



Factors Associated with Intra-hospital Mortality of Peripartum Cardiomyopathy Patients in Northcentral Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OAJ, KPM, DOBF, OA, KIA and OAB designed the study, authors OAJ, OAJ, YIA and DOBF performed the statistical analysis and wrote the draft of the manuscript. Authors OAJ, OAB, DOBF and YIA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: We studied the patient characteristics, intra-hospital outcomes and factors associated with intra-hospital mortality in patients admitted for Peripartum Cardiomyopathy (PPCM) in our centre using data from the Ilorin Heart failure Registry.

Study design: Prospective Observational

Methodology: All the 22 confirmed PPCM patients admitted between January 1, 2016 and December 31, 2019 were recruited and followed up for intra-hospital outcomes. The primary outcome was all-cause intra-hospital mortality.

Results: Intra-hospital death occurred in four out of 22 patients (18.2%). The mean age of all patients was 28.4 ± 4.8 years and it was similar in both survivors and patients who died ($P=0.960$). Majority of patients (14, 63.7%) presented in New York Heart Association Class IV. Mean duration of hospital stay was 11 ± 5.7 days which was similar between patients who died and those who survived hospital admission (9.0 ± 2.8 vs 11.4 ± 6.1 , $P=0.457$). Median ECG heart rate was 120 (116-123) bpm which was similar between both groups. Factors associated with mortality were biochemical parameters serum sodium and eGFR which were significantly lower among those who died (125.0 ± 4.1 vs 133.7 ± 2.5 mmol/L, $P<0.001$; 41.0 ± 18.8 vs 81.9 ± 11.03 ml/min/ 1.73m^2 , $P<0.001$) and the Ejection fraction (EF) and Fractional Shortening (FS) which were also significantly lower in the patients who died $24.0 \pm 8.2\%$ vs $37.9 \pm 6.2\%$, $P=0.002$; $11.0 \pm 4.3\%$ vs 18.4 ± 3.8 , $P=0.003$ respectively. Other echocardiographic parameters were similar between the two groups of patients. A Kaplan-Meier survival curve was drawn to show the time to outcome.

Conclusion: Majority of PPCM patients present in clinically severe heart failure and the intra-hospital mortality is high. The importance of serum sodium, eGFR, EF and FS as factors associated with mortality indicates patient sub-groups requiring greater attention and targeted interventions.

Keywords: *Peripartum cardiomyopathy; Northcentral Nigeria; intra-hospital mortality; Ilorin heart failure registry.*

1. INTRODUCTION

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurring towards the end of pregnancy or in the months following delivery, abortion or miscarriage, without other causes for heart failure, and with a left ventricular (LV) ejection fraction (EF) $<45\%$ on echocardiography [1]. PPCM is a significant cause of HF in women especially in sub-Saharan Africa [2,3]. It is attended by a relatively high intra-hospital mortality [4] and survival rates vary across the world [5].

Compared to other causes of HF, PPCM is a relatively uncommon condition [3]. Hence, most single center experiences with the disease will necessarily be composed of small patient sample sizes. Yet, the heterogenous nature of its epidemiology makes single-centre experiences important in generating a complete understanding of the disease. For example, some of the highest incidence rates of PPCM worldwide are found in Nigeria [6,7] where a widely heterogenous pattern of incidence has been observed. The Northwestern geo-political zone has the highest incidence rate of 1 in 96 live births (the highest in the world) while rates as low as 1 in 1,350 live births are recorded in the Southern geo-political zones [8].

The development of PPCM can be devastating. This is because it occurs in young patients and has potentially negative implications for both fetal outcomes, post-partum maternal well-being and subsequent pregnancies [5].

The objectives of this study were to study the intra-hospital outcomes and factors associated with intra-hospital mortality of PPCM patients managed in our centre.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was a prospective study conducted at the University of Ilorin Teaching Hospital (UIH), Ilorin, Nigeria. UIH is the predominant tertiary health care facility in the city receiving referrals from private and government-owned health facilities in the city and from at least five neighbouring states spread across two geo-political zones- Osun, Oyo, Ekiti (South western Nigeria), Kogi and Niger states (North central Nigeria).

