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ORIGINAL RESEARCH ARTICLE

Disparities in clinical features and outcomes of peripartum cardiomyopathy in high versus low prevalent regions in Nigeria

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Abstract

Aims The prospective, multicentre Peripartum Cardiomyopathy in Nigeria (PEACE) registry originally demonstrated a high prevalence of peripartum cardiomyopathy (PPCM) among patients originating from Kano, North-West Nigeria. In a *post hoc* analysis, we sought to determine if this phenomenon was characterized by a differential case profile and outcome among PPCM cases originating elsewhere.

Methods and results Overall, 199 (81.6%) of a total 244 PPCM patients were recruited from three sites in Kano, compared with 45 patients (18.4%) from 11 widely dispersed centres across Nigeria. Presence and extent of ventricular myocardial remodelling during follow-up, relative to baseline status, were assessed by echocardiography. During median 17 months follow-up, Kano patients demonstrated significantly better myocardial reverse remodelling than patients from other sites. Overall, 50.6% of patients from Kano versus 28.6% from other regions were asymptomatic (P = 0.029) at study completion, with an accompanying difference in all-cause mortality (17.6% vs. 22.2% respectively, P = 0.523) not reaching statistical significance. Alternatively, 135/191 (84.9%) of Kano patients had selenium deficiency (<70 μg/L), and 46/135 (34.1%) of them received oral selenium supplementation. Critically, those that received selenium supplementation demonstrated better survival (6.5% vs. 21.2%; P = 0.025), but the supplement did not have significant impact on myocardial remodelling.

Conclusions This study has shown important non-racial regional disparities in the clinical features and outcomes of PPCM patients in Nigeria, that might partly be explained by selenium supplementation.

Keywords Peripartum cardiomyopathy; Regional disparities; Outcomes; Selenium; PEACE registry

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Introduction

Peripartum cardiomyopathy (PPCM) is a disease with an epidemiology that varies widely across countries and regions.[1] For example, incidence rates as low as 1 in 1000 live births in South Africa, 1 in 3189 live births in the USA, and 1 in 20 000 deliveries in Japan have been reported.[2–4] The Peripartum Cardiomyopathy in Nigeria (PEACE) registry, the largest study of its kind, has also recently reported a wide variation in the incidence of PPCM across this populous country in West Africa.[5] Specifically, this national, prospective, multicentre study demonstrated one case of PPCM per 96 deliveries in the city of Kano (an ancient and highly populous city located in North-West Nigeria[6]). This is the highest ever-reported prevalence (globally) of PPCM to date. This contrasted to a low of one case per 2700 deliveries in the city of Makurdi located in North-Central Nigeria. Accordingly, of the 244 consecutively recruited patients with complete follow-up in PEACE registry, most cases were from the three study sites located in Kano. As originally reported, the independent risk factors for PPCM were a lack of formal education, underweight, unemployment status, and pre-eclampsia.[5] However, the very high prevalence of PPCM in North-West Nigeria is of both clinical and public health significance.

Regional and racial disparities in the outcomes of PPCM have also been reported previously. In the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, clinical outcomes were significantly worse in Black women as only 59% achieved left ventricular (LV) function recovery compared with 77% of those with a Caucasian or other background. Moreover, 26% of Black women had an event or demonstrated a final LV ejection fraction (LVEF) of $<$35%, compared with 8% of the rest.[7] Furthermore, based on the European Society of Cardiology (ESC) PPCM registry, comprising cases from 49 countries in Europe, Africa including Nigeria, the Asian Pacific, and the Middle East, Sliwa and colleagues also reported regional differences in PPCM-related mortality.[8] Specifically, they found a much higher death rate in the Middle East compared with other regions.[8] In the original report of the PEACE registry, we also described elevated mortality rates accompanied by low rates of recovery of LV function in Nigeria overall.[9] However, we did not specifically examine if these were driven by key regional differences.

Aims

Given the potentially important disparity in the number of PPCM patients located across Nigeria (with a predominance of cases occurring in the North-West city of Kano), we performed a *post hoc* analysis of the PEACE registry. Specifically, we compared the clinical profile and subsequent outcomes of those PPCM patients recruited in Kano versus the rest of Nigeria. We hypothesized that such an analysis would reveal potentially important insights into the causes and consequences of PPCM in Kano and other regions of the world in which PPCM remains highly prevalent.

