnostic cardiac imaging were also collected.

Place of residence in Kenya is classified into national administrative units with geographic areas defined from largest to smallest as: County, District, Division, Location, Sublocation, and Village. The residence listed in the paper medical chart was standardized against the most recent Kenyan census survey (2009) including all known administrative units [18]. Both the residences, as listed in the chart and as standardization by the Kenyan census, were recorded. When paper charts had no residence listed, multiple residences listed, unknown Location level information, or a Location of residence that was not listed in the Kenyan census, we searched an electronic hospital record (EHR) to determine residence. If a residence remained unconfirmed through the EHR, we contacted the patient by phone to gather the information directly. After completion of the chart review, we randomly selected charts for quality review for missing or discordant data. We noted a 12% error rate in the 4% of the charts that had been reviewed. These errors appeared to be systematic and related to one data collector. We subsequently reviewed the 220 charts from that one data collector and corrected 100% of errors related to place of residence, demographic information, and cardiac history.

2.3. Statistical analysis

Primary associations of interest included cardiac diagnoses (RHD versus non-RHD) and place of residence (using Division as the geographic unit for analysis). Data analysis was conducted in two stages: cross-sectional analysis to demonstrate the relationship between demographic characteristics and cardiac diagnoses; and geographic analysis to map and quantify the spatial heterogeneity of RHD throughout western Kenya. RHD status was defined as a binary variable (yes/no) for all analyses, with each patient included only once as either having RHD (RHD) or not (non-RHD). We excluded patients without RHD who had a diagnosis of ARF because binary classification of ARF as either non-RHD or RHD could confer bias given ARF patients may be considered pre-RHD on a spectrum of disease and share similar risk factors to patients with RHD. Patients with an existing RHD diagnosis and recurrent ARF were included in the analysis, though, since their disease met our RHD criteria. We grouped the participants from related tribes into larger ethnic sub-group categories for analysis: “Nilote” includes participants from Kalenjin, Luo, and Masaai tribes; “Bantu” includes participants from Kikuyu, Luhya, Kisii, and Kamba tribes; “Cushite” includes participants from the Somali tribe.

For our cross-sectional descriptive analysis, we described the clinical profile of RHD and non-RHD patients and explored associations between demographic variables of age, sex, occupation, and ethnicity and RHD. In our univariate analysis, we used Wilcoxon rank sum test to describe the association between age as a non-normal, continuous variable and chi-square tests or Fisher's exact tests to describe the associations between RHD status sex, occupation and ethnicity as categorical variables. Significance was defined as p-value < 0.05. A fixed effects multivariable logistic regression model was developed to quantify the effects of age, sex, ethnicity and distance from the hospital (in kilometers) on RHD status. Age and distance from the hospital were included as categorical variables after observing a non-linear association between age and distance and RHD status. Ethnicity was transformed into a binary variable of Nilote versus non-Nilote (non-Nilote included Bantu, Cushite and “other” subgroups) since Nilote was the largest ethnic group represented in the dataset. An additional 14 patients with “unknown” or “non-Kenyan” ethnicity were excluded from the multivariable regression analysis. We used logistic regression without any inclusion or exclusion procedure, given the small number of variables included in our model. Random effects for Division were tested in the model but were found to be vanishingly small with no improvement to the output and were ultimately excluded from the model.

Our geospatial analyses used the Euclidean distance (in kilometers) between the centroid of each geographic Division unit and the hospital. We excluded 118 patients with an unknown Division of residence from geospatial analysis. We employed a distance-based spatial weights matrix for our analysis because the Divisions were not strictly contiguous. We further restricted geospatial analyses to participants living within 200 km of the hospital which excluded two remotes, outlying Divisions including seven patients (5 RHD, 2 non-RHD). We used the Moran's I test to determine global clustering of the RHD rate, non-RHD rate and rate difference between RHD and non-RHD per Division, using the 2009 Kenyan census Division populations as the denominator to calculate disease rates for each Division. P-value of <0.05 using 999 permutations was considered significant. Deviance residuals from our multivariate regression analysis were mapped and Moran's I test was performed to assess the amount of global clustering of RHD retained after controlling for age, sex, ethnicity and distance from the hospital. An interaction term between ethnicity and distance was incorporated into the model to assess whether the effect of distance on RHD was independent of ethnicity. Analyses were carried out using STATA (Version 13, College Station, TX: Stata Corporation) and Geoda software (Version 1.6.6).

