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Clinical Features and Outcomes of Peripartum Cardiomyopathy in Nigeria

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ABSTRACT

BACKGROUND Nigeria has the highest incidence of peripartum cardiomyopathy (PPCM) in the world. However, data on PPCM-related outcomes are limited.

OBJECTIVES The purpose of this study was to examine the clinical profile, myocardial remodeling, and survival of patients with PPCM in Nigeria.

METHODS This study consecutively recruited 244 PPCM patients (median 7 months postpartum) at 14 sites in Nigeria and applied structured follow-up for a median of 17 months (interquartile range: 14 to 20 months). Left ventricular reverse remodeling (LVRR) was defined as the composite of left ventricular (LV) end-diastolic dimension <33 mm/m^2 and absolute increase in left ventricular ejection fraction (LVEF) $\geq$10%. LV full recovery was defined as LVEF $\geq$55%.

RESULTS Overall, 45 (18.7%) patients died during follow-up. Maternal age <20 years (hazard ratio [HR]: 2.40; 95% confidence interval (CI): 1.27 to 4.54), hypotension (HR: 1.87; 95% CI: 1.02 to 3.43), tachycardia (HR: 2.38; 95% CI: 1.05 to 5.43), and LVEF <25% at baseline (HR: 2.11; 95% CI: 1.12 to 3.95) independently predicted mortality. Obesity (HR: 0.16; 95% CI: 0.04 to 0.55) and regular use of beta-blockers at 6-month follow-up (HR: 0.20; 95% CI: 0.09 to 0.41) were independently associated with reduced risk for mortality. In total, 48 patients (24.1%) achieved LVRR and 45 (22.6%) achieved LV full recovery. LVEF <25% at baseline (HR: 0.66; 95% CI: 0.47 to 0.92) and regular use of beta-blockers at 6-month follow-up (HR: 1.62; 95% CI: 1.17 to 2.25) independently determined the risk for LV full recovery. Progressive reverse remodeling of all cardiac chambers was observed. In total, 18 patients (7.4%) were hospitalized during the study.

CONCLUSIONS This is the largest study of PPCM in Africa. Consistent with late presentations, the mortality rate was high, whereas frequencies of LVRR and LV full recovery were low. Several variables predicted poor outcomes, and regular use of beta-blockers correlated with late survival and LV functional recovery. (J Am Coll Cardiol 2020;76:2352–64)

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Peripartum cardiomyopathy (PPCM) is a global disease with an epidemiological profile that varies widely within and between countries. Nigeria is reported to have the highest burden of PPCM in the world, with an incidence as high as 1:96 deliveries (1). However, studies in that country describing antecedent factors and health outcomes are single-center-based and are limited by small sample sizes (2–4). Mortality rates as high as 47.4% at 1-year follow-up have been previously reported from Nigeria, while studies from Burkina Faso and South Africa reported mortality rates of 48.3% over 4 years and 13.0% over 6 months, respectively (2,5,6). In contrast, mortality rates as low as 4.1% at 1-year and 1.5% at 5-year follow-up have been reported from the United States and Germany, respectively (7,8). Extent of myocardial recovery in those affected with PPCM appears to be correlated with survival patterns. Left ventricular (LV) functional recovery as low as 29.4% at 1-year and 21% at 6-month follow-up was reported from Nigeria and South Africa, respectively, while rates as high as 71% at 1-year and 95.5% at 5-year follow-up were reported from the United States and Germany, respectively (2,6–8).

Although some researchers have failed to identify precise correlates of mortality or myocardial recovery, it has been suggested that younger age at diagnosis, lower body mass index, Black race, use of guideline-directed treatments, and some key cardiac parameters measured by echocardiography and cardiac magnetic resonance independently influence such outcomes (6–9). In view of the reportedly high rates of PPCM linked to typically poor health outcomes among Nigerian women, we sought to undertake a more definitive, nationwide study of this disease. Accordingly, we established the PEACE (PEripArtum Cardiomyopathy in NigEria) registry study. This prospectively conducted registry collected data on the baseline clinical profile and then the extent of myocardial remodeling and survival status during structured follow-up of women presenting with PPCM in Nigeria.

METHODS

STUDY DESIGN AND OVERSIGHT. The steering committee of the PEACE registry designed and oversaw the conduct of the study. It was conducted and reported in accordance with a previously reported protocol and the statistical analysis plan (10). Patients in the longitudinal arm of the registry were recruited from 14 tertiary-level hospitals spread across the populous (~200 million people) West African country of Nigeria (**Figure 1**). The study was approved by the ethics committee at each center, and the study conformed to the ethical guidelines of the Declaration of Helsinki on the principles for medical research involving human subjects (11). The first draft of the manuscript was prepared by the first author, who had unrestricted access to the data. All of the authors made the decision to submit the manuscript for publication and testify to the standard of conduct of the study.

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STUDY PARTICIPANTS. Study participants were eligible for inclusion if they were a patient at any one of the participating sites and had a confirmed diagnosis of PPCM as defined by the PPCM Working Group of the European Society of Cardiology. Specifically, PPCM is defined as "an idiopathic cardiomyopathy presenting with heart failure (HF) secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the LV ejection fraction (LVEF) is reduced below 45%" (12). For the purpose of this study, patients were required to have developed HF symptoms from the 28th week of gestation if pregnant and up to the first 5 months postpartum; to have LVEF below 45% at enrollment; to be at least 18 years of age; to be in New York Heart Association (NYHA) functional classes II, III, or IV (for new patients only); and to have provided written informed consent. Pre-existing PPCM patients who were being treated and followed-up at any participating center before the commencement of the study were recruited regardless of the presence of symptoms if they had satisfied the other inclusion criteria. Alternatively, patients with chronic hypertension and/or those that lacked reliable contact phone numbers were excluded from participation.

Study participants were expected to receive standard and routinely available HF drug therapies in Nigeria. This included diuretic agents, beta-blockers,

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HF = heart failure
HR = hazard ratio
IQR = interquartile range
NYHA = New York Heart Association
LV = left ventricle
LVEF = left ventricular ejection fraction
LVRR = left ventricular reverse remodeling
PPCM = peripartum cardiomyopathy
TAPSE = tricuspid annular plane systolic excursion

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 *JACC* author instructions page.

