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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

# Etiology and Phenotypes of Cardiomyopathy in Southern Africa

## The IMHOTEP Multicenter Pilot Study

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## ABSTRACT

**BACKGROUND** Cardiomyopathies are an important cause of heart failure in Africa yet there are limited data on etiology and clinical phenotypes.

**OBJECTIVES** The IMHOTEP (African Cardiomyopathy and Myocarditis Registry Program) was designed to systematically collect data on individuals diagnosed with cardiomyopathy living in Africa.

**METHODS** In this multicenter pilot study, patients (age ≥13 years) were eligible for inclusion if they had a diagnosis of cardiomyopathy or myocarditis. Cases were grouped and analyzed according to phenotype; dilated cardiomyopathy (DCM) including myocarditis and peripartum cardiomyopathy, hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (RCM).

**RESULTS** A total of 665 unrelated index cases (median age 35 [27-44] years; 51.1% female) were recruited at 3 centers in South Africa and 1 center in Mozambique. DCM (n = 478) was the most common type of cardiomyopathy, accounting for 72% of the cohort; ACM (n = 78), HCM (n = 70), and RCM (n = 39) were less frequent. While the age of onset and sex distribution of HCM and ACM were similar to European and North American populations, DCM and RCM had a younger age of onset and occurred more frequently in women and those with African ancestry. Causes of cardiomyopathy were diverse; familial (27%), nonfamilial/idiopathic (36%), and secondary (37%) etiologies were observed.

**CONCLUSIONS** In the largest study of cardiomyopathy to-date on the African continent, we observe that DCM is the dominant form of cardiomyopathy in Southern Africa. The age of onset was significantly younger in African patients with notable sex and ethnic disparities in DCM. (JACC Adv. 2024;3:100952) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**ACM** = arrhythmogenic cardiomyopathy

**ART** = antiretroviral therapy

**CMR** = cardiovascular magnetic resonance

**DCM** = dilated cardiomyopathy

**EMF** = endomyocardial fibrosis

**EORP** = EURObservational Research Programme

**HCM** = hypertrophic cardiomyopathy

**HF** = heart failure

**HIVAC** = human immunodeficiency virus-associated cardiomyopathy

**LVEF** = left ventricular ejection fraction

**LVNC** = left ventricular non-compaction

**PPCM** = peripartum cardiomyopathy

**RCM** = restrictive cardiomyopathy

**SCD** = sudden cardiac death

**SSA** = sub-Saharan Africa

**VT** = ventricular tachycardia

Cardiomyopathies contribute significantly to the burden of heart failure (HF) in sub-Saharan Africa (SSA), however, little is known about their etiology, clinical manifestations, and outcomes in African patients.[1-3] While there are some reports from the continent,[4-7] our current understanding of cardiomyopathies is largely based on data generated by registries from Europe, Australia, and the United States,[8-11] countries with restricted ethnic ancestry and high-income economies, with a notable lack of representation from low- and middle-income countries.

Cardiomyopathies are a heterogenous group of disorders characterized by structural and functional abnormalities of the myocardium, in the absence of significant ischemic heart disease, hypertension, valvular heart disease, pericardial disease, congenital heart disease, and cor pulmonale.[12] Distinct subtypes are described; hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM) (including but not limited to arrhythmogenic right ventricular cardiomyopathy [ARVC]), and restrictive cardiomyopathy (RCM), with the most recent guidelines including an additional intermediate phenotype, non-dilated left ventricular cardiomyopathy (NDLVC).[12,13] Left ventricular non-compaction (LVNC), or left ventricular (LV) hypertrabeculation, remains a poorly defined entity in adults, usually existing alongside other distinct phenotypes.[13] While cardiomyopathies are well described in the literature, there is insufficient information on phenotypes and etiologies in African patients, and limited understanding of the role of genetics, infections, and environmental factors in the development of these conditions in local populations.

The principal aim of the African Cardiomyopathy and Myocarditis Registry Program (IMHOTEP) is to systematically collect data on the epidemiology, clinical manifestations, genetics, environmental contributors, and outcomes for patients with cardiomyopathies from SSA.[14] This report summarizes the multicenter pilot phase of the IMHOTEP study conducted in South Africa (SA) and Mozambique, in advance of the expansion of the registry to include other African countries. In this report, we describe the phenotypes, etiologies, and baseline characteristics of 665 unrelated adult and adolescent index patients recruited from 4 centers thus far.

## METHODS

**STUDY DESIGN AND POPULATION.** IMHOTEP is an African-based, multicenter, clinical registry and DNA biorepository, aimed at recruiting patients with cardiomyopathy or myocarditis from health care facilities across SSA.[14] A single-center feasibility study was conducted in Cape Town, SA, between February 2015 and July 2017.[15] The multicenter pilot phase was initiated in October 2016 with the inclusion of additional recruiting centers in SA and Mozambique (**Figure 1A**). As previously described, both *incident* (newly diagnosed) and *prevalent* (existing) cases were recruited (**Figure 1B**).[14] While patients of all ages are eligible, only adult and adolescent patients (≥13 years) were included in this analysis. The age cutoff reflects clinical practice in the region; minors between the age of 13 to 17 years typically present in a similar manner to young adults and are treated at adult facilities. Pediatric data will be reported separately.

Informed consent (and assent) was obtained from all participants prior to collection of clinical data. Data were recorded on a secure electronic database. Study management, data quality control, and statistical analyses were conducted by the Project Coordinating Centre, overseen by the Project Steering Committee.[14] The research study was approved by all affiliated institutional human research ethics committees in accordance with national guidelines.

**PATIENT ELIGIBILITY, CARDIOMYOPATHY SUBTYPES, AND ETIOLOGY.** Patients were eligible if they had a diagnosis of cardiomyopathy or myocarditis