2.2 Study Population

All cases of PPCM aged 18 years old or more admitted into the Cardiology unit of UIH between January 1, 2016 and December 31, 2019 were prospectively enrolled into this study after satisfying the inclusion criteria. A diagnosis of PPCM was made following standard criteria as patients who developed heart failure which occurred in the last months of pregnancy or in the first five months following delivery, without any other cause of heart failure, and with a LV EF $<45\%$ on echocardiography and with no history of congenital heart disease, valvular disease, radiation or cardiotoxic chemotherapy

predating PPCM, and without any other explanation for their heart disease [1,2]. Where there was a doubt that about mimics of new systolic dysfunction or complications of late pregnancy such as pulmonary embolic phenomena could be present, other investigations such as chest x-ray and computed tomography imaging was done to ensure that only patients who fitted into the standard diagnostic criteria for PPCM were included in the study. Patients who fitted into the clinical definition of PPCM but had no echocardiographic confirmation of diagnosis were excluded from the study. Patients who were managed for pre-eclampsia or eclampsia, in which case there confusion with hypertension being the aetiology of the heart failure were also excluded. Patients included were admitted into the cardiology unit from the medical emergency unit, the medical out-patient clinics.

A case report form was used to collect demographic, clinical, and laboratory data of the patients. Electrocardiography (ECG) and echocardiography were carried out on each subject using standard criteria and methods [9-11]. Echocardiography was performed using a commercially available ultrasound system Sonoscape® SSI-8000 echocardiogram (Sonoscape® Co. Ltd., Singapore). Two-dimensional (2D) guided M-mode measurements were made. The LV measurements taken include Left ventricular (LV) internal dimension at end-diastole (LVIDd) and end-systole (LVIDs), LV posterior wall thickness at end-diastole (PWTd) and end-systole (PWTs), and interventricular septal thickness at end-diastole (IVSd) and end-systole (IVSs). Left atrial diameter (LAD) was measured at end-systole from the trailing edge of the posterior aortic root to the leading edge of the posterior left atrial wall. Measurements were obtained in up to 3 cardiac cycles and averaged. Left ventricular mass (LVM) was calculated using the formula of Devereux and Reichek $LVM = 0.8 \times (1.04 \times [(IVSd + LVIDd + PWTd)^3 - LVIDd^3] + 0.6 \text{ grams}$ [9,12] and was indexed to the body surface area (BSA) of the patient to derive the left ventricular mass index (LVMI). LVMI values greater than 95 g/m^2 were used to define left ventricular hypertrophy (LVH) according to established norms [13]. The Relative wall thickness (RWT) was calculated as $2 \times PWTd / LVIDd$. LV geometry was defined according to standard criteria as normal geometry (normal LVMI and RWT < 0.42), LV concentric remodeling (normal LVMI and RWT > 0.42), eccentric LVH (increased LVMI and RWT < 0.42) and concentric

LVH (increased LVMI and RWT ≥ 0.42) [9]. The transmitral and trans-tricuspid flow velocities were obtained with the Doppler sample volume placed just between the tips of the mitral and tricuspid valve leaflets respectively during ventricular diastole and standard measurements were obtained [14].

All patients had assays of their serum sodium, potassium, urea and creatinine. The estimated Glomerular filtration rate (eGFR) was computed using the CKD-epi formula [15,16].

2.3 Statistical Analysis

The data were analyzed using SPSS version 23 (SPSS, Inc., Chicago, Illinois). Continuous variables were evaluated for skewness and normality. Variables that were not normally distributed were expressed as medians and interquartile range (IQR). Continuous variables that were normally distributed were expressed as mean \pm standard deviation (SD). Categorical variables were expressed as percentages. Chi-square test was used to compare proportions of categorical variables and Student independent t-test for comparing means of normally distributed continuous variables. The means of continuous variables that were not normally distributed were compared with Mann-Whitney U test. The primary outcome was defined as death during hospital admission. A Kaplan –Meier survival curve was drawn to show the time to primary outcome.

3. RESULTS

Twenty-two patients who met the inclusion criteria were included in the study. Echocardiography is usually done for suspected heart failure patients within 48 hours of presentation to us. In the study period, 27 patients were referred to our service with a suspicion of PPCM. Two of these had echocardiographic confirmation of rheumatic mitral valve heart disease, one had atrial septal defect, one patient had normal echocardiography findings and a chest x-ray indicative of lobar pneumonia, while one patient died before echocardiography was done (Fig. 1).

The mean age of all the patients was 28.4 ± 4.8 years, with a range of 21-40 years. Intra-hospital death occurred in four out of 22 patients (18.2%). Table 1 shows the clinical and laboratory parameters of all patients and comparisons

between the two groups of patients who died during and those who survived admission. The mean duration of hospital stay was 11 ± 5.7 days and it was similar between patients who died and those who survived hospital admission. Majority of the patients (63.6%) were admitted in New York Heart Association (NYHA) Class IV. Majority were of Yoruba ethnicity (81.8%).