Methods

The PEACE registry was a multicentre longitudinal study carried out in 14 sites spread across the geopolitical zones in Nigeria (*Figures 1* and *2*). The Steering Committee of the Registry designed and oversaw the conduct of the study, which was carried out in accordance with a previously reported protocol and statistical analysis plan.[10] The study conformed to the ethical guidelines of the Declaration of Helsinki on the principles for medical research involving human subjects and was approved by the Ethics Committee at each site.[11] The first author, who had unrestricted access to the data, prepared the first draft of the manuscript. All authors made the decision to submit the manuscript for publication and testify to the standard of conduct of the study. This paper is a *post hoc* analysis of PEACE registry data, and the detailed study protocol has already been published but summarized below.[9,10]

Study participants

To be eligible for inclusion, all study participants had to be patients with a confirmed diagnosis of PPCM at any one of the participating sites. PPCM was defined as 'an idiopathic cardiomyopathy presenting with signs or symptoms of heart failure (HF) secondary to LV systolic dysfunction, towards the end of pregnancy or in the early 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 LVEF is reduced below 45%'.[12] In 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 [New York Heart Association (NYHA) functional classes II, III, or IV (for new patients only)], to have LVEF below 45% at enrolment, an age of at least 18 years, and a written informed consent. We also enrolled into the study PPCM patients who were being treated and followed-up at any participating centre before the commencement of the study, regardless of the presence of symptoms, if they had satisfied the other inclusion criteria. We excluded patients who lacked reliable contact phone numbers, to minimize loss to follow-up.

We encouraged the investigators to prescribe standard and routinely available HF drug therapies in Nigeria. These included a diuretic, beta-blocker, angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker or nitrate-hydralazine combination, and a mineralocorticoid receptor antagonist, unless such use was contraindicated or

Figure 1 Map of Nigeria displaying location of study sites. Map of Nigeria illustrating location of study sites and number of recruited patients.

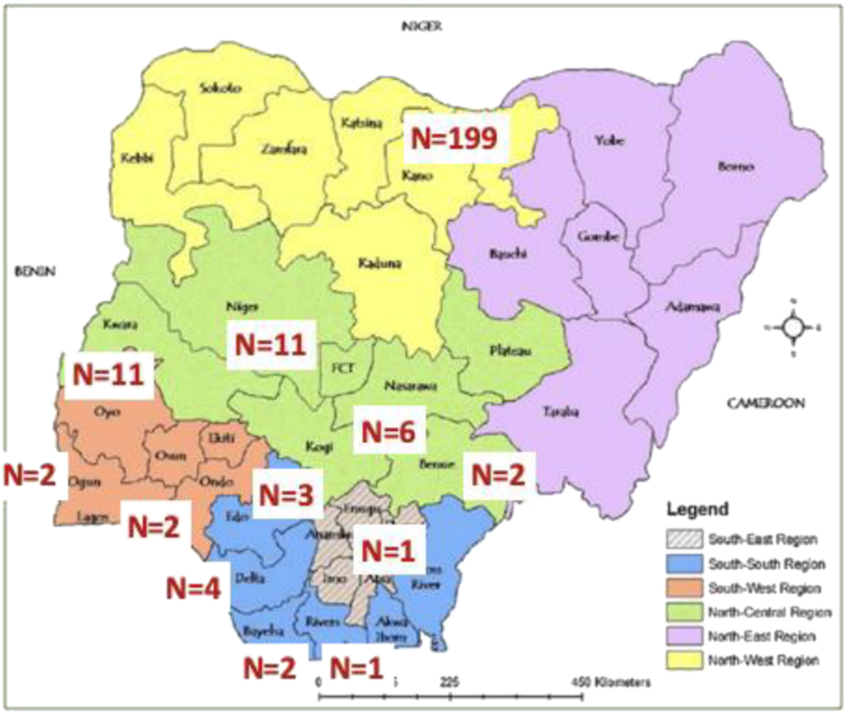
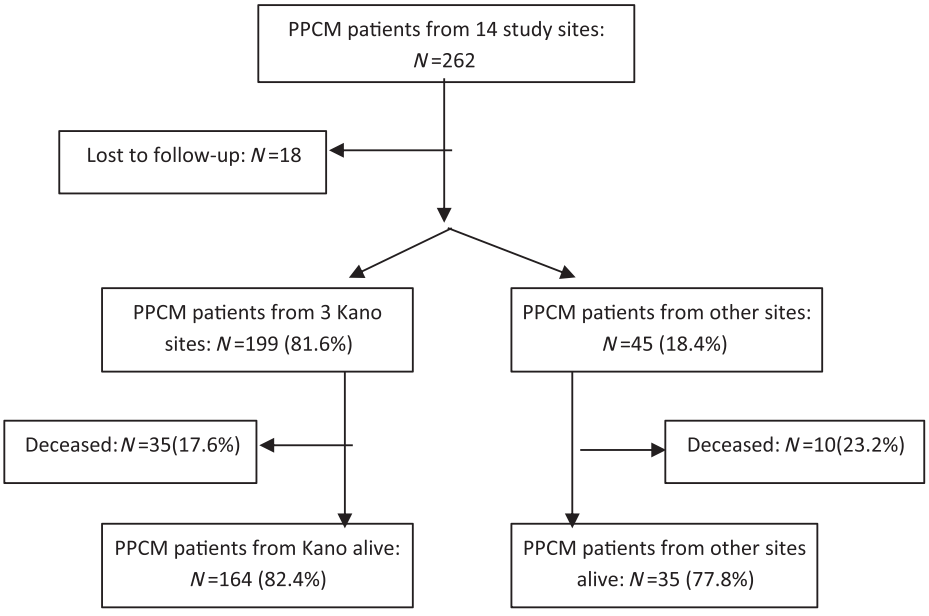