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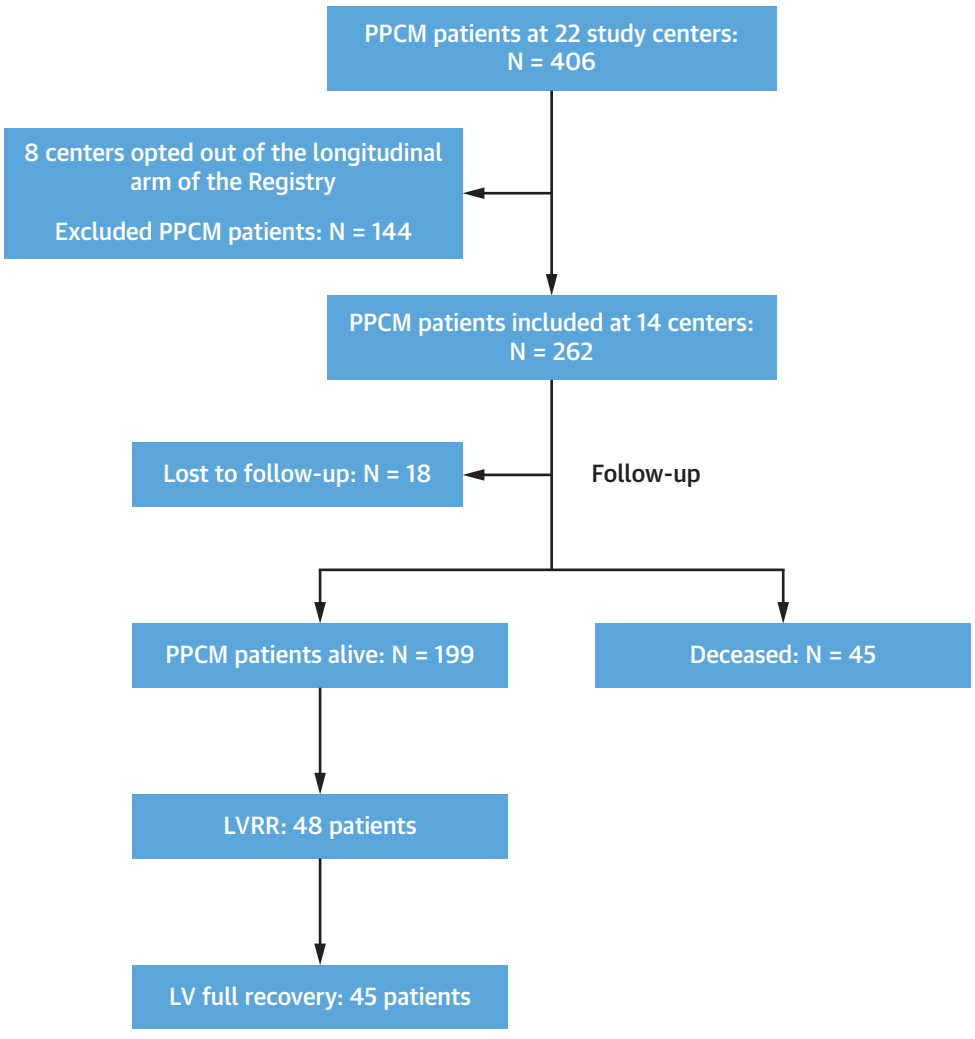
FIGURE 1 Enrollment and Follow-Up of Patients



All the patients were reviewed at 3 monthly intervals until March 31, 2019. LV = left ventricular; LVRR = left ventricular reverse remodeling; PPCM = peripartum cardiomyopathy.

and angiotensin-converting enzyme inhibitors or an angiotensin-receptor blocker or nitrate-hydralazine combination, unless such use was contraindicated or resulted in unacceptable side effects. In addition, the prescription of a mineralocorticoid receptor antagonist was encouraged. Additional therapies for HF were prescribed, and drug doses were individually tailored in accordance with guideline recommendations.

STUDY PROCEDURES. After screening for inclusion and exclusion criteria, pre-existing and de novo patients with PPCM were recruited consecutively at each center between June 2017 and March 2018. Study follow-up was conducted until March 2019. Cardiologists in Nigeria were invited to participate as investigators through the platforms of the Nigerian Cardiac Society.

Following informed consent and study registration, participants were interviewed and clinically evaluated for the purpose of baseline profiling. They were then re-evaluated at 3 monthly intervals, with a focus on assessment of the study's clinical outcomes focusing on myocardial recovery and mortality. For this study, tachycardia was defined as heart rate at rest of above 100 beats/min, whereas hypotension was defined as systolic blood pressure <100 mm Hg. Underweight and obesity were defined as body mass index <18.5 and ≥30 kg/m^2, respectively. Echocardiography and electrocardiography were carried out

and repeated every 6 months until the completion of study follow-up, using standard criteria (13). Echocardiographic information was obtained at individual study centers, then the data were entered into the study questionnaire and sent to the principal investigator. Investigators were requested to use the recommended Simpson's rule for LVEF measurement (13). Pulmonary hypertension was defined as pulmonary artery systolic pressure of 38 mm Hg or higher (13).

OUTCOMES. The primary clinical outcomes of interest were extent/evidence of myocardial remodeling and all-cause mortality. The presence and extent of myocardial remodeling during follow-up was specifically assessed by determining if left ventricular reverse remodeling (LVRR) relative to baseline status had occurred. Potential changes in the sizes of other cardiac chambers and in tricuspid annular plane systolic excursion (TAPSE) reflective of right ventricular (RV) function were also assessed. LVRR was defined as the composite of LV end-diastolic dimension <33 mm/m^2 and absolute increase in LVEF by at least 10% at follow-up. LV full recovery was defined as a LVEF ≥55%. RV systolic dysfunction was defined as TAPSE <16 mm (10,13). For each documented fatality, an independent investigator interviewed the first-degree relatives or attending physicians, or reviewed the patient's medical records, to determine the specific cause of death. Deaths were subsequently categorized as "unknown" when none of these investigations was successful in identifying a specific causality. A related, secondary outcome of interest was the rate of all-cause rehospitalizations during study follow-up within the study cohort.