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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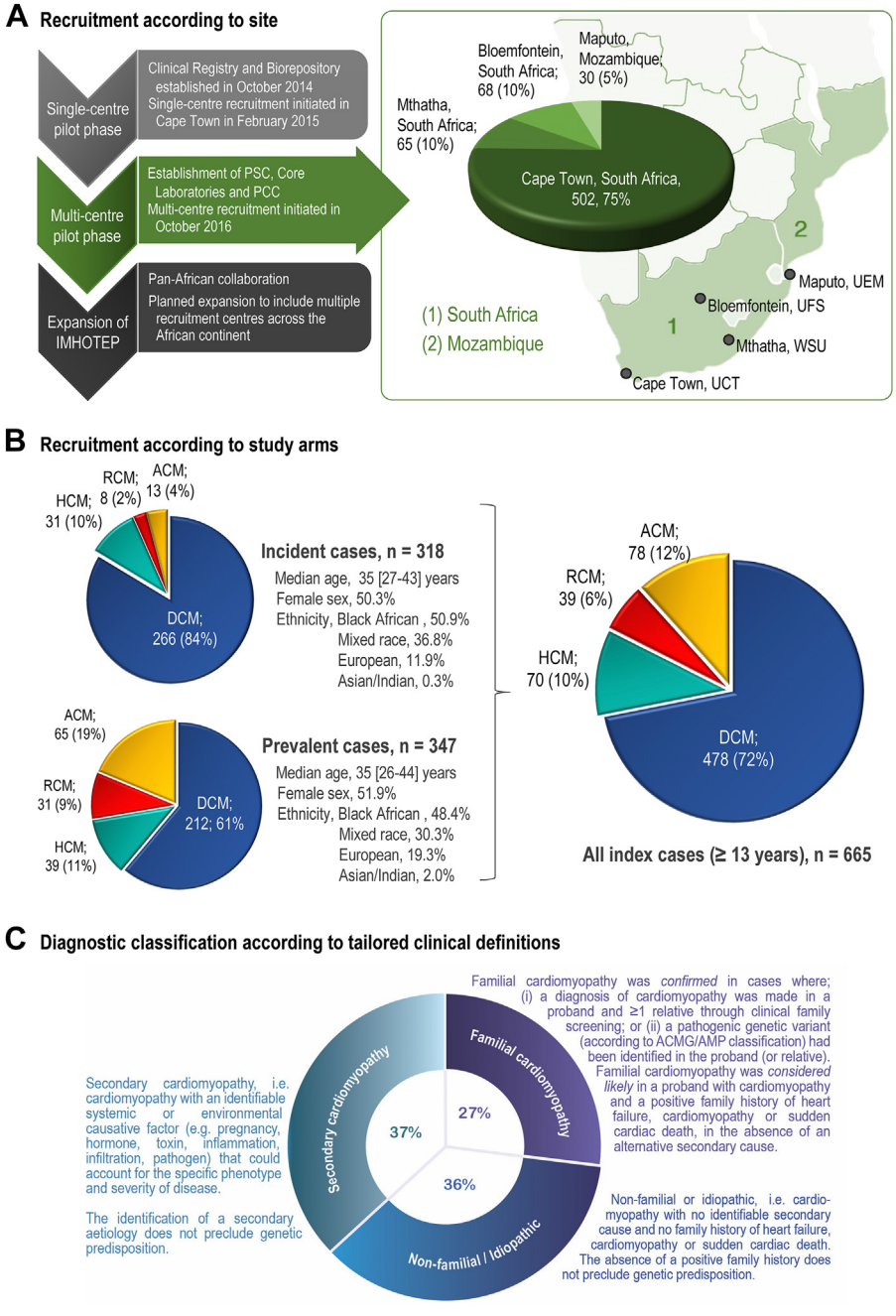
**FIGURE 1** **IMHOTEP Pilot Study Recruitment**




Recruitment according to (A) site, (B) study arm, and (C) diagnostic classification. ACM = arrhythmogenic cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; RCM = restrictive cardiomyopathy.

(Supplemental Table 2).[14] Those with hypertensive heart disease, ischemic heart disease, valvular heart disease, congenital heart disease, pericardial disease, and cor pulmonale were excluded (Supplemental Table 3). Patients were grouped according to subtypes: HCM, DCM, ACM, and RCM. Cases with LVNC, non-dilated left ventricular cardiomyopathy, and myocarditis were incorporated into the above-mentioned groups according to the dominant phenotype. Etiology was determined by clinical assessment

and investigations in line with published guidelines[14,16] and final diagnoses were confirmed by expert consensus. As diagnostic genetic testing and family screening for inherited cardiomyopathies is not readily available in SSA, a diagnosis of familial cardiomyopathy was based on clinical criteria (Figure 1C).

**STATISTICAL ANALYSIS.** Descriptive statistics were used to describe the study sample. Categorical data were reported as number and proportion. Chi-squared test (or Fisher's exact test) was used to determine differences between subtypes, sex, and/or ethnicity for categorical data. Continuous variables were tested for distribution (Shapiro-Wilks/Kolmogorov-Smirnov tests). Non-normally distributed data were reported as median (IQR), and Wilcoxon sum rank (2 samples) and Kruskal-Wallis (>2 samples) were used to determine differences. Normally distributed data were reported as mean and standard deviation, and Student's *t*-test (2 samples) and ANOVA (>2 samples) were used to determine differences. Bonferroni correction was applied post hoc for multiple comparisons. All statistical tests were 2-sided, at $\alpha = 0.05$. International Business Machines (IBM) SPSS Statistics 2021 (Version 28.0.1.0[142]) software was utilized to analyze data.

## RESULTS

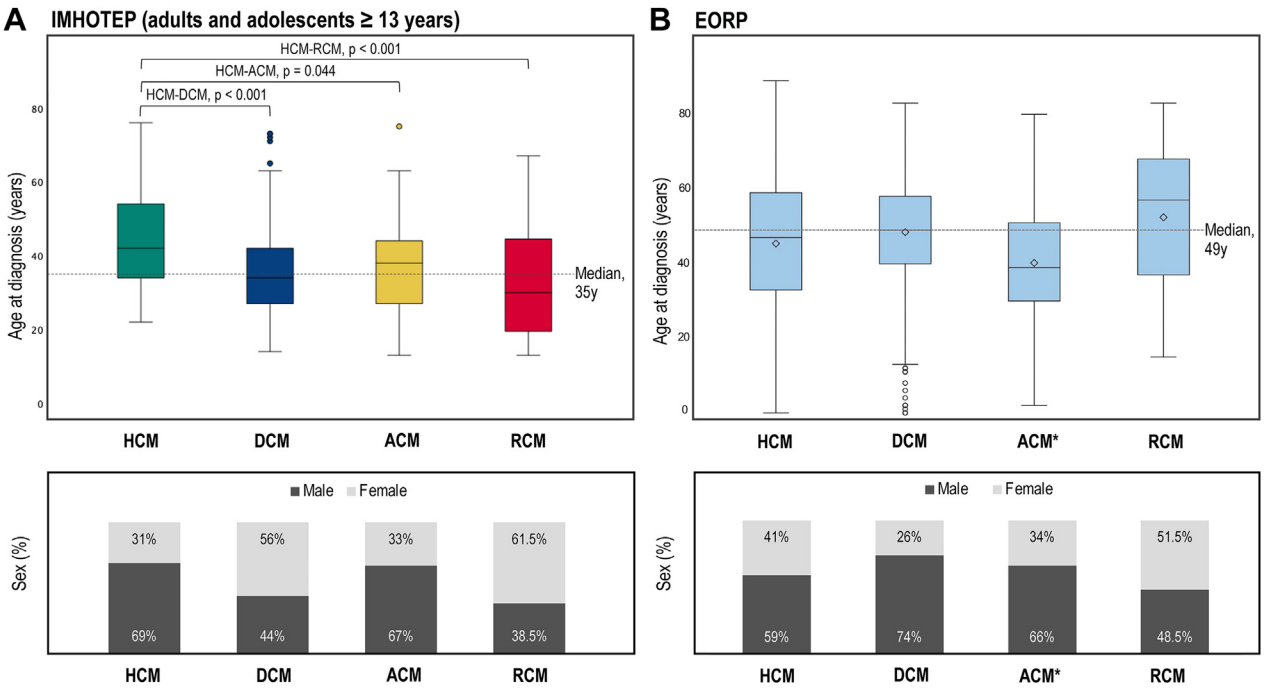
**STUDY POPULATION AND DEMOGRAPHICS.** A total of 665 unrelated adult (n = 638) and adolescent (n = 27) index patients were recruited at 4 state-funded centers in SA and Mozambique (Figure 1A); 318 *incident* and 347 *prevalent* cases (Figure 1B). Due to the inclusion of historical cohorts in the prevalent cases arm[4,5,7,14] and a lack of frequency data on cardiomyopathies in the region, the proportions of cardiomyopathy subtypes do not reflect regional population prevalence. There were no significant differences in the age or sex between *incident* and *prevalent* study participants (age, $P = 0.786$; sex, $P = 0.688$) and ethnic representation was similar (Figure 1B). Male and female patients were near equally represented (female, 51.1%); however, sex distribution did vary according to subtype (Figure 2A). All local ethnic groups were represented (Table 1); the ethnic distribution is in keeping with regional population demographics, particularly the Western Cape Province of SA where most patients were recruited. The higher proportion of European patients in the prevalent ACM cohort is explained by historical inequalities in access to health care.[5] There were notable differences in the age of diagnosis, sex, and etiology according to ethnicity in DCM (described below) (Figure 3). Significant ethnic differences were not demonstrated in other subtypes.