Figure 2 Study flow. PPCM, peripartum cardiomyopathy; *N*, number of patients. PPCM patients recruited from 14 study centres in Nigeria between 12 June 2017 and 31 March 2018. All the patients were reviewed at three monthly intervals till 31 March 2019.



resulted in unacceptable side effects. In addition, drug doses were individually tailored, in accordance with guideline recommendations.[13]

Prevalence of peripartum cardiomyopathy patients in Kano with LVEF <45% at 6 months postpartum were also screened for selenium deficiency (<70 μg/L) and included in the

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Table 1 Baseline characteristics

Variables	Kano sites (N = 199)	Other zones (N = 45)	P-value
Demographic characteristics			
Age, years	29.3 ± 7.7	30.8 ± 8.0	0.013*
Age <20 years	41 (20.6%)	3 (6.7%)	0.031*
Age >30 years	29 (14.6%)	13 (28.9%)	0.03*
Hausa/Fulani ethnicity	195 (98.0%)	2 (4.4%)	<0.001*
Last child birth, months	12 (6–24)	4 (3–9)	0.001*
Twins	41 (20.6%)	2 (4.4%)	0.009*
Multiparity	140 (70.4%)	10 (22.2%)	0.364
Illiteracy	63 (31.7%)	7 (15.6%)	0.043*
Unemployment	152 (76.4%)	25 (55.6%)	0.009*
Clinical characteristics			
NYHA II-IV symptoms	147 (73.9%)	41 (91.1%)	0.011*
Systolic BP, mmHg	109 ± 17	107 ± 17	0.612
Diastolic BP, mmHg	76.2 ± 14	74 ± 16	0.416
Heart rate/min	105 ± 71	99 ± 22	0.359
Body mass index, kg/m^2	20.2 ± 5.2	20.9 ± 8.9	0.500
Preeclampsia	39 (19.6%)	4 (8.9%)	0.125
Pneumonia	9 (4.5%)	4 (8.9%)	0.267
Stroke	7 (3.5)	0	0.355
Atrial fibrillation	3 (1.5%)	1 (2.2%)	0.999
Mural thrombus	1 (0.5%)	2 (4.4%)	0.177

Values are expressed as means ± standard deviations or proportions with percentages in parentheses. NYHA, New York Heart Association functional classes.
*P-value is statistically significant.

Selenium Supplementation Trial, which is a sub-study of the PEACE registry.[14] Patients randomized to the treatment arm in the trial received oral selenium supplementation at a dose of 200 μg/day for 3 months and were included in this *post hoc* analysis.[14] The other study sites in PEACE registry did not participate in the selenium trial.

Outcomes

The clinical outcomes of interest were all-cause mortality, ventricular myocardial remodelling, and the rate of all-cause re-hospitalization during study follow-up. The presence and extent of ventricular myocardial remodelling during follow-up, relative to baseline status, were assessed by determining LV full recovery, significant changes in the size of cardiac chambers, and in tricuspid annular plane systolic excursion (TAPSE) reflective of right ventricular (RV) systolic function. LV full recovery was defined as LVEF ≥55% and RV systolic dysfunction was defined as TAPSE <16 mm, at the last profiling.[15]

To determine the specific causes of death, an independent investigator interviewed the first-degree relatives or attending physicians or reviewed the patient's medical records. Deaths were subsequently categorized as 'unknown' when none of these investigations was successful in identifying a specific causality.

Statistical analysis

Data were cleaned then summarized using standard methods including mean (± standard deviation), median [interquartile range (IQR)] and proportions. Patients were grouped into two (Kano group versus other study sites) and compared for baseline and last profiling characteristics of interest; χ^2, Fisher's exact test, and Student's t and Mann–Whitney tests were used to compare categorical and continuous variables, as appropriate. Mortality (occurring from baseline profiling to end-of-follow-up) was examined in all 244 cases with complete follow-up using 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 (HR) and 95% confidence intervals (CI), as independent correlates of all-cause mortality. Two-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.

Results

A total of 262 PPCM patients from 14 sites in Nigeria who had satisfied the inclusion criteria were consecutively recruited into the registry between 12 June 2017 through 31 March

Table 2 Pharmacologic treatment for HF at recruitment and last follow-up

Heart failure drugs	At recruitment			At last follow-up		
	Kano (N = 199)	Other zones (N = 45)	P-value	Kano (N = 164)	Other zones (N = 35)	P-value
ACE-I or ARB	58 (29.2%)	27 (60.0%)	<0.001*	66 (40.2%)	16 (45.7%)	0.024*
Beta-blockers	44 (22.1%)	13 (28.9%)	0.334	33 (20.1%)	16 (45.7%)	0.004*
Loop diuretics	171 (85.9%)	39 (86.7%)	0.917	59 (35.5%)	17 (48.6%)	0.376
Spironolactone	180 (90.5%)	42 (93.3%)	0.774	77 (47.0%)	19 (54.3%)	0.788
Digoxin	134 (67.3%)	29 (64.4%)	0.664	68 (41.5%)	10 (28.6%)	0.169
Warfarin	5 (2.5%)	11 (24.4%)	<0.001*	0	2 (5.7%)	0.060
Antiplatelets	55 (27.6%)	6 (13.3%)	0.045*	0	2 (5.7%)	0.060

Values are expressed as proportions with percentages in parentheses. ACEI-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
*P-value is statistically significant.