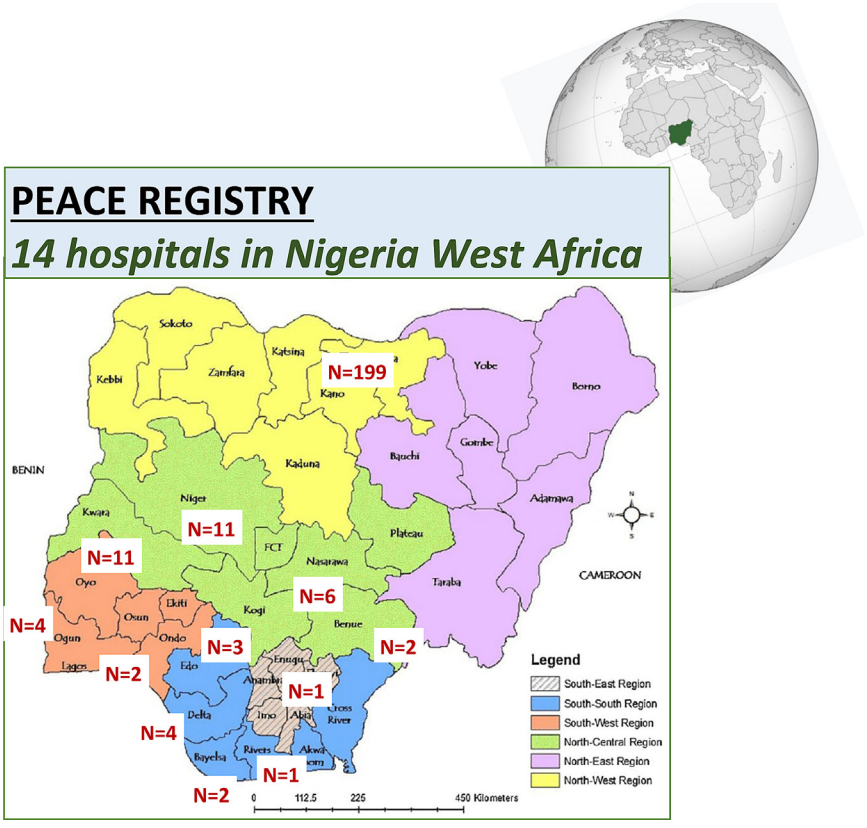
STATISTICAL ANALYSIS. Standard methods for describing and comparing grouped data, including mean ± SD, median (interquartile range [IQR]), and proportions according to baseline and follow-up profiling data were applied. Comparison of baseline, 6-month, and end of follow-up data on the key parameters of ventricular function and the sizes of cardiac chambers were conducted using the Friedman test, a nonparametric test for K-related samples. The independent correlates (adjusted odds ratio and 95% confidence interval [CI]) of achieving LVRR, based on baseline profiling, were examined in the 199 surviving cases in whom their follow-up cardiac status was determined via multiple logistic regression (entry model). Mortality (occurring from baseline profiling to end of follow-up) was examined in all 244 cases with complete follow-up via the Kaplan-Meier method followed by a Cox-proportional hazard model (entry method with proportional hazards confirmed by visual inspection) to derive adjusted hazard ratios (HRs) and 95% CIs, with consideration of baseline demographic and clinical profile and extent of LV remodeling during follow-up as independent correlates of all-cause mortality. A 2-sided p value <0.05 was used as minimum level of statistical significance. Statistical analyses were performed using Statistical Package for Social Sciences version 23.0 software (IBM, Armonk, New York).

TABLE 1 Baseline Demographic and Clinical Characteristics (n = 244 PPCM Patients)

Demographic characteristics	
Age, yrs	28.9 ± 7.2
Age <20 yrs	44 (18.0)
Age >35 yrs	42 (17.2)
Parity	2 (1–4)
Multiparity	175 (71.7)
Formal education for ≥6 yrs	158 (64.8)
Unemployed	177 (72.5)
Hausa/Fulani ethnicity	197 (80.7)
Body mass index, kg/m^2	19.9 ± 6.5
Underweight (body mass index <18.5 kg/m^2)	73 (29.9)
Obesity (body mass index ≥30 kg/m^2)	7 (2.9)
Clinical characteristics	
New York Heart Association functional class	
I	72 (29.5)
II	102 (41.8)
III	40 (16.4)
IV	30 (12.3)
Systolic blood pressure, mm Hg	109 ± 17
Diastolic blood pressure, mm Hg	76 ± 15
Hypotension	64 (26.2)
Heart rate, beats/min	100 ± 20
Tachycardia	154 (63.1)
Regular alcohol ingestion	5 (2.0)
Tobacco smoking	3 (1.2)
Customary hot bath	102 (41.8)
Customary salt-enriched pap	65 (26.6)
Comorbidities	
Gestational hypertension	24 (9.8)
Preeclampsia	43 (17.6)
Atrial fibrillation	4 (1.6)
Anemia (plasma hemoglobin <12 g/dl)	104 (61.9)
Pneumonia	13 (5.3)
Stroke	7 (2.9)
Renal impairment (serum creatinine ≥117 μmol/l)	8 (4.2)
Mural thrombus	10 (4.1)
Pulmonary hypertension (pulmonary artery systolic pressure ≥38 mm Hg)	107 (43.9)
Treatments	
Loop diuretics	210 (86.1)
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	85 (34.8)
Beta-blockers	57 (23.4)
Spironolactone	222 (91.0)
Digoxin	163 (66.8)
Warfarin	16 (6.6)

Values are mean ± SD, n (%), or median (interquartile range) or proportions.

FIGURE 2 Recruitment of PPCM Patients



Map of Nigeria displaying recruitment of peripartum cardiomyopathy (PPCM) patients by states and geopolitical zones.

RESULTS

BASELINE CHARACTERISTICS. From June 12, 2017, through March 31, 2018, 262 PPCM patients who had satisfied all of the inclusion criteria from 14 sites in Nigeria were recruited into the registry. With the exception of 18 patients (6.9%) lost to follow-up, the study cohort was followed-up until March 31, 2019. As shown in Figure 1, 223 surviving participants were assessed at 6 months and 199 participants subsequently had a final assessment at the end of median 17 months (IQR: 14 to 20 months) follow-up. The baseline demographic and clinical characteristics of the 244 patients with complete follow-up data are summarized in Table 1. Most participants (199; 81.6%) were recruited from the 3 centers in the city of Kano, North-West Nigeria (Figure 2). The study cohort was characterized by a large degree of persistent/residual PPCM—the median time since the last childbirth was 7 months (IQR: 5 to 10 months), and 46 (18.9%) of them presented within the first 5 months after delivery. A majority (58.2%) of patients were assessed as NYHA functional class II or III (mild-moderate functional impairment) at recruitment, whereas 17.6% were enrolled while hospitalized with acute decompensated HF. The residual portion of patients (72; 27.5%) diagnosed prior to study commencement were asymptomatic at the point of study recruitment. Overall, 190 (72.5%) patients were recruited as newly diagnosed cases of PPCM. The baseline echocardiographic profile of the study cohort is summarized in Table 2.