The median ECG heart rate of the patients was 120 (IQR116-123) bpm and it did not differ significantly between the patients who died and those who survived ($P=0.857$). The laboratory results of the patients revealed that the mean serum sodium and eGFR were significantly lower among those who died (125.0 ± 4.1 vs 133.7 ± 2.5 mmol/L, $P<0.001$; 41.0 ± 18.8 vs 81.9 ± 11.03 mls/min/ $1.73m^2$, $P<0.001$). The mean serum potassium and urea were similar in both groups. The mean serum sodium and eGFR were associated with intra-hospital mortality being significantly different among the patients who died compared to the survivors. The mean packed cell volume (PCV), hemoglobin, white blood cell count (WBC) and platelet count were similar in both groups of patients.

Table 2 shows the echocardiography parameters of the patients. It shows that the mean LAD,

LVIDd, LVIDs, LVEF, FS, PWTd, LVM and LVMI were 45.5 ± 5.4 mm, 10.2 ± 3.5 mm, 60.1 ± 4.5 mm, 48.5 ± 3.9 mm, 36.9 ± 7.1 mm, 17.9 ± 4.1 mm, 9.9 ± 2.6 mm, 282.1 ± 66.7 g, 174.4 ± 38.4 g/ m^2 respectively. These parameters were similar between patients who died and those who survived admission. The LVEF and FS were associated with intra-hospital mortality being significantly lower in the patients who died on admission than in those who survived $24.0 \pm 8.2\%$ vs $37.9 \pm 6.2\%$, $P=0.002$; $11.0 \pm 4.3\%$ vs 18.4 ± 3.8 , $P=0.003$ respectively.

A Kaplan-Meier survival curve was drawn (Fig. 2) with event being intra-hospital death showing that while surviving patients spent up to 21 days on admission, all events (deaths) occurred before day 12 of admission.

Thirty-day outcome data on the 18 surviving patients revealed that one of them was rehospitalized on account of worsening symptoms (5.6%). The patient survived the admission. By six months post-discharge an additional patient had been re-hospitalized giving a six-month rehospitalization rate of 11.2%. All the 18 patients who survived the first hospital admission were still alive six months post-discharge.

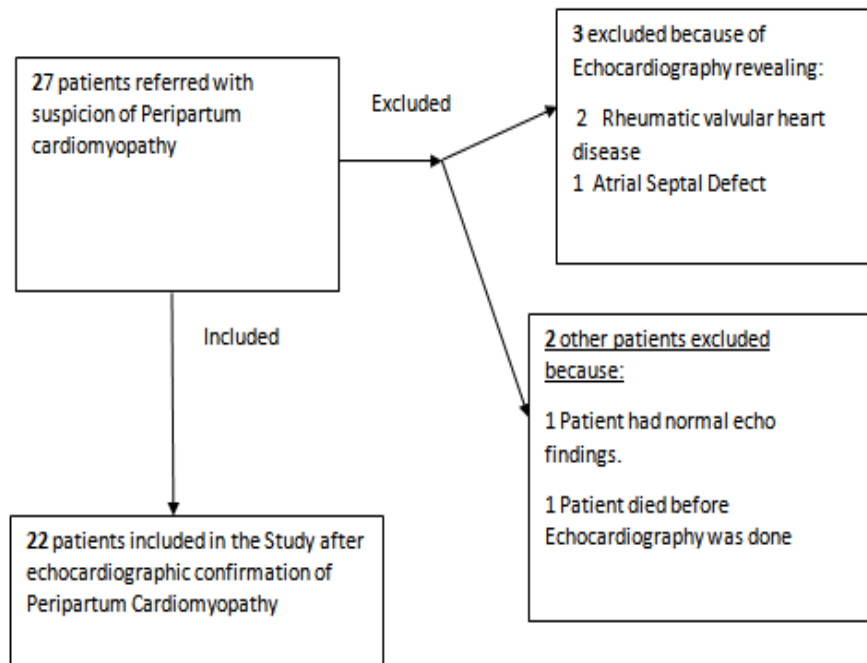


Fig. 1. Flow chart showing the referral of patients to our service and selection into the study after echocardiographic confirmation of peripartum cardiomyopathy