2018. The study cohort was followed-up until 31 March 2019 [median of 17 (IQR 14–20) months], except 18 patients (6.9%) who were lost to follow-up, as shown in *Figure 2*. Of the 244 participants with complete follow-up, 199 (81.6%) were recruited from the three study centres in Kano City, North-West Nigeria, while the remaining 45 (18.4%) were recruited from the North-Central (19; 7.8%), South-West (15; 6.2%), South-South (10; 4.1%), and South-East (1; 0.4%) geopolitical zones as shown in *Figure 1*. The baseline demographic and clinical characteristics of the patients in the two groups are summarized and compared in *Table 1*. This table shows that patients from Kano were younger, presented to the study sites later since last childbirth and were less symptomatic than those from the other sites, at presentation. Stroke was exclusively found among 3.5% of patients in Kano, while atrial fibrillation and mural thrombus were uncommon in both groups.

Table 2 shows the pattern of HF treatment within the two groups. Kano patients received less angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) and beta-blockers during the study, than those from other sites. A high proportion (>85%) of patients in both groups received a loop-diuretic; with one additional patient in Kano receiving bendrofluazide 2.5 mg once daily. Overall, 163 (66.8%) patients also received digoxin in the study; most of them (149; 91.4%) at the dose of 0.125 mg daily. At presentation, warfarin use was more common among patients from other regions (24.4%) compared with those from Kano (2.5%) ($P < 0.001$). A reverse pattern of antiplatelet treatments (aspirin or clopidogrel) (27.6% for Kano vs. 13.3% rest; $P = 0.045$) was observed. In addition, 135 (84.9%) of 191 PPCM patients in Kano with LVEF <45% at 6 months postpartum had selenium deficiency (<70 μg/L). Of these, 46 (34.1%) received oral selenium supplementation at a dose of 200 μg/day for 3 months.

Table 3 and *Figure* 3 shows that Kano patients had larger cardiac chambers and worse right heart function at enrolment. However, they showed greater reverse remodelling of all cardiac chambers than patients from the other zones. These observations were independent of the selenium supplementation as shown in *Table 4*.

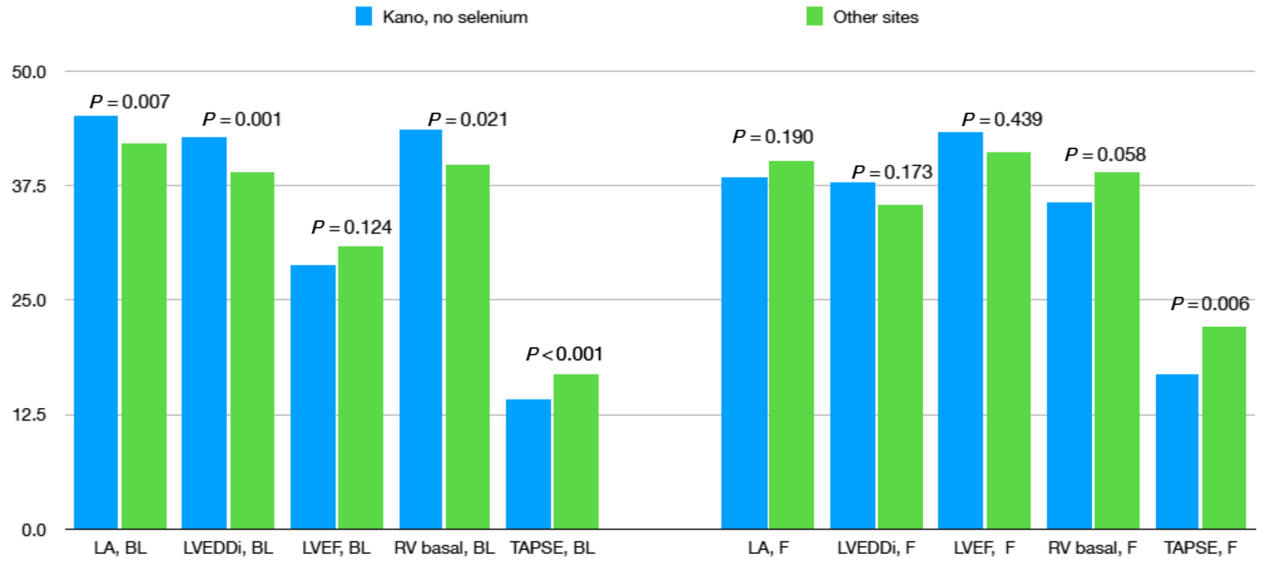
The main study outcomes are summarized in *Table 5*, and the pattern of mortality pattern is illustrated in the Kaplan–Meier curve (*P*-value = 0.180) in *Figure 4*. *Figure 5* shows that worsening HF was the commonest known cause of death in the two groups followed by sudden death. Alternatively, the exact causes of 40% of deaths in the other regions were unknown. In addition, mortality [3/46 (6.5%) vs. 42/198 (21.2%); $P = 0.025$] (*Table 4*) and HF symptoms at the last profiling [18/46 (39.1%) vs. 133/198 (67.2%); $P < 0.001$] were significantly less in the group that received selenium supplementation as compared with the remaining patients. Further analysis shows that 83 of 164 (50.6%) patients from Kano and 10 of 35 (28.6%) from other zones were