3. Results

3.1. Demographic and clinical profile

A total of 1051 cardiology clinic charts were reviewed. Of those, 145 (14%) were excluded from all analyses (114 patients ≥ 50 years old and 31 patients without RHD who carried a diagnosis of ARF), leaving 906 patients included for analysis (Fig. 1). Demographic characteristics are shown in Table 1. Patient age ranged from 14 to 49 years old, with an average age of 28 years. Most of the sample was female (65%). Nilotes were the most represented ethnic group (78%), followed by Bantu (20%) and Cushite (0.4%). Most patients had a history of RHD (64%).

Patients with RHD were younger, on average, than patients without RHD (26 years vs. 33 years, $p < 0.001$) and more often female (69% vs. 59%, $p = 0.001$, Table1). Overall, most patients with RHD were of Nilote ethnicity (84%). Additionally, a significantly larger proportion of Nilotes had RHD than did not (70% versus 30%, $p < 0.001$), unlike the Bantu or Cushite ethnic groups, which had more equal proportions of patients with RHD and non-RHD diagnoses (48% versus 52% and 50% versus 50%, respectively, $p < 0.001$). While a majority of patients' occupations remained unknown (54%), of those with a known occupation, higher

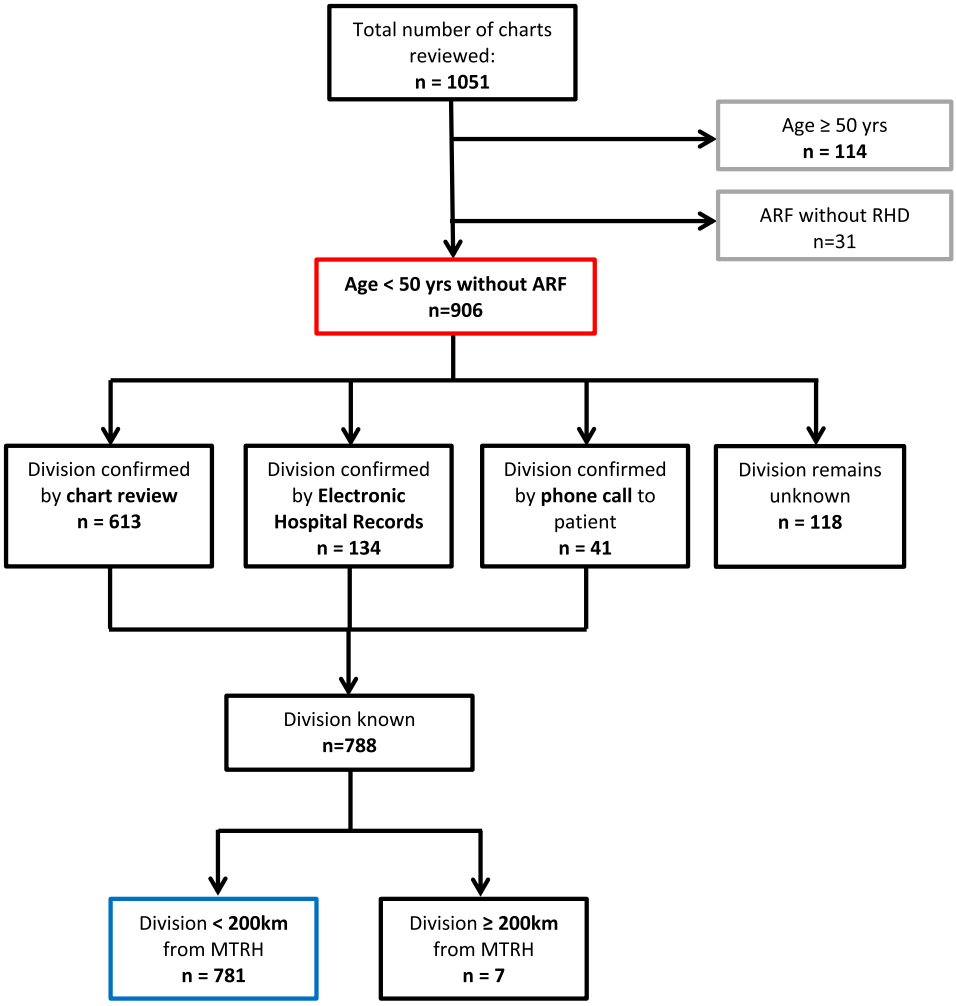

Fig. 1. Flow diagram of inclusion methodology for descriptive and geospatial analyses. The medical charts of all patients seen in cardiology clinic at Moi Teaching and Referral Hospital (MTRH) from January 2012–August 2014 were reviewed. Patients were excluded if age ≥ 50 or with an episode of acute rheumatic fever (ARF) without a history of RHD (gray boxes). Descriptive analysis was performed on all included patients (red box). Geospatial analyses were performed on all patients with a known Division within 200 km of MTRH (blue box), as describe in the text.