**PHENOTYPE AND ETIOLOGY.** Familial disease was confirmed, or considered likely, in 26.8% of patients. Secondary causes of cardiomyopathy were identified in 36.8% of cases, most frequently associated with DCM and RCM. In the absence of genetic testing, the remaining cases with no family history or identifiable secondary cause were labeled as 'nonfamilial' or 'idiopathic' (36.4%). DCM was the most common type of cardiomyopathy (n = 478), accounting for 72% of the cohort (Figure 4). ACM (n = 78), HCM (n = 70), and RCM (n = 39) were seen less frequently, and substantial proportions of these patients were recruited retrospectively (Figure 1B). LV hypertrabeculation (or LVNC) was coexisting in 6% of cases (DCM, n = 38; ACM, n = 1; RCM, n = 1).

The causes of cardiomyopathy were diverse (Figure 4), particularly for DCM. Peripartum cardiomyopathy (PPCM) was the most frequently diagnosed etiology (n = 144), accounting for 30.1% of the DCM cohort and 21.7% of cases overall. Other secondary causes of DCM included toxin exposure (anthracycline, n = 16; methamphetamines, n = 7; alcohol, n = 5; anabolic steroids, n = 1), probable myocarditis (n = 16), human immunodeficiency virus-associated cardiomyopathy (HIVAC) (n = 13), tachycardia-induced cardiomyopathy (n = 5), and systemic disease (thyrotoxicosis, n = 1; connective tissue disease, n = 2). As endomyocardial biopsy was not routinely available, a diagnosis of probable myocarditis was made based on evidence of myocardial injury and imaging criteria (Supplemental Table 2).[14] Most (96%) patients with RCM were recruited from Mozambique, accounting for the high proportion of patients with endomyocardial fibrosis (EMF), a condition endemic in that country but rarely seen in SA.

**CLINICAL CHARACTERISTICS.** The median age at presentation was 35 (27-44) years, with notable variation in the age according to subtype (Figure 2A). In DCM, there were significant differences observed in the median age at presentation for sex (males, 38 [30-45] years vs females, 32 [25-41] years, $P < 0.001$) and ethnicity (Figure 3). Difference in age between men and women was driven by the high proportion of PPCM cases; the median age of women with PPCM was significantly younger compared to both women and men with DCM due to other etiologies (PPCM, 28.5 [23-34] years; vs DCM in women, 36.5 [28-45] years and men, 37 [30-44]; $P < 0.001$]. There were

**FIGURE 2** Age at First Presentation and Sex According to Phenotype




Age and sex in (A) IMHOTEP and (B) EORP (adapted from *Charron et al, Eur Heart J 2018;39(20):1784-1793*). ACM = arrhythmogenic cardiomyopathy; DCM = dilated cardiomyopathy; EORP = EURObservational Research Programme; HCM = hypertrophic cardiomyopathy; IMHOTEP = African Cardiomyopathy and Myocarditis Registry Program; RCM = restrictive cardiomyopathy.

no significant sex-based differences in age in the other subtypes.

Most patients (94.7%) presented with cardiac symptoms. A minority presented with embolic events (2.0%), resuscitated cardiac arrest (1.2%), sudden cardiac death (SCD) (0.3%), or incidentally (asymptomatic) (1.8%). Functional class and symptoms varied according to phenotype (**Table 2**). Baseline presentation occurred within the peripartum period in almost half (47.6%) of all women recruited. In women with DCM, 57.8% had symptom-onset during or after pregnancy compared to 7.7% to 12.5% in other subgroups.

**FAMILY HISTORY AND COMORBIDITIES.** A family history of HF, cardiomyopathy and/or SCD was reported in 31.4% of patients (**Table 2**). A positive family history of HF was recorded in 16.1% and 22.9% of patients with EMF and PPCM, respectively; however, familial cardiomyopathy was not confirmed in these cases. Comorbidities were documented in 31.6% of patients. Human immunodeficiency virus (HIV) was the most frequent comorbidity (13.8%). This is not unexpected as HIV prevalence in SA is estimated to be 19.5% in adults aged 15 to 49 years.[17] Importantly, the majority (79.3%) of patients with HIV were established on antiretroviral therapy (ART) prior to presentation, inferring that HIV was likely a bystander diagnosis rather than causal. Hypertension (11.1%) was the second most common comorbidity. A history of hypertension was observed in 38.6% and 8.4% of HCM and DCM patients, respectively. Again, this is not unexpected as the prevalence of hypertension in SA ranges from 20.1% (15-24 years) to 85% (>65 years).[18] While hypertension may contribute to disease progression, expert consensus was that hypertension could not solely account for the myocardial abnormalities observed in these cases. There were no sex differences in the incidence of hypertension (females, 11.5% vs males, 10.8%, $P = 0.774$), however, hypertension did occur more frequently in those with mixed-race ancestry (mixed-race, 18.5%, Black African, 6.7%, European, 9.5%). A history of significant alcohol use (>30 U/month, or binge drinking >5 U in 1 sitting/month) was reported in 18.2% of patients overall, most frequently in those with DCM, and in men (31.5% vs 6.6% [women],

**TABLE 1 Study Population**

| | All Patients (N = 665) | Morphofunctional Phenotype | | | |
|---|---|---|---|---|---|
| | | ACM (n = 78) | DCM (n = 478) | HCM (n = 70) | RCM (n = 39) |
| Study site | | | | | |
| Groote Schuur Hospital, Cape Town, SA (UCT)[a] | 502 (75.5) | 78 (100) | 348 (72.8) | 67 (95.7) | 9 (23.1) |
| Universitas Academic Hospital, Bloemfontein, SA (UFS) | 68 (10.2) | 0 | 68 (14.2) | 0 | 0 |
| Nelson Mandela Academic Hospital, Mthatha, SA (WSU) | 65 (9.8) | 0 | 62 (13.0) | 3 (4.3) | 0 |
| Hospital Central de Maputo, Mozambique (UEM)[b] | 30 (4.5) | 0 | 0 | 0 | 30 (4.5) |
| Age category | | | | | |
| Adult (≥18 years) | 638 (95.9) | 70 (89.7) | 465 (97.3) | 70 (100) | 33 (84.6) |
| Minor (13-17 years) | 27 (4.1) | 8 (10.3) | 13 (2.7) | 0 | 6 (15.4) |
| Ethnicity | | | | | |
| Black African | 330 (49.6) | 7 (9.0) | 278 (58.2) | 14 (20.0) | 31 (79.5) |
| Mixed-race | 222 (33.4) | 19 (24.4) | 155 (32.4) | 43 (61.4) | 5 (12.8) |
| European (White) | 105 (15.8) | 48 (61.5) | 43 (9.0) | 11 (15.7) | 3 (7.7) |
| Asian/Asian Indian | 8 (1.2) | 5 (5.1) | 2 (0.4) | 2 (2.8) | 0 |
| Employment | | | | | |
| Employed | 277 (41.7) | 31 (39.7) | 192 (40.2) | 38 (54.3) | 16 (41.0) |
| Unemployed | 244 (36.7) | 11 (14.1) | 204 (42.7) | 15 (21.4) | 14 (35.9) |
| Disability grant | 18 (2.7) | 2 (2.6) | 15 (3.1) | 0 | 1 (2.6) |
| Other (student/pensioner) | 54 (8.2) | 13 (16.6) | 31 (6.5) | 3 (4.3) | 7 (8.2) |
| Unknown | 72 (10.8) | 21 (26.9) | 36 (7.5) | 14 (20.0) | 1 (2.6) |
| Highest level of education | | | | | |
| Primary school | 77 (11.6) | 0 | 54 (11.3) | 6 (8.6) | 17 (43.6) |
| High school (incomplete) | 213 (32.0) | 9 (11.5) | 174 (36.4) | 18 (25.7) | 12 (30.8) |
| Matriculation/High school certificate | 109 (16.4) | 2 (2.6) | 99 (20.7) | 7 (10.0) | 1 (2.6) |
| University/College | 96 (15.5) | 16 (20.5) | 64 (13.7) | 12 (17.2) | 4 (10.3) |
| Unknown | 170 (25.6) | 51 (65.4) | 87 (18.2) | 27 (38.6) | 5 (12.8) |

Values are n (%). [a]GSH is a national referral center for ACM; recruitment includes patients from centers elsewhere in South Africa. [b]Includes outreach initiatives to other regions in Mozambique.