Table 3 Myocardial remodelling

Variables	Baseline			Last profiling			P-value (baseline vs. last profiling)	
	Kano	Other zones	*P*-value	Kano	Other zones	*P*-value	Kano	Other zones
LA dimension, mm	45.0 ± 6.0	42.0 ± 8.3	0.005*	38.0 ± 6.2	40.1 ± 8.1	0.092	<0.001*	0.307
Indexed LV end-diastolic dimension, mm/m^2	42.4 ± 5.9	38.9 ± 7.8	0.001*	37.7 ± 8.4	35.3 ± 10.2	0.236	<0.001*	0.088
LVEF, %	29.3 ± 7.7	30.8 ± 8.0	0.223	43.9 ± 13.3	41.1 ± 14.3	0.297	<0.001*	<0.001*
RV end-diastolic dimension, mm	43.3 ± 7.6	39.7 ± 11.3	0.024*	35.3 ± 7.5	39.0 ± 10.3	0.023*	<0.001*	0.773
Tricuspid annular plane systolic excursion, mm	14.2 ± 3.6	16.9 ± 5.8	<0.001*	17.2 ± 3.7	22.1 ± 19.4	0.003*	<0.001*	0.092
Pulmonary artery systolic pressure, mmHg	48.1 ± 22.7	37.8 ± 18.1	0.022*	36.2 ± 27.3	24.4 ± 16.5	0.096	<0.001*	<0.001*

Values are expressed as means ± standard deviations. LA, left atrial dimension; LV, left ventricle; LVEF, left ventricular ejection fraction.
*P-value is statistically significant.

Figure 3 Myocardial remodelling among PPCM patients in Kano versus other zones. Mean sizes of cardiac chambers and indices of ventricular systolic function among PPCM patients in Kano versus other zones at baseline (BL) and final profiling (F). LA, left atrial dimension; LVEDDi, left ventricular end-diastolic dimension indexed to body surface area; LVEF, left ventricular ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic dimension; *P-value is statistically significant. Values are expressed as means.



asymptomatic ($P = 0.029$) at the completion of the study. The asymptomatic patients (NYHA I) had significantly higher mean LVEF (48.6 ± 11.9%) than those with NYHA II to IV (39.3 ± 13.3%) ($P < 0.001$).

The result of the Cox proportional hazard regression model for mortality is presented in *Table 6*. It shows that being from Kano, younger by 0.2 years at recruitment, and regular use of beta-blockers censored at the sixth follow-up month were all significantly associated with lower mortality, while regular use of digoxin censored at the sixth follow-up month was associated with higher mortality, after accounting for time since last childbirth, and use of ACE-I or an ARB and spironolactone at the sixth month of follow-up.

Discussion

In this multicentre longitudinal study spread across the geopolitical zones in Nigeria, 81.6% of the patients were consecutively recruited from the three study centres in the North-Western Nigerian City of Kano. We conducted a *post hoc* analysis based on patient origin to determine if the high prevalence of PPCM in Kano was characterized by a differential case profile and outcomes.

Our results showed that as compared with patients from other geopolitical zones, those from Kano presented to the study centres for confirmation of diagnosis and initiation of appropriate treatments later since last childbirth, had larger cardiac chambers, worse LV and RV systolic function, and received less HF medical therapy, at recruitment. However, about one-quarter of the Kano patients also received a selenium supplement for 3 months, which seemed to be associated with 3.3-fold lower prevalence of mortality. However, the selenium supplement did not appear to have impact on reverse remodelling of cardiac chambers. These findings need to be interpreted with some caution given the fact that they were derived from a *post hoc* analysis of an observational study.

Overall, patients from Kano were less symptomatic throughout the study and appeared to significantly have better positive reverse remodelling of both the sizes and function of cardiac chambers than those from the other regions. Although the reasons for the latter findings are not yet clear, they seem to be unrelated to the selenium supplementation as illustrated by our limited analyses of the cohorts with and without selenium supplementation. For whatever reasons, PPCM patients from Kano seemed to have the typical PPCM syndrome, which is characterized by significant though variable positive myocardial reverse remodelling. LV function recovery in PPCM patients, that was variably defined, was previously reported as 29.4% at 1 year in Nigeria, 71% in the USA, 21% at 6 months in South Africa, 28% at 2 years in Haiti, and 95.5% at 5 years in Germany, of follow-up, respectively.[7,16–19] Consistent with the absence of focal myocardial damage on late gadolinium enhancement imaging, most PPCM patients are expected to exhibit significant improvements in LV and RV systolic function with favourable changes in LV and RV mass and volumes.[20,21] As previously observed, significant myocardial function recovery in PPCM patients occurs even when HF treatment is suboptimal.[9,16]