FOLLOW-UP MANAGEMENT. At the pre-specified 6-month follow-up review (229 participants), prescriptions for either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers had increased from 34.8% (at baseline) to 38.0%. Similarly, prescribed beta-blocker therapy increased from 23.4% at baseline to 50.2%. Information on the specific types of beta-blockers prescribed during the study was available for 188 of the 244 (77.1%) patients. Carvedilol was most commonly prescribed in 188 (52.1%) patients at a daily dose ranging from 3.125

TABLE 2 Pattern of Myocardial Remodeling

	Left Atrium, mm	Indexed LV End-Diastolic Dimension, mm/m²	LVEF, %	Basal Right Ventricular Dimension, mm	TAPSE, mm
Baseline profiling (n = 244)	45.2 ± 6.1	41.8 ± 5.7	30.1 ± 7.4	42.2 ± 7.5	14.8 ± 3.6
6-month profiling (n = 223)	40.6 ± 6.3	39.7 ± 8.1	40.2 ± 13.3	36.8 ± 7.2	15.8 ± 3.3
Δ in mean values (baseline vs. 6-month follow-up)	−4.6 ± 0.2	−2.1 ± 2.4	+10.1 ± 5.9	−5.4 ± 0.3	+1.0 ± 0.3
p value (baseline vs. 6-month follow-up)	<0.001*	0.001*	<0.001*	<0.001*	0.002*
Last profiling (n = 199)	38.1 ± 6.5	37.4 ± 8.3	43.6 ± 13.4	35.3 ± 7.7	17.3 ± 4.0
Δ in mean values (baseline vs. final follow-up)	−7.1 ± 0.4	−4.4 ± 2.6	+13.5 ± 6.0	−6.9 ± 0.2	+2.5 ± 0.4
p value (baseline vs. final follow-up)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

Values are mean ± SD. *p value is statistically significant.
LV = left ventricle; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.

to 25 mg, followed by metoprolol-succinate (37.8%) at a daily dose ranging from 12.5 to 100 mg.

OUTCOMES. Myocardial remodeling. LVRR was observed in 48 of 199 surviving patients (24.1%) and 45 of them (22.6%) recovered LV systolic function. Overall, LV and RV systolic function improved progressively in surviving cases (Table 2, Figure 3). For example, left atrial, indexed LV end-diastolic and RV basal dimensions significantly reduced from 44.5 ± 6.5, 41.8 ± 6.4, and 42.8 ± 8.3 mm at baseline, to 38.3 ± 6.6, 37.3 ± 8.7, and 35.8 ± 8.1 mm at the last follow-up, respectively. LVEF and TAPSE correspondingly increased from 29.6 ± 7.8% and 14.7 ± 4.1 mm at baseline to 43.4 ± 13.5% and 18.0 ± 8.5 mm, respectively.

Independent correlates of LVRR were LVEF <25% at baseline (HR: 0.66; 95% CI: 0.47 to 0.92; p = 0.014) and prescribed beta-blocker therapy at 6 months follow-up (HR: 1.62; 95% CI: 1.17 to 2.25; p = 0.004), after controlling for tachycardia and hypotension at baseline. Several other variables, including the customary birth practices of the Hausa-Fulani ethnic groups of frequent hot bath and use of pap enriched with dried lake salt, were not associated with myocardial remodeling in PPCM patients. No reports of specific customary birth practices were received from other ethnic groups in the country during the study.

Mortality. During median follow-up of 17 months (IQR: 14 to 20 months) and maximal follow-up of 21 months, a total of 45 (18.7%) patients died from any cause (Figure 4). Of these, the primary identified causes of death were worsening HF (17 cases, 37.8%), sudden cardiac death (9 cases, 20.0%; all of which occurred at home), and sepsis (2 cases, 4.4%). Other isolated causes of death such as renal failure were identified in 10 cases (22.2%). Figure 4 presents the Kaplan-Meier survival curves and specific time points of mortality derived from mortality outcomes.

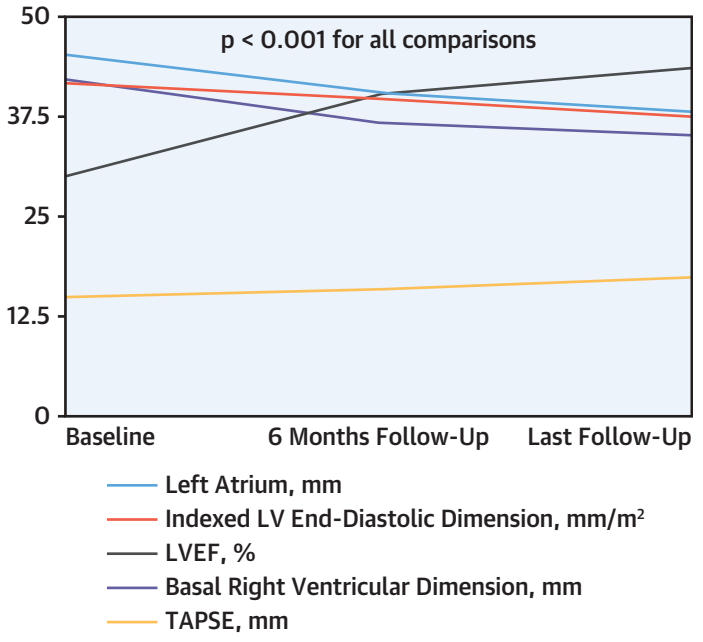
A comparison of the baseline profile of the cohort based on survival status and the independent correlates of all-cause mortality are presented in Table 3. Overall, maternal age below 20 years (HR: 2.40; 95% CI: 1.27 to 4.54), hypotension (HR: 1.87; 95% CI: 1.02 to 3.43), tachycardia (HR: 2.38; 95% CI: 1.05 to 5.43), and LVEF <25% at baseline (HR: 2.11; 95% CI: 1.12 to 3.95) were positively correlated with all-cause mortality. Alternatively, obesity (HR: 0.16; 95% CI: 0.04 to 0.55) and prescribed beta-blocker therapy (HR: 0.20; 95% CI: 0.09 to 0.41) were associated with a reduced risk for mortality.

All-cause rehospitalizations. A total of 18 participants (7.4%) were rehospitalized for various reasons during the study. Of these, 13 (5.3%) were rehospitalized once, whereas the remainder (for a total of 22 all-cause readmissions) were rehospitalized multiple times.