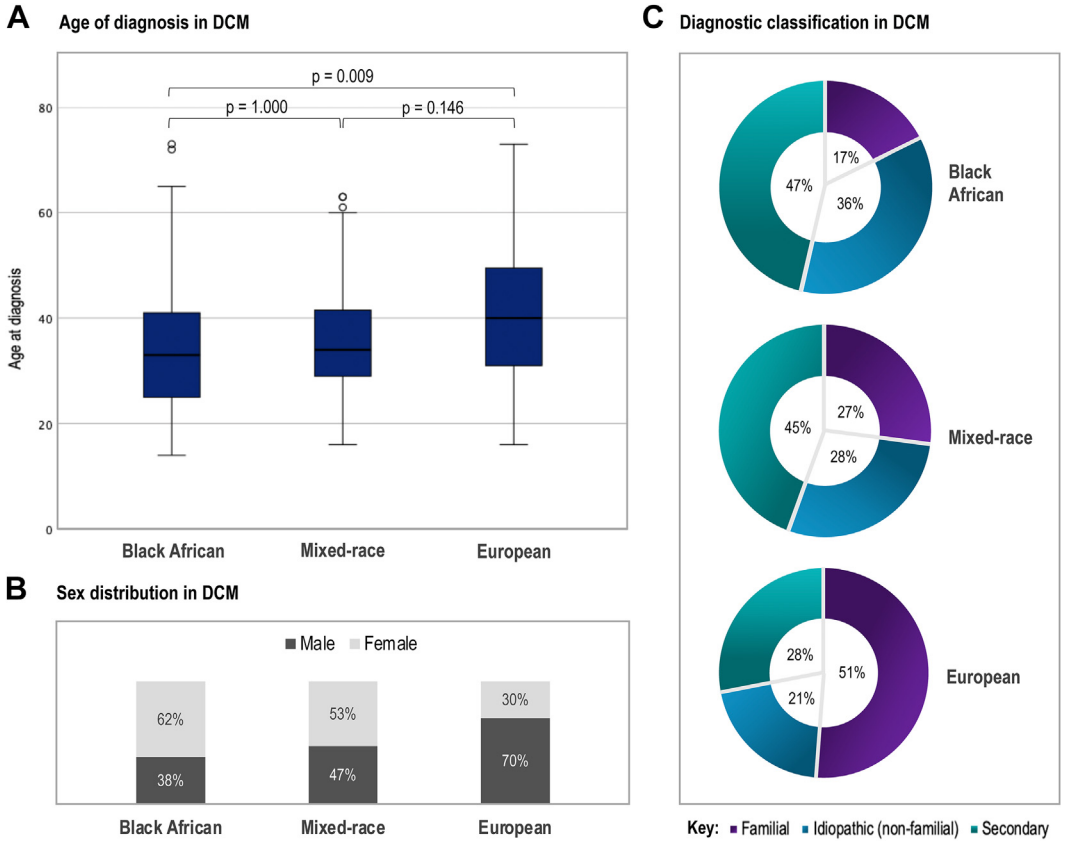
ACM = arrhythmogenic cardiomyopathy; ACMUCT = University of Cape Town; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; RCM = restrictive cardiomyopathy; UCT = University of Cape Town; UEM = Universidade Eduardo Mondlane; UFS = University of Free State; WSU = Walter-Sisulu University.

$P < 0.001$). Illicit drug use was also more frequently reported in men compared to women (10.8% vs 5.7% $P = 0.043$).

**INVESTIGATIONS AND THERAPIES.** Table 3 describes the investigations performed according to clinical indications and resource capacity. Electrocardiograms and echocardiograms were available for almost all patients. As expected, baseline ventricular dimensions and function varied according to phenotype (Table 1). In DCM, men had significantly lower left ventricular ejection fractions (LVEF) at baseline compared to women (LVEF 26.1% vs 29.7%, $P < 0.001$), however, there were no significant sex differences in LV dimensions when corrected for body surface area. Cardiovascular magnetic resonance (CMR) was only accessible at one site and was performed in 31.6% of cases. Blood samples for genetics research were collected in 645 (97%) patients.

Most patients were established on medical therapy at the time of recruitment (median time from first presentation to recruitment, 4.9 [1-22.7] months) (Table 3). HF therapies namely, beta-blockers, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), and mineralocorticoid-receptor antagonists were prescribed in 63.6%, 73.1%, and 50.2% of all cases, respectively. Newer HF therapies such as angiotensin receptor neprilysin inhibitors and sodium-glucose cotransporter-2 inhibitors were not readily available at the time. Anticoagulation therapy was prescribed in 101 (15.8%) patients (indications listed in Table 3). At enrollment, 75 (11.3%) patients had devices in situ. Twelve patients met criteria for cardiac resynchronization therapy. Seven patients had single-chamber pacemakers for conduction disease. Fifty-one patients had implantable cardioverter defibrillators for primary (n = 16) and secondary prevention (n = 35). In those with documented

**FIGURE 3** Ethnic Variation in DCM




Ethnic variation in DCM for (A) age, (B) sex, and (C) etiology. DCM = dilated cardiomyopathy.

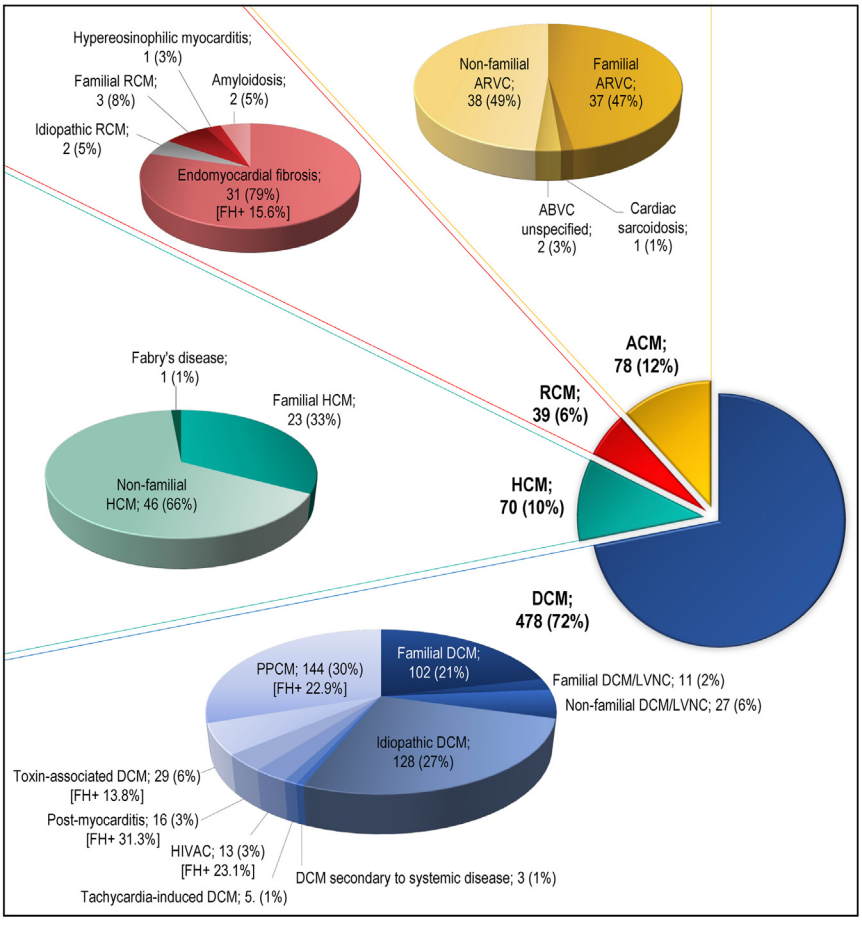
ventricular tachycardia (VT) and/or prior cardiac arrest, 35/60 (58.3%) had implantable cardioverter defibrillators at enrollment.