Table 4 Baseline characteristics and main outcomes of PPCM patients stratified according to use of selenium supplement

Variables	Selenium supplement (N = 46)	No selenium, all sites (N = 198)	P-value	Kano, no selenium (N = 153)	Other zones (N = 45)	P-value
Demographic characteristics						
Age, years	29.6 ± 7.3	28.7 ± 7.2	0.882	31.3 ± 6.5	30.8 ± 8.0	0.006
Age <20 years	6 (13.0%)	3 (6.7%)	0.329	35 (22.9%)	3 (6.7%)	0.017*
Age >30 years	7 (15.2%)	13 (28.9%)	0.662	22 (14.4%)	13 (28.9%)	0.028*
Last child birth <5 months	7 (15.2%)	39 (19.7%)	0.728	25 (16.3%)	14 (31.1%)	0.001*
Multiparity	31 (67.4%)	144 (72.7%%)	0.469	109 (71.2%)	10 (22.2%)	0.387
Unemployment	14 (30.4%)	53 (26.8%)	0.616	120 (78.4%)	25 (55.6%)	0.002*
Clinical characteristics						
NYHA II-IV symptoms	31 (67.4%)	157 (79.3%)	0.084	116 (75.8%)	41 (91.1%)	0.035%
Systolic BP, mmHg	108 ± 16	109 ± 17	0.919	109 ± 17	107 ± 17	0.543
Diastolic BP, mmHg	74 ± 12	76 ± 15	0.609	77 ± 15	74 ± 16	0.269
Heart rate/min	96 ± 18	106 ± 70	0.671	102 ± 18	99 ± 22	0.881
Body mass index, kg/m^2	19.8 ± 6.4	20.5 ± 5.9	0.582	19.9 ± 5.6	20.9 ± 8.9	0.549
Preeclampsia	13 (28.3%)	30 (15.2%)	0.037*	26 (17.0)	4 (8.9%)	0.241
Pneumonia	3 (6.5%)	10 (5.1%)	0.716	6 (3.9%)	4 (8.9%)	0.239
Stroke	3 (6.5%)	4 (2.0%)	0.126	4 (2.6%)	0	0.576
Atrial fibrillation	0	4 (2.0%)	0.862	3 (2.0%)	1 (2.2%)	0.999
Treatment						
Beta-blockers	11 (23.9%)	104 (52.5%)	0.001*	35 (22.9%)	13 (28.9%)	0.408
ACE-I or ARB	24 (52.2%)	54 (27.3%)	0.026*	47 (30.7%)	27 (60.0%)	<0.001*
Digoxin	33 (71.7%)	84 (42.2%)	0.359	101 (66.0%)	29 (64.4%)	0.803
Spironolactone	38 (82.6%)	99 (50.0%)	0.304	138 (90.2%)	42 (93.3%)	0.769
Echocardiography						
LA dimension, mm	45.1 ± 6.5	44.4 ± 6.5	0.907	45.0 ± 5.8	42.0 ± 8.3	0.007*
Indexed LV end-diastolic dimension, mm/m^2	41.6 ± 5.6	41.8 ± 6.6	0.310	42.7 ± 6.0	38.9 ± 7.8	0.001*
LVEF, %	30.9 ± 7.1	29.1 ± 7.9	0.345	28.8 ± 7.8	30.8 ± 8.0	0.124
RV end-diastolic dimension, mm	42.7 ± 7.9	42.9 ± 8.4	0.771	43.5 ± 7.5	39.7 ± 11.3	0.021*
Tricuspid annular plane systolic excursion, mm	14.1 ± 3.7	14.8 ± 4.3	0.364	14.2 ± 3.6	16.9 ± 5.8	<0.001*
Pulmonary artery systolic pressure, mmHg	42.8 ± 19.0	47.5 ± 23.0	0.432	49.8 ± 2.1	37.8 ± 18.1	0.011*
Outcomes						
All-cause mortality	3 (6.5%)	42 (21.2%)	0.025*	32 (20.9%)	10 (22.2%)	0.850
All-cause rehospitalization	3 (6.5%)	13 (6.6%)	0.999	13 (8.5%)	13 (28.9%)	<0.001*
LVEF ≥55%	33 (71.7%)	124 (62.6%)	0.422	97 (63.4%)	27 (60%)	0.653

Values are expressed as means ± standard deviations or proportions with percentages in parentheses. BP, blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classes.
*P-value is statistically significant.

Table 5 Study outcomes

Variables	Kano sites (N = 199)	Other zones (N = 45)	P-value
All-cause mortality	35 (17.6%)	10 (22.2%)	0.523
All-cause rehospitalization	17 (8.5%)	0	0.055
LVEF ≥55%	39 (23.8%)	6 (17.1%)	0.394

Values are expressed as proportions with percentages in parentheses. LVEF, left ventricular ejection fraction.