DISCUSSION

In this prospective longitudinal study carried out in 14 tertiary-level hospitals across Nigeria, the clinical profile, myocardial remodeling, and mortality of well-characterized PPCM patients were determined (Central Illustration). To the best of our knowledge, this is the largest PPCM study in Africa and one of the largest in the world. Our observation in respect to the profile of those affected, their subsequent outcomes, and, indeed, the impact of clinical management and LV remodeling, are particularly important when considering the high burden of PPCM in Nigeria and wider sub-Saharan Africa. In this respect, a key feature of the study cohort was the large proportion of women with residual/persistent PPCM (median enrollment being 7 months postpartum and most with severe LV dysfunction) that undoubtedly influenced subsequent clinical outcomes. Accordingly, it is well-established that PPCM is characterized by a high rate of improvement in the first 3 to 6 months, but this

FIGURE 3 Myocardial Remodeling Among Patients



Changes in left atrial, LV, and right ventricular sizes, and in LVEF and tricuspid annular plane systolic excursion, at baseline, 6 months, and final follow-up. LV = left ventricle; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.

predicates the type of early detection and proactive management available in other parts of the world.

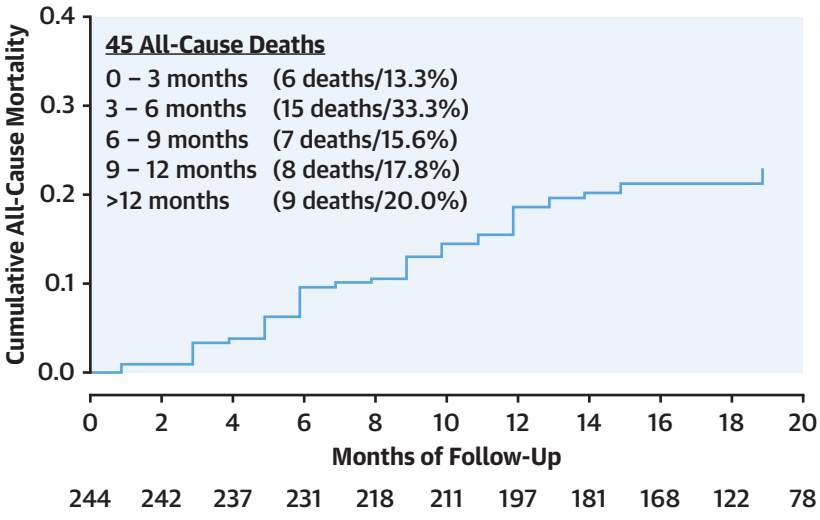
CLINICAL PROFILE OF THE PPCM PATIENTS. The clinical profile of the PEACE registry cohort differs in many respects with those studied in other countries (Table 4) (6-8). Typically, patients were age 20 to 35 years, literate, unemployed, multiparous, with low-normal body weight and of Hausa-Fulani ethnicity. Notably, the majority were "late" referrals for the definitive diagnosis and definitive treatment of PPCM. This implies that the majority of patients had survived the critical first few postpartum months that are associated with relatively higher mortality, using mainly diuretic agents and digoxin, and before the confirmation of diagnosis (2,6,12). More than one-half presented as NYHA functional class II or III, almost two-thirds were tachycardic, and one-quarter were hypotensive. Anemia was also common (in 6 of 10 cases), and preeclampsia was diagnosed in 18% of cases. Alternatively, other comorbidities, including atrial fibrillation and mural thrombus, were uncommon. Given significant differences in study design, variable therapies, and variations in the parameters analyzed (Table 4), it is difficult to directly compare our results with those of other investigators elsewhere (6-8). For example, in a German cohort, 48% of PPCM cases were diagnosed at the time of delivery, and nearly all presented with NYHA functional classes III or IV. However, broadly consistent with the PEACE registry cohort, 3% had gestational hypertension and 13.6% had preeclampsia (8). In a North American cohort, there was a preponderance of early detected (61% of cases) PPCM. However, unlike our own and the German cohort, there was a high prevalence of gestational hypertension (45%) and diabetes mellitus (11%) (7). In a South African cohort, most (82%) PPCM cases presented in NYHA functional class III or IV and 11.1% had LV thrombus (6).

The earliest studies of peripartum HF in northern Nigeria reported more than 40 years ago implicated certain customary birth practices of local Hausa and Fulani ethnic groups in the etiopathogenesis of a type of high-output HF: the postpartum cardiac failure (14,15). The customary birth practices of the Hausa-Fulani, believed to improve the health of new mothers, included regular twice-daily hot baths ("Wankan Jego" in Hausa language), regular ingestion of pap enriched with dry lake salt ("Kunun Kanwa" in Hausa language), and lying on a traditional bed (made of baked clay) that is heated with firewood from beneath, starting from shortly after giving birth and continuing for 3 months (14). However, recent contemporary PPCM studies in Nigeria using standard case definitions have consistently reported that the customary birth practices are not risk factors for PPCM; these earlier conclusions were reinforced by this more definitive study (1,16).

MORTALITY OF THE PPCM PATIENTS. After a median follow-up of 17 months, a high mortality rate of 18.7% was recorded within this vulnerable cohort. As noted, many women were diagnosed late with PPCM because of their lack of recovery/persistent LV dysfunction. This undoubtedly influenced both the observed pattern of myocardial recovery (with potential to improve once properly diagnosed and managed) and the latent risk of mortality in those who had failed to recover within the first 3 to 6 months postpartum. Consequently, most deaths occurred within the first 12 months, with a particularly high rate of mortality between 3- and 6-month follow-up.

On an adjusted basis, maternal age below 20 years, tachycardia, hypotension, and an LVEF <25% at baseline independently increased the risk for mortality each by approximately 2-fold. These variables seem to be markers of disease severity that should be taken into consideration in the prognostication of PPCM patients, particularly when they occur together. On the other hand, regular use of beta-blockers and obesity were independently associated with a reduced

FIGURE 4 Kaplan-Meier Survival Curve



Kaplan-Meier survival curve showing the number of patients at risk of mortality at each month of follow-up.

risk of mortality. The use of other HF medications did not appear to significantly influence survival. However, sacubitril/valsartan, ivabradine, and bromocriptine were not prescribed for any of the patients during the study. Despite this, our results reaffirm the pivotal role of beta-blockers in the long-term management of PPCM patients. Beta-blockers have been shown to reduce mortality and morbidity in symptomatic patients with HF and reduced ejection fraction, and are strongly recommended for treatment of PPCM patients except when contraindicated (17-19). Unfortunately, at recruitment, consistent with a large degree of previously undiagnosed PPCM, only 23.4% and 34.8% of the patients in the present study were prescribed beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, respectively. The suboptimal application of these disease-modifying treatments was most likely due to an interplay of several factors. First, as already noted, the definitive diagnosis of PPCM was delayed for many patients. This likely reflected poor access to specialized care (26.2% of them were hypotensive at presentation), and poor knowledge of some of the medical practitioners on how to treat the disease. Despite some improvements (at 6 months, prescriptions for beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers increased to 50.2% and 38.0%, respectively, among surviving patients), overall treatment patterns remained suboptimal. This mandates stronger efforts to engage medical practitioners and health care teams, particularly those practicing in regions with high PPCM burden, in continuing medical education on how to appropriately recognize and treat PPCM. The better health outcomes associated with PPCM in South Africa, Germany, and North America undoubtedly resulted from more optimal/gold-standard treatments. For example, in the German cohort, 83% received bromocriptine and 25% received HF device treatments; their application probably explains the

