Original Article

Influence of Systolic Blood Pressure on Outcomes in Nigerians with **Peripartum Cardiomyopathy**

H Sa'idu^{1,2}, SA Balarabe³, NA Ishaq⁴, UG Adamu⁵, IY Mohammed⁶, I Oboirien⁷, EM Umuerri⁸, AC Mankwe⁹, VY Shidali¹⁰, P Njoku¹¹, S Dodiyi-Manuel¹², T Olunuga¹³, V Josephs¹⁴, AC Mbakwem¹⁵, H Okolie¹⁶, MA Talle¹⁷, MS Isa¹⁸, RA Adebayo¹⁹, J Tukur¹, SA Isezuo²⁰, H Umar²⁰, MN Shehu²¹, OS Ogah^{22,23}, KM Karaye^{1,4,24,25}; on behalf of PEACE Registry Investigators

¹Department of Medicine, Bayero University, Kano, 2Department of Medicine, Murtala Mohammed Specialist Hospital, Kano, ³Department of Medicine, Muhammad Abdullahi Wase Specialist Hospital, Kano, ⁴Department of Medicine, Aminu Kano Teaching Hospital, Kano, 5Department of Medicine, Federal Medical Center Bidda, Bidda, 6Department of Chemical Pathology, Bayero University/Aminu Kano Teaching Hospital, Kano, ⁷Department of Medicine, Dalhatu Araf Specialist Hospital, Lafia, ⁸Department of Medicine, Delta State University Teaching Hospital, Oghara, 9Department of Medicine, Federal Medical Center Yenagoa, Yenagoa, 10Department of Medicine, Federal Medical Center Keffi, Keffi, 11Department of Medicine, University of Nigeria Teaching Hospital, Enugu, 12Department of Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, 13Department of Medicine, Federal Medical Center Abeokuta, Abeokuta, ¹⁴Department of Medicine, University of Benin Teaching Hospital, Benin, ¹⁵Department of Medicine, University of Lagos Teaching Hospital, Lagos, ¹⁶Department of Medicine, Federal Teaching Hospital, Gombe, 17Department of Medicine, University of Maiduguri Teaching Hospital, Maiduguri, 18Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, 19Department of Medicine, Obafemi Awolowo University Teaching Hospital, Ile-Ife, ²⁰Department of Medicine, Usman Danfodio University Teaching Hospital, Sokoto, ²¹Department of

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Background: The relationship between blood pressure (BP) trajectories and outcomes in patients with peripartum cardiomyopathy (PPCM) is not clear. Aim: The study aimed to assess the clinical features and outcomes (all-cause mortality and unrecovered left ventricular [LV] systolic function) of PPCM patients grouped according to their baseline systolic BP (SBP). Patients and Methods: PPCM patients presenting to 14 tertiary hospitals in Nigeria were consecutively recruited between June 2017 and March 2018 and then followed up till March 2019. SBP at first presentation was used to categorize the patients into seven groups: <90, 90–99, $100-109, 110-119, 120-129, 130-139, and \ge 140 \text{ mmHg}$. Unrecovered LV systolic function was defined as echocardiographic LV ejection fraction (LVEF) below 55% at the last profiling. Results: Two hundred and twenty-seven patients were recruited and followed up for a median of 18 months. Of these, 4.0% had <90 mmHg, 16.3% had 90-99 mmHg, 24.7% had 100-109 mmHg, 24.7% had 110-119 mmHg, 18.5% had 120–129 mmHg, 7.5% had 130–139 mmHg, and 4.4% had ≥140 mmHg of SBP at presentation. The highest frequency of all-cause mortality was recorded among patients with SBP $\leq 90 \text{ mmHg}$ (30.8%) followed by those with 90–99 mmHg (20.5%) (P = 0.076), while unrecovered LV systolic function did not differ significantly between the groups (P = 0.659). In a Cox proportional regression model for all-cause mortality, SBP <90 mmHg had a hazard ratio (HR) of 4.00 (95% confidence interval [CI] 1.49–10.78, P = 0.006), LVEF had an HR of 0.94 (95% CI 0.91–0.98, P = 0.003, B = 0.06%), and use of angiotensin-converting enzyme or angiotensin receptor and/or β -receptor blockers had an HR of 1.71 (95% CI 0.93-3.16, P = 0.085). However, SBP was not associated with LV function recovery. Conclusion: In our cohort of PPCM patients, one-fifth was hypotensive at presentation. SBP <90 mmHg at presentation was associated with a four-fold higher risk of all-cause mortality during a median follow-up of 18 months.