In the present study, the proportion of specific causes of deaths due to worsening HF and sudden deaths were similar in the two groups, although the proportion of unknown causes of deaths was lower in Kano than the other study sites, perhaps due to a more meticulous data collection. The factors independently associated with reduced risk of mortality in this study included Kano residency, a unit change in age, and regular use of beta-blockers at the sixth follow-up month. The effect of beta-blockers seems to persist as an independent correlate of mortality in our PEACE registry cohort regardless of the Cox proportional hazard regression model.[9] However, the reduction in the risk of all-cause mortality by 97% among the PPCM patients simply by Kano residency, who correspondingly have a significantly better myocardial recovery, is an important novel finding that needs further elucidation.

Although the reasons behind the regional variations associated with PPCM are not yet clear, it seems sensible to hypothesize that they are caused by an interplay between environmental and genetic factors. A key environmental factor in PPCM could be selenium deficiency, which was recently found in up to 85% of PPCM patients in Kano, and associated with 3.3-fold lower prevalence of mortality. In the first-ever Selenium Supplementation Trial in PPCM however, we showed that a 3 month course of selenium supplementation significantly reduced HF symptoms, with a positive trend towards survival benefit but without significant impact on myocardial reverse remodelling.[14] In contrast, selenium deficiency was found in only 22% of apparently healthy puerperal women in Kano.[22] Another possibility is a genetic factor with racial significance such as the TT genotype of guanine nucleotide–binding proteins β-3 subunit.[23] This TT genotype was associated with lower LVEF at 6 and 12 months in women with PPCM, that was particularly evident in Blacks, but has not yet been assessed in Nigerian PPCM patients.[23] Thus, it seems reasonable to suggest that the PPCM syndrome in Kano, and by extension North-West Nigeria (given the similar PPCM incidence rate), is different from that of the other zones in the country.[5] These findings further support the notion that PPCM is a heterogeneous disease, with intra- and inter-regional epidemiological variations.

In our cohort, more than 60% of the patients were receiving digoxin while less than 30% were receiving beta-blockers at presentation to the referral study centres, although the frequency of atrial fibrillation was low, and therefore, the prescription pattern was not clearly in conformity with standard HF treatment guidelines.[18,24,25] The prescription pattern improved at the last profiling, though sub-optimally, while the patients received care at the study centres. The serum levels of digoxin were not routinely monitored in PEACE registry although nearly all patients on digoxin received the low daily dose of 0.125 mg. Our result on the relationship between

Figure 4 Kaplan–Meier survival curves. Number of patients at risk of mortality. Kaplan–Meier survival curves showing patients at risk of mortality at each month of follow-up in Kano and other study sites.

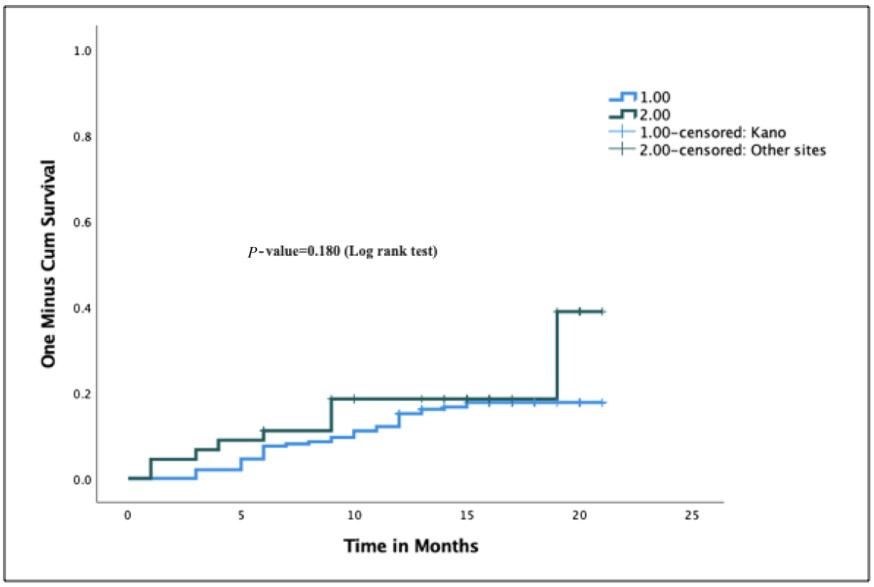


Figure 5 Causes of deaths among PPCM patients by zones in Nigeria. Pie charts showing the specific causes of deaths in Kano and other study sites.