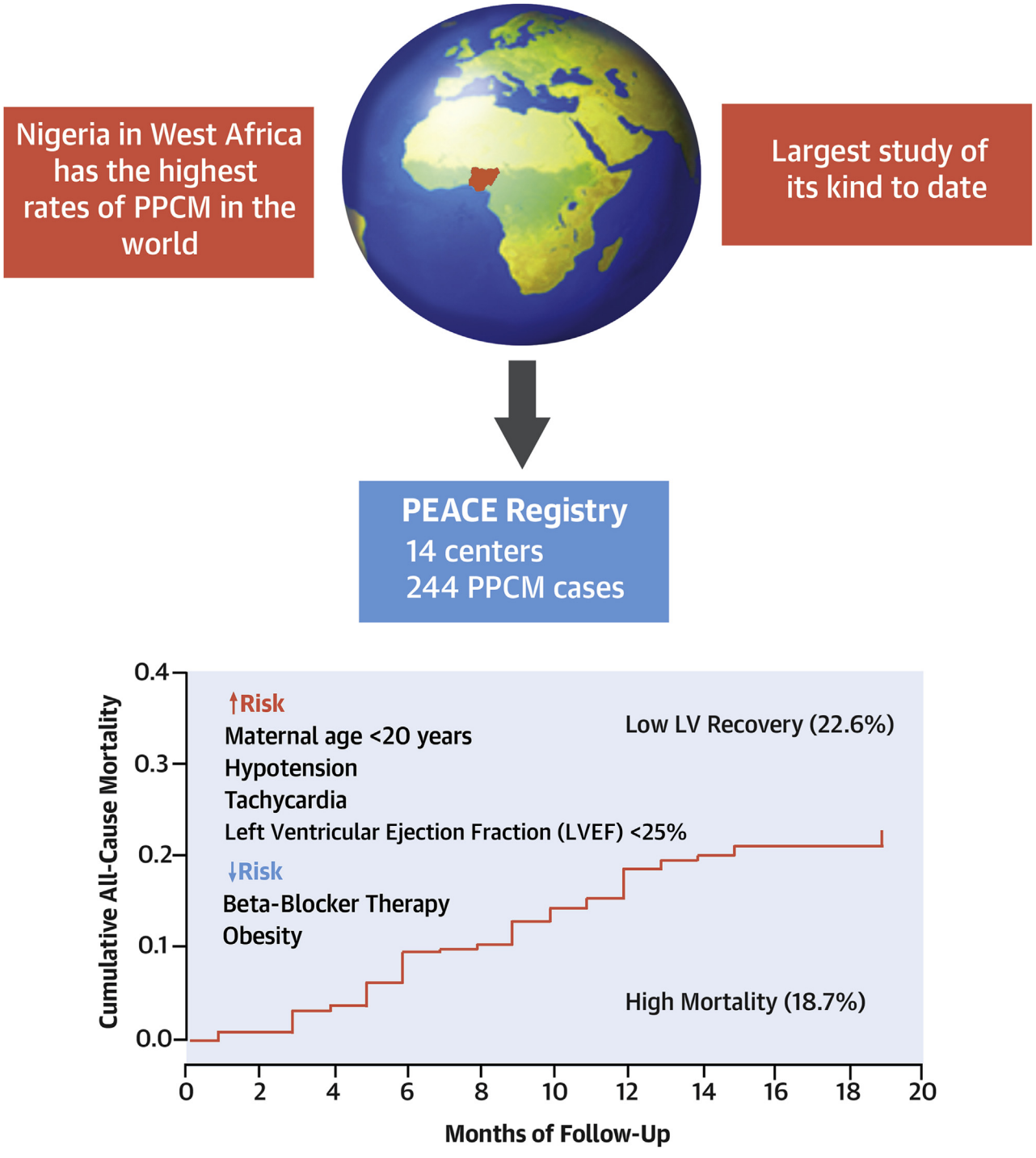
TABLE 3 Correlates of All-Cause Mortality

	Present	Absent	Unadjusted HR (95% CI)	p Values	Adjusted HR (95% CI)	p Values
Age <20 yrs	10/21 (47.6)	35/222 (15.7)	3.44 (1.89-6.24)	<0.001*	2.40 (1.27-4.54)	0.007*
Obesity	3/7 (42.9)	42/237 (17.7)	0.30 (0.09-0.97)	0.045*	0.16 (0.04-0.55)	0.004*
Tachycardia	38/154 (24.7)	7/90 (7.8)	8.76 (2.09-36.68)	0.003*	2.38 (1.05-5.43)	0.038*
Hypotension	19/64 (29.7)	26/180 (14.4)	2.42 (1.34-4.38)	0.043*	1.87 (1.02-3.43)	0.043*
LVEF <25	25/77 (32.5)	20/167 (12.0)	3.12 (1.73-5.61)	<0.001*	2.11 (1.12-3.95)	0.020*
Beta-blockers (6 months)	9/129 (7.0)	36/115 (31.3)	0.17 (0.08-0.36)	<0.001*	0.20 (0.09-0.41)	<0.001*

Values are n/N (%) unless otherwise indicated. Beta-blocker use included in the analyses was censored at 6-month follow-up. Variables used to calculate the adjusted hazard ratios were age <20 years, obesity, tachycardia, hypotension, and LVEF <25% at baseline, and use of beta-blockers at 6 months follow-up. *p value statistically significant.

LV = left ventricle; LVEF = left ventricular ejection fraction.

CENTRAL ILLUSTRATION **Outcomes of Peripartum Cardiomyopathy in Nigeria**



Karaye, K.M. et al. J Am Coll Cardiol. 2020;76(20):2352-64.

Study flow of the PEACE (Peripartum Cardiomyopathy in Nigeria) Registry, with results on mortality rate and its predictors, left ventricular (LV) reverse remodeling, LV full recovery, and its predictors and rehospitalization rate. PPCM = peripartum cardiomyopathy.

relatively low mortality rate (1.5%) and high LV systolic function recovery (95.5%) reported at 5 years (8). The salient point for Nigeria and wider Africa is that increased awareness of PPCM will undoubtedly lead to earlier diagnosis, more proactive treatments, and improved survival rates. How to achieve this in a pragmatic cost-effective way in the low-resource, complex environment of Africa remains the challenge.