Table 1
Demographic characteristics of study participants.

	Total (n = 906)	RHD (n = 582)	Non-RHD (n = 324)	p-value
Age, yrs mean (SD)	28.4 (10)	25.8 (10)	32.8 (11)	<0.001
Female, % (n)	65.4 (593)	69.2 (403)	58.6 (190)	0.001
Occupation, % (n)				<0.001
Employed	5.9 (53)	3.4 (20)	10.2 (33)	
Self-employed	10.8 (98)	9.8 (57)	12.7 (41)	
Unemployed	3.3 (30)	3.4 (20)	3.1 (10)	
Student	15.3 (139)	18.7 (109)	9.3 (30)	
Housewife	11.2 (101)	11.7 (68)	10.2 (33)	
Not recorded	53.5 (485)	52.9 (308)	54.6 (324)	
Ethnicity, % (n)				<0.001
Nilotes	77.6 (703)	84 (489)	66.1 (214)	
Bantu	20.1 (182)	15 (87)	29.3 (95)	
Cushites	0.4 (4)	0.3 (2)	0.6 (2)	
Other	1.9 (17)	0.7 (4)	4 (13)	

RHD = rheumatic heart disease.

percentages of patients with RHD were students and housewives compared to those who were employed, self-employed or unemployed.

Multivariable logistic regression revealed odds of RHD to be inversely related to age in both the unadjusted model and the adjusted model including age, sex, ethnicity (Nilote/non-Nilote) and distance to the hospital (Table 2). Adolescents (aged 14–18 years) had the highest odds of RHD (adjusted OR = 3.19, 95%CI = 1.86–5.48) when compared to the mean age group (24–28 years) whereas the odds of RHD inpatients between 44 and 49 years were one third of that in the comparison group (adjusted OR = 0.30, 95%CI = 0.16–0.53). Patients of Nilote ethnicity were more than two times as likely to have RHD compared to patients of non-Nilote ethnicity in both models (adjusted OR = 2.52, 95% CI = 1.70–3.74).

Of patients with RHD, the most common valvular involvement was a combination of mitral and aortic valves (n = 298, 51%) followed by mitral valve alone (n = 220, 38%). Only 82% of patients with RHD were prescribed monthly penicillin injections for secondary prophylaxis of RHD, leaving 104 RHD patients not receiving any secondary antibiotic prophylaxis. Most patients had undergone echocardiogram (87%) or electrocardiogram (57%) testing at least once. A total of 76 patients (8%) had a history of cardiac surgery, 65 of whom had RHD. Of the patients with RHD who underwent cardiac surgery, valve replacement was performed in 45 (69%), valve repair done in 19 (29%), and two patients had a history of both valve replacement and repair. Reasons for surgery in the non-RHD patients included correction of congenital heart disease, ventricular myomectomy or pericardectomy. The most common concurrent cardiac diagnoses in patients with RHD were arrhythmia (20%), systolic heart failure (19%), and infective endocarditis (7%). In contrast, the most common cardiac diagnoses for patients without RHD were systolic heart failure (25%), hypertension (24%), and pulmonary hypertension/cor pulmonale (17%) (Fig. 2).

Table 2
Multivariable logistic regression of RHD diagnosis by sex, ethnicity, age, distance from the hospital.

RHD	Unadjusted OR	Unadjusted 95% CI	Adjusted OR	Adjusted 95% CI	p-value
Sex, female	1.48	1.09–2.01	1.85	1.31–2.62	0.001
Ethnicity, Nilote	2.80	1.95–4.01	2.52	1.70–3.74	0.000
Age, yrs					
14–18 yrs	2.81	1.68–4.70	3.19	1.86–5.48	0.000
19–23 yrs	1.57	0.92–2.67	1.52	0.88–2.65	0.136
24–28 yrs	1.0	Ref	1.0	Ref	Ref
29–33 yrs	1.68	0.95–3.00	1.98	1.08–3.62	0.027
34–38 yrs	0.84	0.47–1.49	0.96	0.52–1.78	0.902
39–43 yrs	0.51	0.29–0.89	0.51	0.28–0.90	0.021
44–49 yrs	0.27	0.15–0.48	0.30	0.16–0.53	0.000
Distance from MTRH, km					
0–24 km	1.0	Ref	1.0	Ref	Ref
25–49 km	1.63	1.12–2.37	1.30	0.85–1.97	0.222
50–74 km	1.31	0.80–2.16	1.18	0.68–2.05	0.555
75–199 km	1.29	0.76–2.18	1.20	0.67–2.15	0.529

RHD = rheumatic heart disease; OR = odds ratio; CI = confidence interval; yrs = years of age; Ref = reference group for analysis; MTRH = Moi Teaching and Referral Hospital; km = kilometers.