KEYWORDS: Blood pressure, outcomes, PEACE registry, peripartum cardiomyopathy

Medicine, General Ahmadi Kurfi Specialist Hospital, Katsina, 22Department of Medicine, University College Hospital, Ibadan, ²³Institute of Advanced Medical Research and Training, University of Ibadan, Nigeria, ²⁴Department of Public Health and Clinical Medicine, Umea University, Umea, Sweden, ²⁵Hatter Institute for Cardiovascular Research in Africa, Capetown, South Africa

> Address for correspondence: Dr. H Sa'idu, Department of Medicine, Bayero University/Murtala Muhammed Specialist Hospital, Kano, Nigeria. E-mail: hsaidu2006@yahoo.com

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INTRODUCTION

Deripartum cardiomyopathy (PPCM) is an important cause of heart failure (HF) with reduced left ventricular ejection fraction (LVEF) that exclusively affects women without preexisting heart disease toward the end of pregnancy or in the first few months after delivery.^[1] It is a global disease with epidemiology that varies widely. However, hospital-based studies have suggested its prevalence to be highest in North-West Nigeria, with significant morbidity and mortality, as clearly demonstrated in the Peripartum Cardiomyopathy in Nigeria (PEACE) Registry.^[2] The highest ever reported incidence rate of 1:96 live births was from Kano, Nigeria, but previous studies in Nigeria had similarly reported an incidence of 1:102 live births and a prevalence of 4.2% of all patients referred for echocardiography, representing 52.4% of all cardiomyopathies.^[3,4]

Blood pressure (BP) is reported to have an inverse relationship with worse outcomes in patients with acute or chronic HF.^[5-8] Among patients hospitalized for HF with varying etiologies, higher BP at presentation was significantly associated with a lower risk of dving.^[4-7] Several studies had further described the association between levels of systolic BP (SBP) to short-and long-term mortality in HF patients, exploring varying cutoffs from <90 to 160 mmHg.^[9-13] The prognostic influence of high BP on mortality was also found to be consistent across age, gender, and race groups.^[6-9] The Japanese Nationwide survey of PPCM has also demonstrated the effect of the interaction between LVEF and BP on mortality.^[14] Patients with PPCM complicated by hypertensive disorders in pregnancy were older, hospitalized for a shorter duration of time, and had better cardiac function at 7 months.[14] The investigators concluded that hypertensive disorders in pregnancy were independently associated with a shorter hospital stay and a higher LVEF at the last follow-up.^[14]

In PEACE registry, prescriptions for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (51%) and β -blockers (BBs; 24.4%), which are disease-modifying agents, were clearly poor.^[15] Although this was perceived to be due to several factors such as poor health-care financing and delayed diagnosis, patient-specific variables including low BP were also considered to be important.

To the best of our knowledge, there is paucity of data on the relationship between BP trajectories and outcomes in patients with PPCM. The present study, therefore, aimed

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to assess the clinical features and outcomes of PPCM patients grouped according to their baseline SBP.

MATERIALS AND METHODS

PEACE Registry was a multicenter longitudinal study carried out in 14 sites spread across the geopolitical zones in Nigeria. This paper is a post hoc analysis of the PEACE Registry data, and the detailed study protocol and main results have already been published, but are summarized below.^[2,15-17]

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. All PPCM patients presenting to the study centers between June 2017 and March 2018 were consecutively recruited after they satisfied the inclusion criteria and were followed up till March 2019. Preexisting PPCM patients who were being followed up at any of the study were also recruited regardless of the presence of symptoms, if they had satisfied other inclusion criteria. Patients who lacked reliable phone numbers were excluded to minimize the loss to follow-up.