In the present study, obesity was independently associated with a substantive reduction in the risk of all-cause mortality. This potentially paradoxical finding is not unprecedented. In an earlier study conducted by Blauwet et al. (6) in South Africa, a similar phenomenon of higher mortality among African PPCM patients with lower as compared with higher body mass index was observed. Although obesity is an important risk factor for cardiovascular disease, a meta-analysis of 9 observational HF studies, in which patients were followed for an average of 2.7 years, demonstrated that compared with patients with normal body mass index, overweight and obese HF patients had reductions in cardiovascular (19% and 40%, respectively) and all-cause (16% and 33%, respectively) mortality (20). Therefore, the relationship between obesity and HF is complex, hence the so-called "obesity paradox."

Because recovery of LV function and mortality occurred in other studies mostly within 6 months after the delivery, the PEACE registry cohort is notable for its recruitment of those who survived the early stages of PPCM but presented with residual LV dysfunction (2,6–8). Whether early mortality associated with PPCM in Nigeria is better or worse than reported here is, therefore, difficult to determine and requires further investigation. The low LV recovery observed in this cohort could also partially reflect the "late" diagnosis of PPCM. It could also be related to the late initiation of definitive medical therapy, which has been noted in African-American women in the United States, and is dissimilar to non-African-American women, in whom recovery often occurs within a few weeks (even before effective therapy can be achieved) (7).

Consistent with potential improvements in therapy, the commonest cause of death was worsening HF, and a further 20% of patients died suddenly, likely due to fatal arrhythmias (although these were uncommon at baseline). Studies of patients with PPCM using wearable cardioverter-defibrillators have demonstrated a high risk for ventricular tachyarrhythmias and sudden death, which tend to be more common in the acute phase of the disease but may occur even after LV functional recovery (21,22). Although the use of wearable cardioverter-defibrillators could be a life-saving treatment strategy, it is unlikely to be adoptable in our low-resource setting given that majority of PPCM patients are poor and unemployed, and would therefore be unable to afford it (1). The high prevalence of sudden deaths relative to the low prevalence of arrhythmias on resting electrocardiograms calls for a management strategy that is adoptable in low-resource settings, such as close monitoring and correction of electrolyte abnormalities including hypokalemia, hypocalcemia, and hypomagnesemia, that could result in life threatening cardiac arrhythmias, improvement in the use of beta-blockers, and a low threshold by physicians for Holter electrocardiography.

TABLE 4 Clinical Profile of PPCM Patients in Various Studies

	Cohorts			
	PEACE, Nigeria	South Africa	IPAC, United States	Germany
Total number of patients	244	141	100	67
Follow-up	17 months	6 months	1 yr	5 yrs
LV systolic function recovery, %	24.1	21	71	95.5
Treatment at baseline, %				
Beta-blockers	23.4	57	88	97
ACE inhibitor or angiotensin II receptor blockers	34.8	80	81	94
Mineralocorticoid receptor antagonists	91	N/A	N/A	83
Digoxin	66.8	64	N/A	6
Bromocriptine	0	N/A	1	83
Intracardiac devices for HF	0	0	2	25.4

Data from Blauwet et al. (6), McNamara et al. (7), and Moulig et al. (8).

ACE = angiotensin-converting enzyme; HF = heart failure. IPAC = Investigations of Pregnancy-Associated Cardiomyopathy; LV = left ventricle; N/A = data not available; PEACE = Peripartum Cardiomyopathy in Nigeria Registry.

MYOCARDIAL REMODELING. Progressive reverse remodeling of all cardiac chambers was observed during the study with significant improvement in both LV and RV systolic function. Unsurprisingly, given the potential for improvement with detection and proactive management, LV full recovery was predicted by regular use of beta-blockers. In addition, the likelihood of full recovery of LV function was reduced by poor LV function (LVEF <25%) at baseline. Our results imply that even patients who present late and did not improve early could still have a high rate of subsequent improvement in LV function. LV function recovery in PPCM patients was previously reported as 29.4% at 1 year in Nigeria, 21% at 6 months of follow-up in South Africa, 28% at 2 years of follow-up in Haiti, 71% at 1 year of follow-up in the United States, and 95.5% at 5 years of follow-up in Germany (**Table 4**) (2,6–8,23). Additional genetic, biomarker, and medication adherence studies would be needed to identify more predictors of poor outcomes and mortality. However, the Investigations

of Pregnancy-Associated Cardiomyopathy registry investigators in the United States found a lower LV function recovery rate (59% vs. 77%; $p = 0.13$) and had a higher prevalence of the TT genotype of guanine nucleotide-binding proteins β-3 subunit (52% vs. 10%; $p < 0.001$), among Blacks compared with Caucasian PPCM patients, respectively (7,24). This TT genotype was associated with lower LVEF at 6 and 12 months in women with PPCM, and this was particularly evident in Blacks (24). In addition, the frequency of angiotensin-converting enzyme-DD genotype (24%) and D allele (44%) were found to be significantly higher in patients with PPCM than in control subjects (4.3% and 17.9%, respectively) in an Indian cohort, and were associated with worse echocardiographic systolic performance indexes (25). These reasons may explain why the disease progression associated with PPCM in patients of African descent appears to be more aggressive with a worse prognosis.

In the present study, we also observed a significant decrease in the left atrial and RV dimensions, with a corresponding increase in the TAPSE, suggesting that PPCM is a multichamber disease, reaffirming previous observations (3,26). None of TAPSE, RV basal dimension, or pulmonary artery systolic pressure assessed in the present was directly correlated with mortality or LV full recovery. However, in another series, reduced RV fractional area change on echocardiogram was found to be an independent predictor of poor outcome, including death and lack of LV recovery during 1-year follow-up (26).

REHOSPITALIZATIONS. The reasons for the unexpectedly low rehospitalization rates observed in this cohort are not yet immediately clear given the high rates of functional impairment and subsequent mortality. However, given that most PPCM patients in Nigeria are unemployed and poor, socioeconomic factors would undoubtedly play a part (1). The total computed cost of care of HF in one of the study sites was estimated 10 years ago to be 319,200 Nigerian Naira ($2,128) per patient per year (27). Unfortunately, the Heart Failure in Africa, Asia, the Middle East and South America study reported that only 33% of HF patients in Africa had health insurance compared with above 75% in China, South America, and the Middle East; therefore, patients mostly have to pay for care out of pocket (28).