**EVENTS AT PRESENTATION.** Cardiovascular events were reported in 28.3% of cases at baseline and varied according to phenotype (Table 2). VT was documented at baseline in 67.9% of patients with ACM but was infrequent in other subtypes (0.2-2.6%). Intracardiac thrombi were present in 9.8% of cases, most commonly in EMF. Atrial arrhythmias and embolic stroke occurred in 7.1% and 3.5% of all cases, respectively. There were notable sex differences in the number of events at baseline in DCM (31% [men] vs 16.4% [women], $P < 0.001$); specifically, intracardiac thrombus (14.8% [men] vs 7.1% [women], $P = 0.007$), embolic stroke (6.7% [men] vs 2.6% [women], $P = 0.042$), and atrial arrhythmias (8.6% [men] vs 4.1% [women], $P = 0.042$) occurred more frequently in men compared to women with DCM.

## DISCUSSION

This is the first multicenter cohort study that examines the full spectrum of cardiomyopathies in Southern African patients. IMHOTEP represents the largest cardiomyopathy registry based in Africa, providing unique insights into the causes and manifestations of heart muscle disease in local populations. In this study, a total of 665 adult (and adolescent) patients with cardiomyopathy were recruited from SA and Mozambique (Central Illustration). DCM was the most common subtype, with ACM, HCM, and RCM occurring less frequently. Myocarditis was infrequently diagnosed. Clinical assessment indicated that underlying familial disease was confirmed, or considered likely, in 27% of cases and a secondary cause was identifiable in over a third of patients. While there were variations in age and sex distribution between subtypes, the median age at presentation was 35 years with a slight female predominance overall.

**FIGURE 4 Phenotypes and Etiology**




ABVC = arrhythmogenic biventricular cardiomyopathy; ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; FH+ = positive family history; HCM = hypertrophic cardiomyopathy; HIVAC = human immunodeficiency virus-associated cardiomyopathy; LVNC = left ventricular noncompaction; PPCM = peripartum cardiomyopathy; RCM = restrictive cardiomyopathy.

Remarkably, almost half of the women recruited presented during the peripartum period. Cardiovascular events at baseline varied according to phenotype; VT was most frequently associated with ACM, and intracardiac thrombi were more common in patients with EMF and DCM. There were notable sex-related disparities in age of onset, baseline LVEF, and the number of events occurring in patients with DCM. When compared to women, male patients were slightly older with lower baseline LVEF and had a 2-fold higher risk of intracardiac thrombus, embolic stroke, and atrial fibrillation. Importantly, there was no significant difference in the median time between onset of symptoms and presentation to a medical facility between men and women, inferring that health-seeking behavior could not account for these differences. Our data have important implications for the screening, diagnosis, and management of cardiomyopathy in Africa—efforts must target younger Africans and ministries of health need to urgently develop capacity for optimal diagnosis and management of cardiomyopathy on the continent.

Based on similarities in study design, the best international comparative study to IMHOTEP is the Cardiomyopathy Registry of the EORP (EURObservational Research Programme).[8] Compared to European cohorts where HCM is considered the most common form of cardiomyopathy,[8] DCM appears to be the dominant phenotype encountered in IMHOTEP, accounting for more than two-thirds of all cases

**TABLE 2 Baseline Characteristics for Patients ≥13 Years of Age According to Phenotype**

| | ACM (n = 78) | DCM (n = 478) | HCM (n = 70) | RCM (n = 39) |
|---|---|---|---|---|
| Female | 26 (33.3) | 268 (56.1) | 22 (31.4) | 24 (61.5) |
| Age, y[c] | 38 (26.8-44) | 34 (27-42) | 42 (33.8-54) | 30 (19-45) |
| Symptoms | | | | |
| Syncope | 30 (38.5) | 22 (4.6) | 10 (14.3) | 0 |
| Palpitations | 57 (73.1) | 228 (47.7) | 37 (52.9) | 9 (23.1) |
| Orthopnea | 2 (2.6) | 316 (66.1) | 7 (10.0) | 11 (28.2) |
| Paroxysmal nocturnal dyspnea | 0 | 236 (49.4) | 8 (11.4) | 3 (7.7) |
| Body swelling/edema | 1 (1.3) | 293 (61.3) | 5 (7.1) | 8 (20.5) |
| NYHA functional class | | | | |
| I | 63/74 (85.1) | 34/469 (7.2) | 29/67 (43.3) | 5 (12.8) |
| II | 10/469 (13.5) | 144/469 (30.7) | 29/67 (43.3) | 22 (56.4) |
| III | 1/67 (1.4) | 234/469 (49.9) | 8/67 (11.9) | 11 (28.2) |
| IV | 0 | 57/469 (12.2) | 1/67 (1.5) | 1 (2.6) |
| Peripartum onset (females) | 2/26 (7.7) | 155/268 (57.8) | 2/22 (9.1) | 3/24 (12.5) |
| Viral illness at presentation | 5 (6.4) | 79 (16.5) | 4 (5.7) | 8 (20.5) |
| Positive family history | 22 (28.2%) | 156 (32.6) | 23 (32.9) | 8 (20.5) |
| Family history of heart failure | 2 (2.6) | 117 (24.5) | 10 (14.3) | 7 (17.9) |
| Family history of cardiomyopathy | 6 (7.7) | 39 (8.2) | 8 (11.4) | 2 (5.1) |
| Family history of SCD <35 y | 6 (7.7) | 23 (4.8) | 5 (7.1) | 0 |
| Family history of SCD >35 y | 9 (11.5) | 57 (11.9) | 12 (17.1) | 1 (2.6) |
| Comorbidities | 14 (17.9) | 154 (32.2) | 34 (48.6) | 8 (20.5) |
| HIV positive [% on ART] | 0 | 84 (17.6) [77.4%] | 3 (4.3) [100%] | 5 (12.8) [100%] |
| Essential hypertension | 6 (7.7) | 40 (8.4) | 27 (38.6) | 1 (2.6) |
| Chronic pulmonary disease | 1 (1.3) | 16 (3.3) | 6 (8.6) | 2 (5.1) |
| Diabetes | 3 (3.8) | 14 (2.9) | 5 (7.1) | 0 |
| Thyroid disease | 3 (3.8) | 9 (1.9) | 1 (1.4) | 0 |
| Connective tissue disease | 3 (3.8) | 4 (0.8) | 0 | 0 |
| Toxin exposure | | | | |
| Significant alcohol use[a] | 3/48 (6.3) | 93/415 (22.4) | 3/45 (6.7) | 0 |
| Illicit drug use[b] | 1/29 (3.4) | 35/383 (9.1) | 3/35 (8.6) | 0 |
| Cardiotoxic medications | 0 | 17 (3.6) | 0 | 1 (2.6) |
| Examination | | | | |
| Heart rate (beats/min)[c] | 60 (54-71.5) | 88 (73.8-104.3) | 70 (55.3-80) | 80 (65-93) |
| Systolic BP (mm Hg)[c] | 120 (110-130) | 110 (100-120) | 130 (120-140) | 103 (95-112) |
| Diastolic BP (mm Hg)[c] | 75 (68-80) | 70 (60-80) | 80 (70-85) | 70 (61-79) |
| BMI (kg/m$^2$)[c] | 25.5 (22-30) | 26.2 (22-31) | 26.2 (24-31) | 21 (18-25) |
| Congestive heart failure | 7/76 (9.2) | 234 (49.0) | 5 (7.1) | 30 (78.9) |