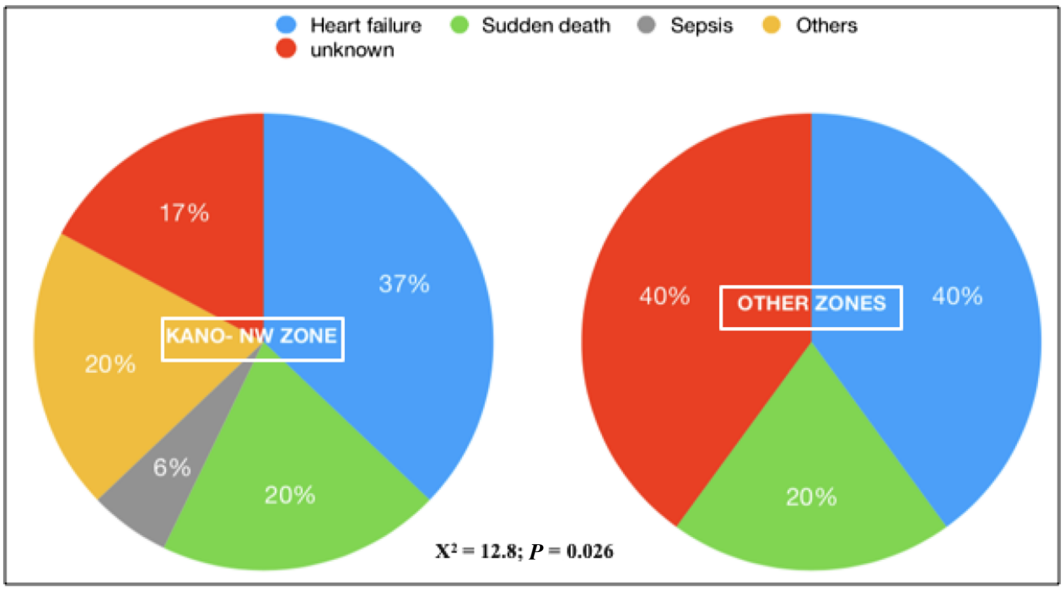


Table 6 Correlates of mortality

Variables	Adjusted hazard ratios	95% confidence intervals	*P*-value
Age, years	0.82	0.71–0.95	0.010*
Kano versus other zones	0.03	0.00–0.36	0.006*
Time since LCB, months	0.97	0.90–1.04	0.437
Beta-blockers, 6 months	0.13	0.03–0.54	0.005*
ACE-I/ARB, 6 months	0.96	0.26–3.60	0.955
Spironolactone, 6 months	3.27	0.30–35.67	0.331
Digoxin, 6 months	10.07	1.33–76.41	0.026*

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; LCB, last childbirth.
**P*-value statistically significant.

digoxin and mortality should be interpreted with caution because it was derived from a *post hoc* analysis of an observational study. The expert panel on the management of PPCM of the Heart Failure Association of the European Society of Cardiology (ESC) and the Task Force on HF of the ESC both recommend that digoxin may be considered in patients in sinus rhythm with symptomatic HF with reduced EF, to reduce the risk of both all-cause and HF hospitalizations, mainly based on the results of the DIG (Digitalis Investigation Group) trial.[18,24,25] Furthermore, a *post hoc* analysis of the DIG trial showed that digoxin therapy was associated with a 23% increase in the relative risk (absolute difference of 5.8%) of death from any cause among women, but not men, with HF and depressed LV systolic function.[26] However, another *post hoc* analysis of the DIG trial then showed a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/mL, whereas serum concentrations ≥1.2 ng/mL seemed to be harmful.[27]

For several logistical reasons, patients in the PEACE registry cohort were sub-optimally managed with guidelines-recommended HF medications, which are associated with improved clinical outcomes.[13] In addition, none of the patients received bromocriptine or any device therapy for HF. On the contrary, at the time of diagnosis, 76% of PPCM patients in a German PPCM cohort were on a combination of a beta-blocker, an angiotensin converting enzyme inhibitor or angiotensin-receptor blockers and a mineralocorticoid receptor antagonist, 83% received bromocriptine and 25% received HF device treatment; their usage probably explains the relatively low mortality rate (1.5%) and high LV systolic function recovery (95.5%) reported at 5 years.[18]

Stroke was exclusively found in up to 3.5% of the patients in Kano at presentation, in spite of the fact that there were no significant between-group differences for the frequency of atrial fibrillation and mural thrombi. This finding might be explained by the more frequent use of prophylactic warfarin in the other zones than Kano (24.4% vs. 2.5%) at presentation, which is recommended for treatment of PPCM in the context of poor LV function (LVEF <35%) during or immediately after pregnancy.[12,13]

Limitations

It is important to emphasize the *post hoc* nature of our analyses and the overall pragmatic design of the PEACE registry; given the study location and the inherent difficulties in optimally diagnosing and treating PPCM on the African continent. Accordingly, although it is desirable to collect

genetic, serum selenium, and other relevant biomarkers that could explore the regional differences between study participants, due to prohibiting logistical reasons, these were beyond the scope of the original PEACE registry. We hope to address these and other important limitations in future studies.

Conclusions

This study confirms the existence of a significant non-racial regional variation in the epidemiology of PPCM in Nigeria. About one-quarter of the PPCM patients from Kano received selenium supplementation. Pending confirmation from definitive studies, it appears probable that such therapy contributed to their significantly better survival than those from the other geopolitical zones. However, PPCM patients from Kano also had significantly better myocardial remodelling than those from the other geopolitical zones that was independent of the selenium supplementation. This important finding also merits further investigation.

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