To be included in this study, patients were required to have developed HF symptoms (New York Heart Association [NYHA] functional classes II, III, or IV) 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, and to provide written informed consent. Ethical approval for the study was obtained from the ethical research committees of the participating centers before commencement of the study. The study conformed to the ethical guidelines of the Declaration of Helsinki on the principles of medical research on human subjects.^[18]

A pretested questionnaire was used to collect demographic, clinical, and laboratory data of the patients. The prescribed HF drug therapies and dosages were also documented. These included loop diuretics, mineralocorticoid receptor antagonists (MRAs), BBs, ACEIs, ARBs, hydralazine–isosorbide combination, and digoxin.

BP was measured either by auscultation of the Korotkoff sounds using mercury sphygmomanometer or using validated oscillometric BP measuring devices and following all other protocols in accordance with the recommendations of the European Society of Hypertension.^[19] SBP at the first presentation was used to categorize the patients into seven groups: <90, 90–99, 100–109, 110–119, 120–129, 130–139,

and \geq 140 mmHg. Rate pressure product (RPP) was calculated by multiplying the heart rate (HR) by SBP recorded at the time of admission. High RPP was defined as values >10,000.^[20]

Electrocardiography and echocardiography were carried out on each subject using standard criteria and methods.^[21,22] The patients were re-evaluated at three-monthly interval and echocardiogram repeated six monthly to assess for the presence and extent of ventricular myocardial remodeling and changes in the size of the cardiac chambers. Unrecovered left ventricular (LV) systolic function was defined as echocardiographic LVEF below 55% at the last profiling.

Data analysis

Continuous variables were explored for the presence of skewness. Proportions, median (interquartile range [IQR]), and means with standard deviations were used to summarize subjects' characteristics. Chi-square, Fisher's exact, Student's *t*, and Mann–Whitney tests were used to compare continuous and categorical variables, as appropriate.

Associations between all-cause mortality and BP categories and other variables of interest were determined using Cox regression models (entry method with

proportional hazards confirmed by visual inspection) to derive adjusted hazard ratios (HRs) and 95% confidence interval (95% CI) as independent correlates of all-cause mortality. Regression models were developed to explore the relationship between LV functional recovery and SBP and its groupings to derive adjusted odds ratios (ORs) and 95% CI. Two- sided *P* value <0.05 was used as the minimum level of statistical significance. The statistical analysis was carried out using Statistical Package for Social Sciences software version 27.0.

RESULTS

A total of 227 patients were recruited and followed up for a median of 18 (IQR: 14–20) months. Of these, 4.0% had <90 mmHg, 16.3% had 90–99 mmHg, 24.7% had 100–109 mmHg, 24.7% had 110–119 mmHg, 18.5% had 120–129 mmHg, 7.5% had 130–139 mmHg, and 4.4% had \geq 140 mmHg of SBP at baseline. The distribution and clinical characteristics of the patients are summarized and compared in Table 1 and Figure 1. The HR and frequency of NYHA III or IV functional class seemed to display a U-shaped relationship with the SBP, being the highest in the SBP <90 mmHg group and the lowest in the SBP 120–129 mmHg group, while the reverse was the case for body mass index (BMI) [Table 1]. A total of