3.2. Geospatial analysis

Of the 906 patients, 788 (87%) had a known Division of residence; 613 were known from the medical chart, 134 were confirmed from the EHR, and 41 patients were called by phone to confirm their residence (Fig. 1). Patients resided in 103 of the 228 Divisions located within a 200 km radius of MTRH. Three quarters of patients (n = 579) lived within 50 km of the hospital, with most RHD and non-RHD patients living 25–49 km away (Fig. 3). Univariate analysis of the difference between rate of RHD and rate of non-RHD per Division revealed a non-random spatial distribution (Moran's I: 0.283; p-value: 0.001) with higher rates of RHD than non-RHD clustered around MTRH (Fig. 4). After controlling for age, sex, and ethnicity in the multivariable logistic regression, the odds of having RHD did not significantly change with distance to MTRH. Performing Moran's I testing on the mean deviance residuals for each Division revealed no global clustering (Moran's I: −0.001, p-value: 0.453, Fig. 5), indicating that the covariates included in the regression model adequately accounted for the observed clustering of rates of disease around the hospital.

Given the odds of RHD were unchanged by distance in our regression model yet significant geographic clustering was observed in rates

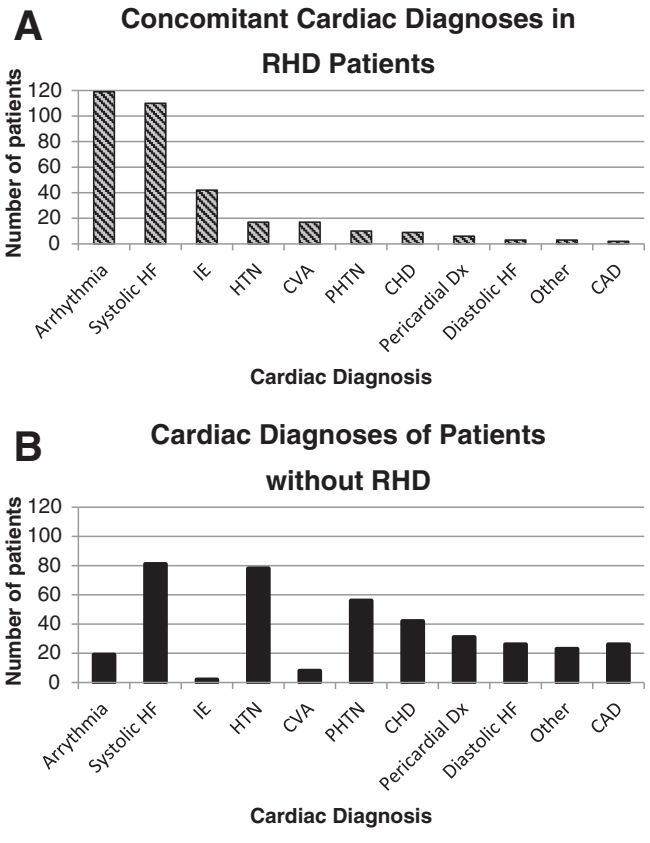

Fig. 2. Cardiac diagnoses for study participants with and without RHD. HF = heart failure; IE = infective endocarditis; HTN = hypertension as recorded as a diagnosis in the medical record; CVA = cerebrovascular event; PHTN = pulmonary hypertension and includes diagnoses of cor pulmonale; CAD = coronary artery disease. "Other" diagnoses include pheochromocytoma, left ventricular hypertrophy, non-RHD valvular heart disease, aortic aneurysm, heart block, and endomyocardial fibrosis.