*Continued on the next page*

recruited. While selection bias (ie, recruitment of predominantly symptomatic cases) may be contributing to the lower proportion of HCM cases in IMHOTEP, it does not fully account for the very high burden of DCM observed in this cohort. In EORP, the age distribution was wider than in IMHOTEP, with a median age around 50 years and male predominance across all subtypes.[8] In comparison, the median age of onset of cardiomyopathy in Southern African patients was significantly younger (35 years), with a slight female predominance overall. Importantly, age was not significantly altered by the inclusion of adolescent cases (median age in patients ≥18 years, 36 [28-44] years). While the age of onset, sex distribution, and clinical presentation of HCM and ACM were similar to what has been reported in European and North American populations,[8-10] DCM and RCM had a notably younger age of onset and occurred more frequently in women and in those with African ancestry.

The ethnic distribution in IMHOTEP is representative of local population demographics with expected regional variation between sites. Historically, Black African and mixed-race individuals have been under-represented in cardiomyopathy studies and most publications exploring ethnic disparities have focused on differences between White and Black African Americans.[19] Although there are no population-

**TABLE 2 Continued**

| | ACM (n = 78) | DCM (n = 478) | HCM (n = 70) | RCM (n = 39) |
|---|---|---|---|---|
| Events at baseline | | | | |
| Atrial arrhythmia or SVT | 2 (2.6) | 32 (6.7) | 5 (7.1) | 11 (28.2) |
| Ventricular arrhythmia | 53 (67.9) | 1 (0.2) | 1 (1.4) | 1 (2.6) |
| Heart block | 4 (5.1) | 3 (0.6) | 0 | 1 (2.6) |
| Cardiac arrest-survived/SCD | 4 (5.1)/1 (1.3) | 4 (0.8)/1 (0.2) | 0 | 0 |
| Intracardiac thrombus | 2 (2.6) | 50 (10.5) | 1 (1.4) | 12 (30.8) |
| Embolic stroke/TIA | 0 | 21 (4.4) | 2 (2.9) | 0 |
| Pulmonary embolism | 1 (1.3) | 5 (1.0) | 0 | 0 |
| Electrocardiogram | | | | |
| Sinus rhythm | 71 (93.4) | 440 (92.8) | 67 (95.7) | 8 (23.5) |
| Right/left bundle branch block | 5 (6.6)/1 (1.3) | 10 (2.1)/62 (13.1) | 4 (5.7)/2 (2.9) | 6 (17.6)/1 (2.9) |
| QTc (ms)[c] | 436 (412-461) | 443 (413-473) | 426 (412-455) | 450 (436-491) |
| Echocardiogram | | | | |
| LVEF (%)[c] | 62 (55-66) | 26 (20-35) | 70 (65-78) | 60 (24-74) |
| LVEDD (mm)[c] | 51 (45-55) | 63 (58-70) | 43 (38-49) | 45 (37-50) |
| MWT (mm)[c] | 10 (9-12) | 9.7 (8.2-11) | 19 (15-22) | 9 (8-10) |
| LA diameter (mm) | 34 ± 6.3 | 44 ± 7.9 | 41 ± 7.6 | 50 ± 13.5 |
| RVSP (mm Hg)[c] | 22 (18-26) | 35 (26.5-47) | 22 (12-30.5) | 34 (24-73.5) |

Values are n (%), median (IQR), or mean ± SD. [a]>30 U/month or binge drinking >5 U in 1 sitting per month. [b]Methamphetamines/cocaine. [c]Kruskal-Wallis Test, $P \leq 0.01$.

ACM = arrhythmogenic cardiomyopathy; ART = antiretroviral therapy; BMI = body mass index; BP = blood pressure; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LA = left atrium; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; MWT = maximal wall thickness; QTc = corrected QT interval; RCM = restrictive cardiomyopathy; RVSP = right ventricular systolic pressure; SCD = sudden cardiac death; SD = standard deviation; SVT = supraventricular tachycardia; TIA = transient ischemic attack.

based epidemiological studies on DCM from SSA, HF studies from the continent report that DCM accounts for 25 to 30% of HF hospitalizations.[1] The disproportionately high burden of DCM in IMHOTEP—84% of *incident* cases—further supports that DCM is an important cause of HF in the region. In our cohort, DCM occurred more frequently and at a younger age in patients with Black African (and mixed-race) ancestry compared to those of European descent. In addition, sex distribution and etiology appeared to vary according to ancestry (**Figure 3**). The female-to-male ratio in DCM was 1.6 and 1.2 for Black African and mixed-race patients, compared to 0.4 for White patients. Sex discrepancies in DCM were driven by significantly higher proportions of PPCM cases in Black African and mixed-race groups. When PPCM cases were excluded, sex distribution changed with higher proportions of male patients compared to female patients across all ethnic groups, in keeping with what has been reported elsewhere (female-to-male ratios of 0.7, 0.5, and 0.4 in Black African, mixed-race, and European groups, respectively). Secondary etiologies accounted for ~45% of mixed-race and Black African DCM cases, compared to 27% of those with European ancestry. Furthermore, familial disease was diagnosed in a much higher proportion of DCM cases with European ancestry compared to those of African descent (52.3% vs 17.3% [Black African] and 27.1% [mixed-race]). Of note, patients were recruited at state-funded institutions servicing middle- and low-income communities in urban settings. While there were some differences in employment and educational parameters, socioeconomic and environment factors are unlikely to account for the differences observed between the ethnic groups. The lower proportion of familial disease, ethnic variation, and diverse etiology demonstrated in DCM, suggests a polygenetic underpinning with complex environmental interactions.