Table 1: Clinical characteristics, echocardiographic features, and outcomes of the patients							
Variable	<90 (<i>n</i> =9;	Systolic	blood	pressure	(mmHg)	groups	≥140 (<i>n</i> =10;
	4.0%)	90-99 (<i>n</i> =37;	100-109	110-119	120-129	130-139	4.4%)
		16.3%)	(<i>n</i> =56; 24.7%)	(<i>n</i> =56; 24.7%)	(<i>n</i> =42; 18.5%)	(<i>n</i> =17; 7.5%)	
			Clinical feature	S			
Age, years	29.0 ± 8.0	27.9±7.0	28.8 ± 6.8	28.5±7.4	31.0±7.6	30.8±7.2	26.4±5.9
Systolic BP, mmHg	81±2	90±1	100±1	110±2	120±1	130±2	153±17
Diastolic BP, mmHg	63±5	65±8	69±10	75±8	82±11	92±11	110 ± 18
Heart rate, beats/min	104 ± 16	106±22	101 ± 17	98±18	94±17	102 ± 15	108 ± 14
NYHA III/IV, n (%)	6 (66.7)	13 (35.1)	15 (26.8)	15 (26.8)	7 (16.7)	4 (23.5)	3 (30.0)
RPP, <i>n</i> (%)	9 (11.4)	22 (27.8)	26 (32.9)	13 (16.5)	9 (11.4)	0 (0)	0 (0)
RPP>10,000, <i>n</i> (%)	0 (0)	13 (9.6)	28 (20.6)	40 (29.4)	30 (22.1)	15 (11.0)	10 (7.4)
BMI, kg/m ²	17.77	18.73	20.42	21.22	22.08	20.48	17.78
Preeclampsia, n (%)	2 (22.2)	3 (8.1)	5 (8.9)	14 (25.0)	6 (14.3)	6 (35.3)	5 (50.0)
History of twins	0 (0)	5 (13.5)	9 (16.1)	14 (25%)	8 (19)	4 (23.5)	1 (10)
History of stroke, n (%)	1 (11.1)	1 (27)	0 (0)	0 (0)	4 (9.5)	0 (0)	0 (0)
Pneumonia, n (%)	1 (11.1)	1 (27)	6 (10.7)	2 (3.6)	2 (4.8)	0 (0)	0 (0)
ACEI/ARB/ β -blockers, n (%)	1 (11.1)	12 (32.4)	19 (33.9)	28 (50.0)	25 (59.5)	12 (70.6)	6 (60.0)
Follow-up, months, median (IQR)	12 (6-14.5)	18 (10-19)	18.5 (16-20)	18.5 (15.3-20)	19 (15-20)	17 (12.5-18.5)	19 (9.8-20.3)
		E	chocardiograph	ıy			
Left atrium, mm	41.3±5.8	43.9±5.7	44.5±8.5	45.3±6.2	45.1±5.6	44.7±4.7	44.4±5.7
LV end-diastolic dimension, mm	64.6 ± 6.9	65.4±6.2	61.4±9.5	63.7±7.5	61.6 ± 6.5	62.7 ± 8.4	59.7±6.7
LVEF, %	22.9 ± 7.0	26.9±7.4	30.6±8.1	30.1±7.9	29.9 ± 7.9	29.6 ± 6.7	30.3±5.0
			Outcomes				
Mortality,* n (%)	5 (55.9)	8 (21.6)	8 (14.3)	7 (12.5)	7 (16.7)	2 (11.8)	2 (20.0)
Unrecovered LVSF,§ n (%)	4 (44.4)	23 (62.2)	39 (69.6)	37 (66.1)	28 (66.7)	13 (76.5)	4 (40.0)

ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, BP=blood pressure, IQR=interquartile range, LV=left ventricular, LVEF=left ventricular ejection fraction, LVSF=left ventricular systolic function, NYHA=New York Heart Association, RPP=rate pressure product. *P=0.076, $^{\circ}P$ =0.659



Figure 1: Clinical outcomes of PPCM patients categorized according to their baseline systolic BP. The bars represent the percentages of the outcomes. LVSF = left ventricular systolic function, SBP (mmHg) = systolic blood pressure

136 patients (59.9%) had a frequency of RPP >10,000 with significant variation between the groups – none in the SBP group <90 mmHg and all of those with SBP \geq 140 mmHg (P = <0.001).

The highest frequency of all-cause mortality was recorded among patients with SBP <90 mmHg followed by those with 90–99 mmHg (P = 0.076), while unrecovered LV systolic function did not display any relationship with the SBP groups (P = 0.659) [Table 1 and Figure 1]. In a Cox proportional regression model for all-cause mortality, SBP <90 mmHg had an HR of 4.00 (95% CI 1.49–10.78, P = 0.006), LVEF had an HR of 0.94 (95% CI 0.91–0.98, P = 0.003), and use of ACEI or ARB and/or BB had an HR of 1.71 (95% CI 0.93–3.16, P = 0.085).

DISCUSSION

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PEACE registry is the largest longitudinal multicenter study of PPCM in Africa. In this post hoc analysis of the data, we aimed to determine the clinical features and outcomes of PPCM patients grouped according to their baseline SBP. We found that one-fifth of the patients were hypotensive at enrollment and SBP <90 mmHg increased the risk for all-cause mortality by four-fold. In addition, a unit increase in LVEF was independently associated with improved survival. However, SBP was not associated with LV systolic function recovery.