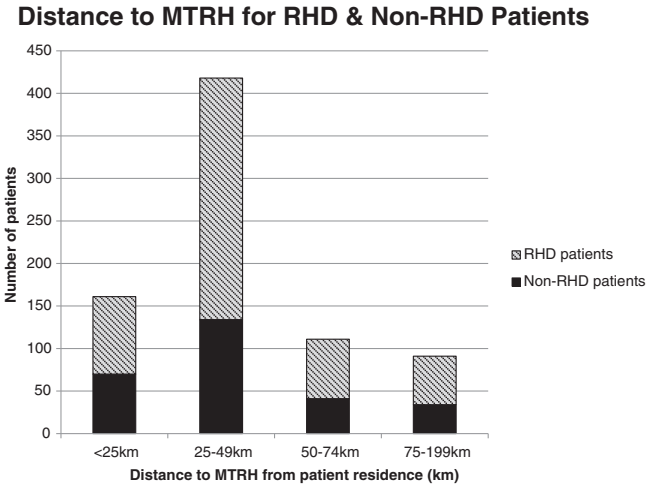

Fig. 3. Distance to MTRH from Division of patient residence for RHD and non-RHD patients. MTRH = Moi Teaching and Referral Hospital; RHD = rheumatic heart disease; km = kilometers.

of RHD, we postulated that there may be an interaction between ethnicity and distance to MTRH. The addition of an interaction term between ethnicity and distance to MTRH was significant. A multivariable model stratified by ethnicity (Nilote versus non-Nilote) revealed a variable effect of distance from the hospital on odds of RHD by ethnicity. For Nilotes, there is a non-significant trend of increased odds of RHD with further distance from the hospital for Nilotes, whereas the odds of RHD seem to decline with further distance from the hospital for non-Nilotes (Table 3).

4. Discussion

Rheumatic heart disease remains a leading cause of cardiac morbidity and mortality in sub-Saharan Africa, where true incidence and prevalence rates are largely unknown. Uncovering epidemiological patterns of disease is critical to identify target populations for secondary prophylactic therapy and early intervention and to inform public health strategies [14]. Understanding this need, our study identified demographic and geographic patterns of RHD in Kenya using data from the largest, outpatient cardiology clinic in western Kenya and revealed that RHD is the most common cardiac diagnosis in patients less than 50 years old. Young patients, females and patients of Nilote ethnicity had the highest odds of RHD, with higher rates of RHD relative to non-RHD disease seen clustered around the hospital. While there was no direct relationship between distance from the hospital and RHD, an interaction between distance from the hospital and ethnicity was found to influence RHD status.

In SSA, CVD accounts for only 8.8% of all deaths and 3.5% of disability-adjust life years (DALYs) [19]. While infection and inflammatory causes of CVD are still relatively more common causes of CVD in SSA, increases in life expectancy, economic development, and urbanization are shifting the CVD burden towards non-communicable diseases (NCDs) [19]. Between 1990 and 2010, RHD fell from the 5th to the 6th leading cause of CVD burden in SSA, although absolute numbers of cases increased [19], and non-communicable cardiovascular causes of stroke, atrial fibrillation and peripheral artery disease increased [19]. Studies from rural Kenya have also reflected this shifting epidemiology with proportional increases in NCD deaths relative to communicable disease (CD) deaths between 1990 and 2003 [20]. Of the one-third of patients without RHD in our study, hypertension, systolic heart failure, and pulmonary hypertension were the leading cardiac diagnoses, reflecting a