The high proportion of patients with PPCM in IMHOTEP is notable. PPCM accounted for more than half of women presenting with a DCM phenotype, and a fifth of cardiomyopathy cases overall. Importantly, PPCM accounted for 28.2% to 32.4% of DCM cases recruited across South African sites, suggesting that the high proportion of PPCM cases is not region-specific and selection bias cannot account for this observation. PPCM occurred more frequently in Black African and mixed-race women (~57%) presenting with a DCM phenotype, compared to women with European descent (7.7%). While there are overlapping features between PPCM and pregnancy-associated hypertensive heart disease with HF,[20,21] we were careful not to include

**TABLE 3 Investigations and Management at the Time of Recruitment**

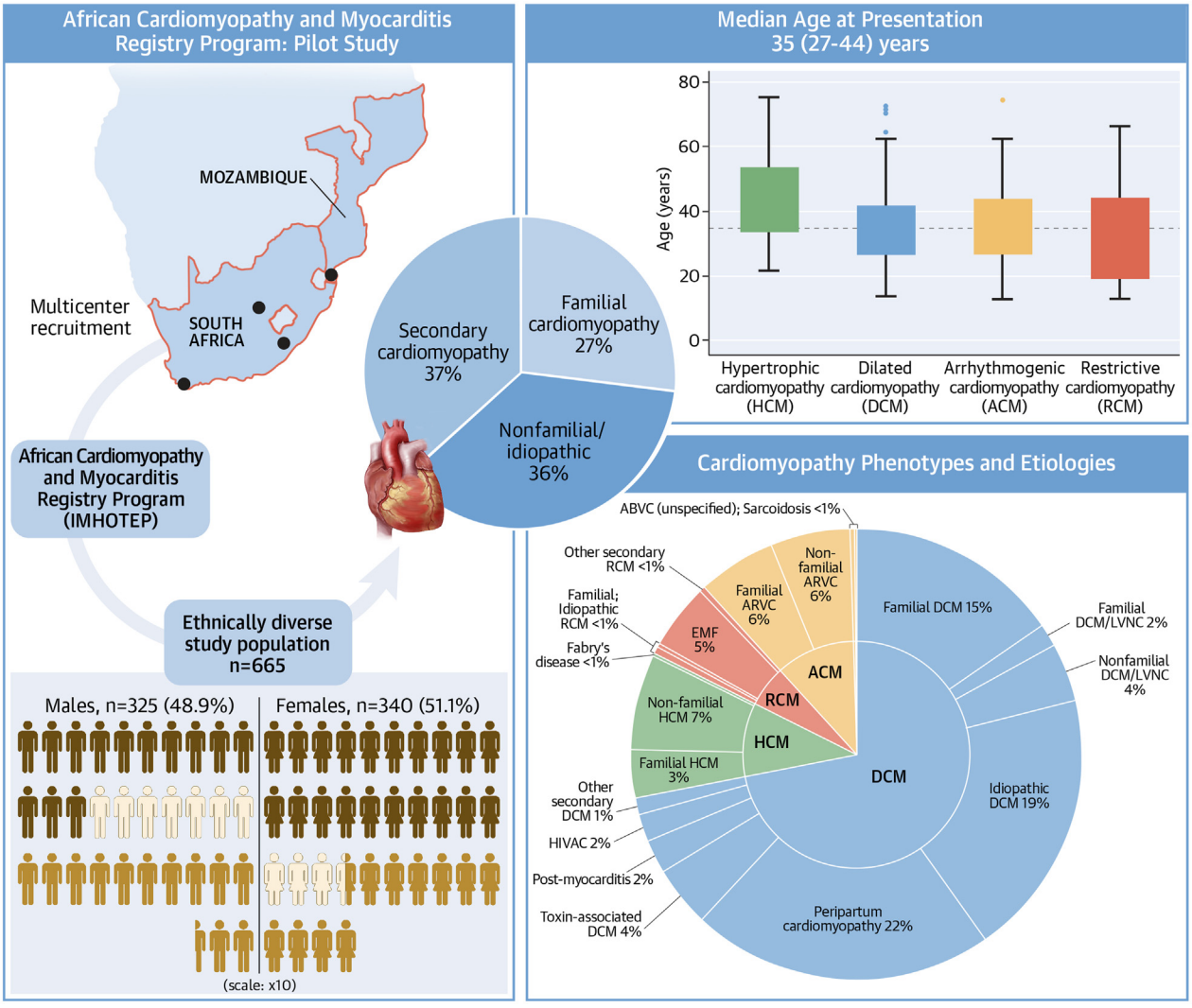
| | All Patients (N = 665) | ACM (n = 78) | DCM (n = 478) | HCM (n = 70) | RCM (n = 39) |
|---|---|---|---|---|---|
| Investigations according to the 3-stage diagnostic approach | | | | | |
| Stage 1: core noninvasive | | | | | |
| Electrocardiogram | 654 (98.3) | 76 (97.4) | 474 (99.2) | 70 (100) | 34 (87.2) |
| Echocardiogram | 652 (98.0) | 68 (87.2) | 476 (99.6) | 69 (98.6) | 39 (100) |
| Chest radiograph[a] | 355 (53.4) | 34 (43.6) | 262 (54.8) | 39 (55.7) | 20 (51.3) |
| Blood investigations[b] | 510 (76.7) | 37 (47.4) | 414 (86.6) | 31 (44.3) | 28 (71.8) |
| Stage 1: extended noninvasive | | | | | |
| CMR[c] | 210 (31.6) | 36 (46.2) | 137 (28.7) | 31 (44.3) | 6 (15.4) |
| 24-hour Holter | 77 (11.6) | 32 (41.0) | 19 (4.0) | 26 (37.1) | 0 |
| EST | 39 (5.9) | 28 (35.9) | 5 (1.0) | 6 (8.6) | 0 |
| SAECG | 59 (8.9) | 53 (67.9) | 3 (0.6) | 3 (4.3) | 0 |
| Stage 2: invasive | | | | | |
| Angiography | 122 (18.3) | 47 (60.3) | 45 (9.4) | 25 (35.7) | 5 (12.8) |
| EMB | 53 (8.0) | 34 (43.6) | 12 (2.5) | 3 (4.3) | 4 (10.3) |
| EPS | 55 (8.3) | 49 (62.8) | 3 (0.6) | 2 (2.9) | 1 (2.6) |
| Stage 3: genetics | | | | | |
| DNA samples collected | 645 (97.0) | 71 (91.0) | 466 (97.5) | 69 (98.6) | 39 (100) |
| Medical and interventional therapies | | | | | |
| HF drug therapies | | | | | |
| Diuretics | 482/654 (73.7) | 6/76 (7.9) | 421/471 (89.4) | 19/69 (27.5) | 36/38 (94.7) |
| Beta-blockers | 416/654 (63.6) | 37/76 (48.7) | 330/471 (70.1) | 43/69 (62.3) | 6/38 (15.8) |
| ACE inhibitors/ARB | 478/654 (73.1) | 14/76 (18.4) | 428/471 (90.9) | 22/69 (31.9) | 14/38 (36.8) |
| MRA | 328/654 (50.2) | 6/76 (7.9) | 288/471 (61.1) | 2/69 (2.9) | 32/38 (84.2) |
| Ivabradine | 3/654 (0.5) | 0 | 3/471 (0.6) | 0 | 0 |
| Digoxin | 146/654 (22.3) | 0 | 134/471 (28.5) | 1/69 (1.4) | 11/38 (28.9) |
| Other drug therapies | | | | | |
| Amiodarone | 30/654 (4.6) | 19 (23.7) | 8/471 (1.7) | 2/69 (2.9) | 2/38 (5.3) |
| Disopyramide | 5/654 (0.7) | 2 (2.6) | 0 | 3/69 (4.3) | 0 |
| CCB | 23/654 (3.5) | 4 (5.3) | 5/471 (1.1) | 13/69 (19.8) | 1/38 (2.6) |
| Anticoagulation[d] | | | | | |
| Warfarin (or NOAC*) | 101/654 (15.4) | 5/76 (6.6) | 86/471 (18.3) | 3/69 (4.3) | 7/38 (18.4) |
| Device | | | | | |
| Pacemaker | 7 (1.1) | 2 (2.6) | 3 (0.6) | 0 | 2 (5.1) |
| CRT-P | 7 (1.1) | 1 (1.3) | 6 (1.3) | 0 | 0 |
| CRT-D | 5 (0.8) | 0 | 5 (1.0) | 0 | 0 |
| ICD | 51 (7.7) | 42 (53.8) | 6 (1.3) | 2 (2.9) | 1 (2.6) |

Values are n (%). [a]Images available for review. [b]Conducted according to clinical indications. [c]CMR only available at Cape Town site. [d]Indications included intracardiac thrombus (n = 21), atrial arrhythmia (n = 16), stroke (n = 8), pulmonary embolus (n = 4), venous thrombosis (n = 2), multiple indications (n = 8), not documented (n = 42). *NOAC (rivaroxaban) prescribed in 2 patients only.