In our cohort, patients with SBP <90 mmHg had a frequency of all-cause mortality of 55.9% and unrecovered LV systolic function of 44.4%. In addition, SBP <90 mmHg independently increased the risk for all-cause mortality by four-fold. Previous studies have also demonstrated the prognostic significance of SBP in HF patients.^[5-7,9,12-14,23] A BP cutoff above 115 mmHg was shown to be the best indicator for lower mortality risk.^[6,24] In the present study, however, we specifically found the lowest frequency of mortality in the group with SBP 130-139 mmHg. The association between SBP ≤90 mmHg and higher mortality in our study is a clear testimony to the fact that our study centers were not capable of optimally treating HF patients with hypotension and/or shock, which are features of advanced HF. In addition to the high mortality rate, patients with SBP <90 mmHg were also the most symptomatic with a frequency of NYHA III/IV of 66.7% and they had the lowest LVEF of 22.9%. These clinical features suggest advanced HF, with therapeutic options that include circulatory mechanical support (MCS) and heart transplantation. In the setting of PPCM, percutaneous MCS has emerged as a successful tool for hemodynamic stabilization in a bridge-to-recovery and bridge-to-destination therapy.^[25] Unfortunately, these therapeutic facilities are not available at the study sites, which may contribute to the high mortality. In addition, there may be possible roles of renal impairment in excess mortality of PPCM patients with hypotension.

Previous studies have demonstrated an association between relatively high SBP or hypertension with better outcomes in PPCM patients as well as others with chronic stable HF.^[1,2,3,5,7,26-30]

Although the mechanism of this association is not clear, it may be related to differences in treatment patterns or responses. Understandably, physicians may be more aggressive in using lifesaving vasodilator therapies such as ACEIs/ARBs and BBs, at the highest tolerable doses, in patients with higher BP levels. In the present study, the use of ACEIs/ARBs and BBs was least frequent in patients with SBP <90 mmHg, and their use did not correlate with mortality. The RPP is a strong determinant of myocardial oxygen consumption and correlates significantly with important indices for morbidity and cardiovascular mortality.^[31] Of note, high RPP value (>10,000) has been found to be associated with increased risk of myocardial ischemia, even if silent.^[32] In the present study, we found a prevalence of high RPP of 59.9%, which is similar to the value we previously found (65%) in HF patients with various etiologies including PPCM.^[20] In both studies, however, it was not associated with poor clinical outcomes.

In the present study, a unit increase in LVEF was independently associated with 6% lower risk of death from all causes. In previous studies, low LVEF had consistently shown poor prognosis in PPCM patients.^[33-35] In a group of PPCM patients, Demakis *et al.*^[34] reported a mortality rate of 85% over a period of 5 years among patients with persistent LV systolic

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dysfunction, with no mortality recorded in those that had recovered LV systolic function during the period. These findings were corroborated by another study that reported a higher mean ejection fraction (23% vs. 11%) and a smaller mean LV cavity size (5.8 vs. 6.9 cm) at diagnosis among survivors than among the deceased, respectively. In addition, we recently showed that PPCM patients presenting with LVEF <25% had a two-fold higher risk for all-cause deaths and 34% lower odds for LV function recovery compared to patients with higher values.

Limitations

The findings in this paper were derived from a post hoc analysis of the PEACE registry data; the groups compared were, therefore, not initially matched for potential confounders. However, we controlled for potential confounders in the Cox proportional hazard regression models for all-cause mortality, in line with our statistical analysis plan. Secondly, our cohort included PPCM patients who had survived the first 3–6 months postpartum with residual LV dysfunction, which might have increased their risk for subsequent mortality.

CONCLUSION

Hypotension is not uncommon among patients with PPCM. SBP \leq 90 mmHg was associated with a four-fold higher risk of all-cause mortality. We recommend establishment of HF clinics and provision of circulatory support and heart transplant services for the care of PPCM and other HF patients with advanced disease in line with standard recommendations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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