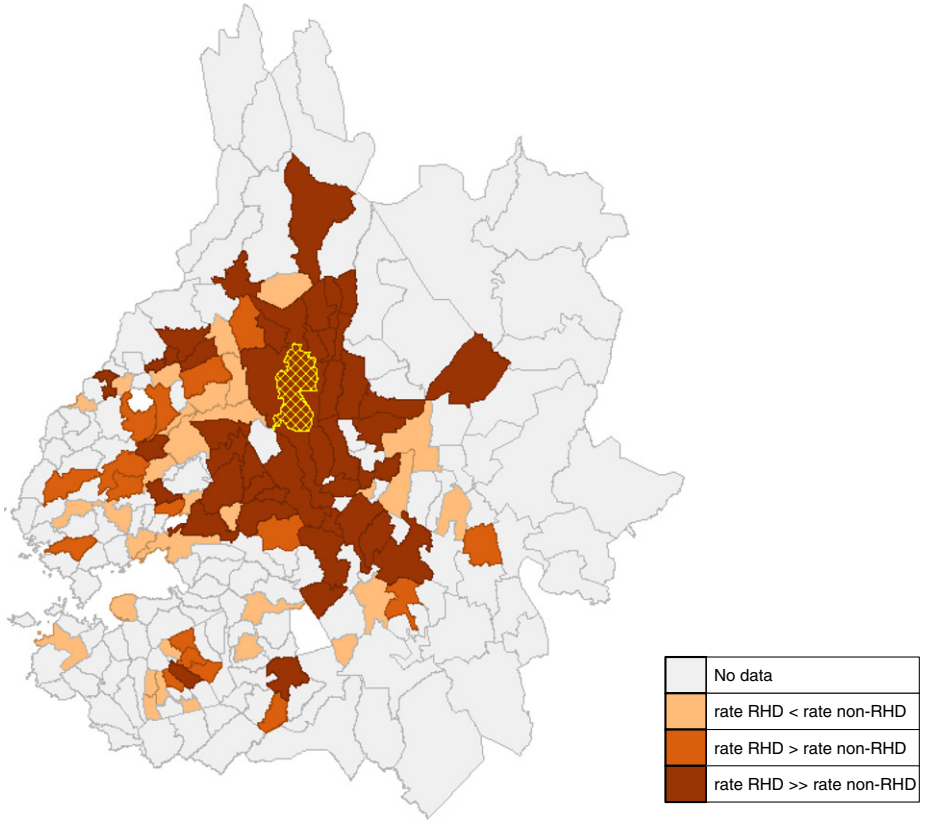

Fig. 4. Difference between RHD rates and non-RHD rates per Division in the study area. MTRH is located within the yellow highlighted Division. Significant clustering is seen across the study area as measured by Moran's I. Dark brown areas represent divisions where the rates of RHD are much greater than non-RHD rates and are mostly clustered around MTRH.

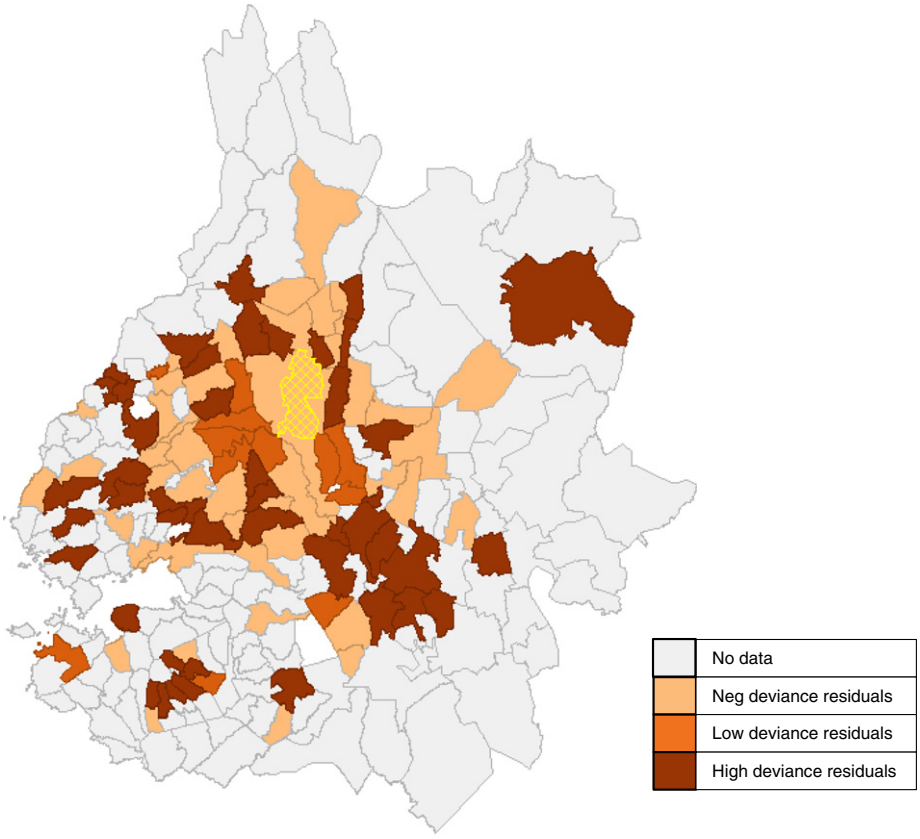

Fig. 5. Average deviance residuals from multivariable regression model per division. No significant global clustering of deviance residuals in the study area as tested by Moran's I ($p < 0.05$) suggest that the variables included in the regression (age, sex, ethnicity, and distance from the hospital) account for the spatial structure of the data seen in Fig. 4.

collision of non-communicable and communicable causes of cardiovascular disease present at MTRH. Despite this transition, RHD currently remains a significant burden of disease in SSA, representing the greatest cardiovascular-related loss of DALYs due to the young population it affects [21] and barriers to surgical treatment throughout SSA [12]. Additionally, most asymptomatic cases remain undiagnosed due to limitations of the clinical exam in detecting RHD and lack of widespread access to echocardiography across much of SSA [14]. These undetected cases contribute to underestimation of disease prevalence and difficulty in providing effective secondary prevention to prevent disease progression [1].