STUDY LIMITATIONS. Some study limitations, many of which reflect the challenge of undertaking longitudinal surveillance studies in Africa, need to be considered when interpreting our findings and their broader interpretation. As highlighted, the study cohort was characterized by a predominance of women who had survived the first 3 to 6 months postpartum with PPCM and then enrolled because of them typically presenting with residual LV dysfunction and a high risk for subsequent mortality. Any interpretation of health outcomes and comparisons to other cohorts necessitates consideration of this important caveat. Despite our ability to minimize loss to follow-up, we relied on verbal autopsy to determine the specific causes of death, which was partly necessitated by the widespread cultural rejection of postmortem examinations in Northern Nigeria. We also did not collect some data that would have provided a more in-depth understanding of PPCM and its impact. This included information on breastfeeding practices, mode of delivery, and some important echocardiographic parameters including left atrial volume, RV fractional area change, and LV strain.

CONCLUSIONS

Despite the challenging environment and some important limitations around its interpretation, the PEACE Registry represents the largest study of PPCM in Africa to date. Our key findings (**Central Illustration**) have relevance to the timely detection and gold-standard management of PPCM in wider sub-Saharan Africa and beyond. Overall, we found a high rate of mortality associated with typically late presentations of PPCM in a setting of low myocardial recovery rates. Suboptimal treatment patterns and low rates of hospitalization reflect the limitations (and key targets for strategic interventions) of both the health care system and the socioeconomic resources of affected individuals to affect positive changes to improve poor health outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women in Nigeria exhibit a high incidence of peripartum cardiomyopathy and associated HF, residual LV dysfunction, sudden death, and mortality. Young maternal age, hypotension, tachycardia, and impaired LV function at presentation correlate with higher mortality, whereas obesity and β-blocker therapy correlate with better outcomes.

TRANSLATIONAL OUTLOOK: The results of genetic, biomarker, and medication adherence studies that identify additional predictors of adverse outcomes in women with peripartum cardiomyopathy should be communicated to relevant health agencies to promote preventive strategies.

REFERENCES

1. Karaye KM, Ishaq NA, Sa'idu H, et al., for the PEACE Registry Investigators. Incidence, clinical characteristics and risk factors of peripartum cardiomyopathy in Nigeria: results from the peripartum cardiomyopathy in Nigeria Registry. ESC Heart Fail 2020;7:236–44.

2. Karaye KM, Lindmark K, Henein MY. One-year survival in Nigerians with peripartum cardiomyopathy. Heart Views 2016;17:55–61.

3. Karaye KM, Lindmark K, Henein MY. Right ventricular systolic dysfunction and remodelling in Nigerians with peripartum cardiomyopathy: a longitudinal study. BMC Cardiovasc Disord 2016;16:27.

4. Karaye KM, Lindmark K, Henein MY. Prevalence and predictors of right ventricular diastolic dysfunction in peripartum cardiomyopathy. J Echocardiogr 2017;15:135–40.

5. Yaméogo NV, Samadoulougou AK, Kagambèga LJ, et al. Maternal and fetal prognosis of subsequent pregnancy in black African women with peripartum cardiomyopathy. BMC Cardiovasc Disord 2018;18:119.

6. Blauwet LA, Libhaber E, Forster O, et al. Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. Heart 2013;99:308–13.

7. McNamara DM, Elkayam U, Alharethi R, et al., for the IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy- Associated Cardiomyopathy). J Am Coll Cardiol 2015;66:905–14.

8. Moulig V, Pfeffer TJ, Ricke-Hoch M. Long-term follow-up in peripartum cardiomyopathy patients with contemporary treatment: low mortality, high cardiac recovery, but significant cardiovascular co-morbidities. Eur J Heart Fail 2019;21:1534–42.

9. Liang YD, Xu YW, Li WH, et al. Left ventricular function recovery in peripartum cardiomyopathy: a cardiovascular magnetic resonance study by myocardial T1 and T2 mapping. J Cardiovasc Magn Reson 2020;22:2.

10. Karaye KM, Mohammed IY, Ogah OS, Okeahialam BN. Rationale and design for the Peripartum Cardiomyopathy in Nigeria (PEACE) registry. International Cardiovascular Forum Journal 2017;12:12–7.

11. World Medical Association. Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. J Postgrad Med 2002;48:206–8.

12. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. for the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Eur J Heart Fail 2010;12:767–78.

13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

14. Davidson NM, Trevitt L, Parry EH. Peripartum cardiac failure. An explanation for the observed geographic distribution in Nigeria. Bull World Health Organ 1974;51:203–8.

15. Sanderson JE, Adesanya CO, Anjorin FI, Parry EHO. Postpartum cardiac failure-heart failure due to volume overload? Am Heart J 1979;97:613–21.

16. Karaye KM, Yahaya IA, Lindmark K, Henein MY. Serum selenium and ceruloplasmin in Nigerians with peripartum cardiomyopathy. Int J Mol Sci 2015;16:7644–54.

17. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

18. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.

19. Sliwa K, Petrie MC, Hilfiker-Kleiner D, et al. Long-term prognosis, subsequent pregnancy, contraception and overall management of peripartum cardiomyopathy: practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail 2018;20:951–62.

20. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13–22.

21. Duncker D, Haghikia A, Konig T, et al. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. Eur J Heart Fail 2014;16:1331–6.

22. Duncker D, Konig T, Hohmann S, Bauersachs J, Veltmann C. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator-the PROLONG Study. J Am Heart Assoc 2017;6:e004512.

23. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Proceeds 2005;80:1602–6.

24. Sheppard R, Hsich E, Damp J, et al., for the IPAC Investigators. GNB3 C825T polymorphism and myocardial recovery in peripartum cardiomyopathy: results of the Multicenter Investigations of Pregnancy-Associated Cardiomyopathy study. Circ Heart Fail 2016;9:e002683.

25. Yaqoob I, Tramboo NA, Bhat IA, et al. Insertion/deletion polymorphism of ACE gene in females with peripartum cardiomyopathy: a case-control study. Indian Heart J 2018;70:66–70.

26. Blauwet LA, Delgado-Montero A, Ryo K, et al., for the IPAC Investigators. Right ventricular function in peripartum cardiomyopathy at presentation is associated with subsequent left ventricular recovery and clinical outcomes. Circ Heart Fail 2016;9:e002756.

27. Ogah OS, Stewart S, Onwujekwe OE, et al. Economic burden of heart failure: investigating outpatient and inpatient costs in Abeokuta, Southwest Nigeria. PLoS ONE 2014;9:e113032.

28. Dokainish H, Teo K, Zhu J, for the INTER-CHF Investigators. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Health 2017;5:e665–72.

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