ACE = angiotensin-converting enzyme; ACM = arrhythmogenic cardiomyopathy; ARB = angiotensin receptor blockers; CCB = calcium channel blocker; CMR = cardiovascular magnetic resonance; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; EPS = electrophysiology study; EST = exercise stress test; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid receptor antagonist; NOAC = new oral anticoagulants; RCM = restrictive cardiomyopathy; SAECG = signal average electrocardiogram.

patients where hypertension was considered the driving factor for myocardial dysfunction. It is, therefore, not surprising that the proportion of women with chronic hypertension (4.1%) or a history of gestational hypertension (18.5%) was lower in IMHOTEP, compared to the EORP PPCM Registry where hypertension was present in up to 40% of patients.[21] Importantly, the incidence of hypertension in women and men presenting with a 'DCM phenotype' was similar (9.0% and 7.6%, $P = 0.601$). This suggests that hypertension is unlikely to account for the high incidence of PPCM. There is growing evidence that some women with PPCM have underlying genetic susceptibility.[22] Although a family history of HF was reported in a fifth of women with PPCM, familial disease was not demonstrated in these cases. PPCM is associated with significant maternal morbidity and mortality,[21] imposing additional layers of complexity to the management of these women, and potential social welfare consequences for African families and communities.

**CENTRAL ILLUSTRATION** **The IMHOTEP Multicenter Pilot Study on Cardiomyopathies in Southern Africa**




**Kraus SM, et al. JACC Adv. 2024;3(12):100952.**

ABVC = arrhythmogenic biventricular cardiomyopathy; ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; HCM = hypertrophic cardiomyopathy; HIVAN = human immunodeficiency virus-associated cardiomyopathy; LVNC = left ventricular noncompaction/left ventricular hypertrabeculation; RCM = restrictive cardiomyopathy.

The contribution of myocarditis as a cause for DCM in the African population remains undetermined. Due to later presentation and limited access to CMR and endomyocardial biopsy, definitive exclusion of myocarditis as a cause for DCM was not possible in most cases. Even with the use of CMR and other accepted clinical parameters for myocardial injury,[14] probable myocarditis was diagnosed in surprisingly few (3%) cases, although it is likely that some cases of idiopathic DCM were due to myocarditis. While HIV was the most common comorbidity, HIVAC was diagnosed infrequently. Since the introduction of ART, HIVAC with systolic dysfunction has become relatively uncommon[23] accounting for the low number of cases of HIVAC in IMHOTEP. However, this observation may not be reflected in other parts of Africa where ART may not be readily available. Due to the high prevalence and younger age of onset of hypertension in the region,[18] the proportion of patients with coexisting hypertension was not unexpected.

Furthermore, the presence of hypertension in a third of HCM cases is in keeping with what has been reported in other series.[24]

While IMHOTEP has provided new insights into the etiology, clinical manifestations, and common phenotypes in Southern Africa, the true prevalence of these conditions on the continent remains undetermined. As the patient population in this pilot study was limited to SA and Mozambique, the findings may not be reflected in other regions across Africa. While we anticipate regional variation in epidemiology across the continent, the observation that DCM is the commonest form of cardiomyopathy in African communities, is consistent with what has been reported in other African-based HF studies.[1,3] The detailing of the diverse spectrum of etiologies, and the description of ethnic and gender diversity underpinning DCM in an African-based population, is unique to this study and represents a new perspective. The low proportion of HCM in IMHOTEP may, in part, reflect underdiagnosis of mild or asymptomatic cases due to limited access to echocardiography. However, the burden of symptomatic or advanced cardiomyopathy is strongly weighted towards DCM, likely driven by a much greater than usual incidence of DCM rather than low levels of HCM. The higher percentage of ACM cases overall is explained by the incorporation of existing cases from the Arrhythmogenic Right Ventricular Cardiomyopathy Registry of SA into IMHOTEP,[5,14] and the proportion (4%) of cases represented in the *incident* cases arm is likely a more accurate reflection of burden of disease. Most RCM cases were recruited from Mozambique where the prevalence of EMF has been reported to be as high as 19.8%,[25] which explains the relatively high proportion of EMF cases and the younger age of onset within the RCM group. As expected, in non-endemic areas (SA), the incidence of EMF was extremely low. It was not possible to distinguish between eosinophilic and primary EMF as most EMF cases were recruited retrospectively. While the cause of EMF remains elusive, current evidence still supports environmental factors and (incidental or polygenic) familial clustering, over monogenic predisposition.[26]

**STRENGTHS AND LIMITATIONS.** Most patients were recruited at a tertiary level referral center in SA and likely reflect the more severe end of the disease spectrum. The number of cases presenting with SCD is likely underestimated as patients presenting with SCD were not routinely referred for recruitment. Although there are limitations associated with retrospective recruitment, there were no significant differences in baseline characteristics between existing and newly diagnosed patients, and the inclusion of prevalent cases provided the necessary power to conduct more meaningful analysis. As the classification of familial disease was largely reliant on family history reporting, the proportions of patients with familial disease may be under-represented. This may be particularly relevant to those with Black African and mixed-race ethnicity where historical inequalities in access to health care may contribute to under-reporting of familial disease. In the absence of genetic testing, we are unable to comment on the contribution of genetics in the development of cardiomyopathies, gene-environmental interactions, or potential overlapping phenotypes. Despite these limitations, IMHOTEP has provided new insights into the profile of disease affecting local populations, highlighting key differences in phenotypes, etiology, age of onset, sex distribution, and ethnicity, when compared with international cohorts. The contribution of secondary cardiomyopathies, particularly PPCM and EMF, in younger female patients is notable. The younger age of onset and sex differences within this cohort have important implications for public health policy in SSA, particularly with regard to maternal health care and the role of specialist services in resource-restricted settings. Furthermore, the socioeconomic burden of disease on this patient population is evident, with only 42% of patients employed at the time of recruitment. Follow-up data will provide much needed insights into clinical outcomes and socioeconomical impact of heart muscle disease in this young population of patients with diverse etiological profiles.

## CONCLUSIONS

In the largest study of cardiomyopathy to-date from the African continent, we observe that, compared to international cohorts, the age of onset was significantly younger in African patients, with notable sex and ethnic disparities in DCM and RCM. Our findings concur with previous observations that DCM is an important cause of HF in Africa. The diverse etiology in DCM further supports the heterogenous nature of this condition and the likelihood of both genetic and environmental modifiers in disease development. Importantly, the identification of secondary etiologies does not preclude genetic predisposition. Planned genetic analysis will provide further insight into the genetic underpinning of cardiomyopathies in African populations and the interplay between genetics and the environment.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The causes of cardiomyopathy in Southern Africa are diverse, particularly for DCM, the dominant phenotype presenting to hospital with HF.

**TRANSLATIONAL OUTLOOK 1:** The younger age of onset of DCM in African populations, particularly in women of child-bearing age, poses additional health care and socioeconomic challenges for local policymakers.

**TRANSLATIONAL OUTLOOK 2:** Secondary, potentially treatable causes, contribute significantly to disease burden in Southern Africa.

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**KEY WORDS** **Africa, cardiomyopathy, dilated cardiomyopathy, heart failure, myocarditis, South Africa**

**APPENDIX** **For supplemental tables, please see the online version of this paper.**