Table 3
Multivariable logistic regression of RHD diagnosis by sex, age and distance from the hospital, stratified by ethnicity (Nilotes versus non-Nilotes).

RHD	Nilotes			Non-Nilotes		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex, female	1.79	1.21–2.67	0.004	2.06	0.94–4.51	0.07
Age, yrs						
14–18 yrs	3.19	1.86–5.48	0.000	4.68	1.39–15.7	0.013
19–23 yrs	1.52	0.88–2.65	0.136	1.50	0.38–5.94	0.558
24–28 yrs	1.0	Ref	Ref	1.0	Ref	Ref
29–33 yrs	1.98	1.08–3.62	0.027	0.562	0.44–4.43	0.558
34–38 yrs	0.96	0.52–1.78	0.902	0.54	0.13–2.31	0.404
39–43 yrs	0.51	0.28–0.90	0.021	0.63	0.18–2.19	0.470
44–49 yrs	0.30	0.16–0.53	0.000	0.26	0.07–0.95	0.042
Distance from MTRH, km						
0–24 km	1.0	Ref	Ref	1.0	Ref	Ref
25–49 km	1.30	0.85–2.0	0.222	1.93	0.75–4.98	0.172
50–74 km	1.18	0.68–2.05	0.555	1.39	0.49–4.03	0.547
75–199 km	1.20	0.67–2.15	0.529	3.36	1.07–10.5	0.037

RHD = rheumatic heart disease; OR = odds ratio; CI = confidence interval; yrs = years of age; Ref = reference group for analysis; MTRH = Moi Teaching and Referral Hospital; km = kilometers.

Young patients and females in our study had the greatest odds of RHD. Teenagers, ages 14–18, were the mostly likely to have RHD, with increased odds of disease in patients up to 33 years old. This trend is also found in other endemic populations. In the Global Rheumatic Heart Disease Registry (REMEDY study), a prospective registry of RHD patients from 25 sites in 12 African countries, the median age of patients was 28 years, with a younger median age in LMICs compared to upper-middle-income countries (24 years versus 39 years, respectively) [21]. Similarly, the highest incidence rate of RHD in the highly burdened Aboriginal Australian population is between 10 and 14 years [2], and almost 70% of Ethiopians with RHD die before the age of 26 [22]. The severity of the initial cardiac insult, recurrent episodes of rheumatic fever, variation in streptococcal strain virulence, and magnitude of host-mediated immunological response may all contribute to the faster disease progression and younger age of development of RHD in SSA [5]. Additionally, females appear to be disproportionately affected by RHD and represent a particularly vulnerable group of patients with higher overall mortality rates and pregnancy-related complications. Studies across SSA have shown increased prevalence of RHD in females as compared to males [11,14,23] with higher rates of mitral stenosis [5]. Nearly 70% of all RHD patients in our study were females of reproductive age. This has significant clinical implications given the poor pregnancy outcomes associated with cardiac disease in pregnancy in SSA. A study from Senegal showed that RHD is associated with a maternal mortality rate of 34% and high rates of fetal loss [24]. Concurrently, only 3.6% of females of reproductive age with RHD in the REMEDY study were on contraception [21]. Given this high risk subgroup, echocardiographic screening of pregnant women should be considered early in antenatal care in areas with high rates of RHD [5].

In addition to understanding high risk populations, identifying geospatial patterns of RHD enhances our knowledge of disease risk factors, which allows for more targeted intervention in highly affected

areas. We uncovered clustering of RHD in the areas surrounding the hospital, with nearly 75% of all RHD cases presenting from within 50 km of the hospital. This is a surprising finding given that, in Africa, the distribution of RHD is more common in rural than urban areas [4], although higher rates of overcrowding and poverty, as typically seen in urban sprawl, increase risk of RHD development [3]. Additionally, increased access to health care services is associated with lower incidence of RHD [25], so we would expect to see a lower burden of disease closest to the public hospital. An alternative explanation for this finding could be due to challenges within the referral process of the Kenyan medical system. Effective referral for specialized treatment at MTRH requires initial clinical suspicion or presumptive diagnosis from a smaller medical facility, most of which are not equipped with echocardiography for accurate RHD diagnosis. Cost of transportation and long travel are additional barriers to specialized care for patients living in western Kenya [26]. Given these factors, it is possible that a smaller number of very severe cases of RHD are presenting from farther, whereas a higher number of more mild cases of RHD are being diagnosed closer to MTRH in areas with better access to echocardiography and easier access to specialized cardiac care. Therefore, the higher rates of RHD seen in areas surrounding the hospital may reflect a selection bias within our study population. Similar effects have been seen in a study in rural Kenya, where hospital admission rates decreased by up to 20% for every five kilometers distance increase from the hospital [27], supporting the hypothesis that RHD patients who lived further from the hospital accessed routine care at MTRH less often. These health seeking behaviors are therefore reflected in our study sample and likely influence the relationship seen between distance and RHD. Our study sample was comprised of those who had ever enrolled at the cardiology clinic, however, we do not know what proportion of those patients were active and maintained in care. This is also likely to be highly affected by distance and could be the subject of a future study.

The implications of the association between ethnicity and RHD warrant further investigation. We found patients of Nilote ethnicity to have over twice the odds of RHD compared to non-Nilotes, with different effects of distance from the hospital on RHD status between Nilote and non-Nilote ethnicities. It is difficult to draw any concrete conclusions from this, given the hospital is located in a largely Nilote-populated region of the country resulting in a high percentage of Nilotes represented in our study population. Some of the relationship between distance and RHD in the non-Nilote model could be related to ethnicity being unequally distributed geographically since the non-Nilote group is very diverse with non-Nilote subtribes typically living in areas further from the hospital. Despite the uncertain implications of the results, our findings are interesting to note, nonetheless, because host genetics may contribute to disease promotion and thus geographic clustering of disease [28]. Associations between rheumatic heart disease and major histocompatibility complex (MHC) class II human leukocyte antigens (HLA) have been elucidated in many populations [29,30]. While there is considerable heterogeneity in which alleles serve as susceptibility or protective markers among different populations and geographic regions, it is suggested that there is an ethnic specific susceptibility of alleles [29]. Ethnic differences in RHD also predispose to RHD-related complications [31]. The extent to which our findings relate to genetic, environmental, or social factors inherent to ethnic affiliation is beyond the scope of this study. Further studies in this domain are needed.

The strengths of this study include its contemporary timing, the novel use of geospatial analysis in exploring epidemiological patterns of disease, and our well-established study site, an NHLBI-funded Center of Excellence in cardiovascular research allowing for specialized care from trained Kenyan cardiologists [17]. Our study also has limitations which should be considered when interpreting the results. Given this was a retrospective review of medical charts, classification of RHD diagnosis relied on provider notes and echocardiogram reports and could not be standardized using international criteria; while RHD classification was verified by a trained cardiologist at MTRH, lack of standardization potentially allowed inconsistent diagnosis of RHD in this cohort [14]. Since we were relying on retrospective clinical data from patient medical charts we were also limited in the number of variables we could reliably collect from the medical charts, resulting in a narrow analysis of the risk factors associated with RHD. Our convenience sampling design limited our study size to the number of patients attending clinic, resulting in small numbers of participants within certain subgroups of our sample that may make subtle differences between groups undetectable. Selection bias may have contributed to an overestimate of RHD in our sample as patients attending MTRH outpatient cardiology clinic represent cases that have successfully been identified in the community and referred for specialized care, and therefore may be more severe cases than seen in the general population. Because we limited our inclusion age to focus on a younger population, our study was not designed to describe the full range of non-RHD cardiac disease, and our results do not reflect the complete range of cardiac disease in the western Kenyan population. Additionally, there may be inaccuracies in self-reported place of residence in Kenya, where many people may not know their official, government-ascribed residence as the Kenyan administrative classification for housing was restructured in 2009. Lastly, the currency of residence information in the paper chart or EHR was not able to be confirmed. Relocation of patients could skew our geospatial analysis and could blur any epidemiologic patterns of RHD. This effect would likely be strongest in the urban areas where people move around more often, as compared to the rural areas.

5. Conclusion

Using retrospective data from an outpatient cardiology clinic at a national referral hospital in western Kenya, we found that RHD is the most common cardiovascular disease among patients less than 50 years old seeking specialized care, affecting two-thirds of this population. Females and patients less than 33 years old carried increased odds of RHD, reflecting a known, high risk subgroup of reproductive-age females with cardiac disease in SSA who should be a priority for RHD screening, prevention and early treatment. Geographic clustering of high RHD rates surrounding the hospital is likely influenced by environmental factors and differences in health seeking behavior of the local population as compared to those living further away. An association between Nilote ethnicity and increased RHD risk may be present, although more research is needed around the role of ethnicity in susceptibility to RHD disease in Kenya. This was the first study to attempt to describe the patterns of RHD across western Kenya. Future studies addressing the true incidence and prevalence of RHD in the area are warranted in order to address the rising mortality rate from cardiovascular disease in SSA.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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