Table 1. Clinical and laboratory parameters of patients

Variable	All Patients Mean±SD/ Median (IQR)	Died Mean±SD/ Median (IQR)	Survived Mean±SD/ Median (IQR)	P-value
Age (years)	28.4 ± 4.8	28.3 ± 5.4	28.4 ± 4.8	0.960
NYHA Class on Admission				
NYHA Class III, n (%)	8 (36.4)	2(25.0)	6 (75.0)	
NYHA Class IV, n (%)	14(63.6)	2(14.3)	12 (85.7)	0.531
Duration of Admission (days)	11.0 ± 5.7	9.0 ± 2.8	11.4 ± 6.1	0.457
Marital status:				
Married, n (%)	15 (68.2)	3 (20.0)	12 (80.0)	
Unmarried, n (%)	7 (31.8)	1 (14.3)	6 (85.7)	0.746 ^Y
Ethnicity, n (%)				
Yoruba	18(81.8)	3(16.7)	15(83.3)	0.695 ^Y
Nupe	2 (9.2)	1(50)	1(50)	
Igbo	1 (4.5)	0(0)	1(100)	
Fulani	1 (4.5)	0(0)	1 (100)	
Formal Education, n (%)				
Yes	20(90.9)	4 (20)	16 (80)	0.069 ^Y
No	2(9.1)	0(0)	2(100)	
Systolic Blood Pressure (mmHg)	102.17± 15.31	95± 7.02	103.6 ± 16.4	0.45
Diastolic Blood Pressure (mmHg)	66.67± 21.03	60 ± 14.1	70± 21.08	0.236
ECG Heart rate (bpm)	120 (116-123)	120.0 (108.0- 130.0)	118.5 (115.8-126.8)	0.857
Serum Sodium (mmol/l)	132.0 ± 4.4	125.0 ± 4.1	133.7 ± 2.5	<0.001*
Serum Potassium (mmol/l)	3.94 ± 0.42	3.95 ± 0.04	3.93 ± 0.47	0.945
Serum Urea (mmol/l)	6.0 ± 2.4	7.5 ± 3.7	5.7 ± 1.97	0.167
eGFR	74.4 ± 20.2	41.0 ± 18.8	81.9 ± 11.03	<0.001*
Packed Cell Volume	38.0 ± 8.0	38.0 ± 8.6	38.0 ± 8.5	0.995
Hemoglobin	11.8 ± 2.6	12.7 ± 2.8	11.6 ± 2.6	0.616
White Blood cell count (x 10 ⁹ /l)	7.6 ± 3.3	8.2 ± 0.9	7.4 ± 3.7	0.783
Platelet count (x 10 ⁹ /l)	265.6 ± 82.8	259.0 ± 81	267.6 ± 89.2	0.861

bpm- beats per minute; ECG- Electrocardiogram; eGFR- Estimated Glomerular Filtration Rate; IQR- Inter quartile range; NYHA- New York Heart Association; Y- Yates corrected chi square P value: *P<0.05

Table 2. Echocardiographic parameters of patients

Variable	All Patients Mean±SD/ Median (IQR)	Died Mean±SD/ Median (IQR)	Survived Mean±SD/ Median (IQR)	P-value
LAD (mm)	45.5 ± 5.4	49.4± 7.3	45.2 ± 5.5	0.205
IVSTD (mm)	10.2 (7.2-11.8)	10.5 (7.5-11.5)	9.7 (8.5-10.9)	0.769
LVIDd (mm)	60.1 ± 4.5	54.4 ± 9.7	60.5 ± 4.3	0.057
LVIDs (mm)	48.5 ± 3.9	48.3 ± 4.4	48.6 ± 4.2	0.952
LVEF (%)	36.9 ± 7.1	24.0 ± 8.2	37.9 ± 6.2	0.002*
FS (%)	17.9 ± 4.1	11.0 ± 4.3	18.4 ± 3.8	0.003*
PWTd (mm)	9.9 ± 2.6	11.7 ± 4.9	9.8 ± 2.7	0.505
LVM (g)	282.1 ± 66.7	286.2 ± 71.2	281.8 ± 69.7	0.952
LVMI (g/m ²)	174.4 ± 38.4	168.3 ± 62.1	175.0 ± 40.6	0.879
Mitral E/A ratio	2.8 ± 0.7	3.4 ± 1.3	2.7 ± 0.7	0.137
Tricuspid E/A ratio	1.55± 0.87	2.45± 0.67	1.45±0.86	0.299
Pericardial effusion:				
Present	7 (31.8)	1 (14.7)	6 (85.3)	0.131
Absent	15 (68.2)	4 (26.7)	11 (73.3)	

EF - ejection fraction; FS - fractional shortening; IQR- Inter quartile range; IVSTD - interventricular septal wall thickness in diastole; LAD- Left Atrial Dimension; LV- Left ventricular; LVH- Left ventricular hypertrophy; LVIDd - left ventricular internal diameter in diastole; LVIDs - left ventricular internal diameter in systole; LVM - left ventricular mass; LVMI - left ventricular mass index; Mitral EA ratio – Ratio of Mitral E wave velocity and A wave velocity; PWTd - left ventricular posterior wall thickness in diastole; RWT- relative wall thickness. P value; *P<0.05

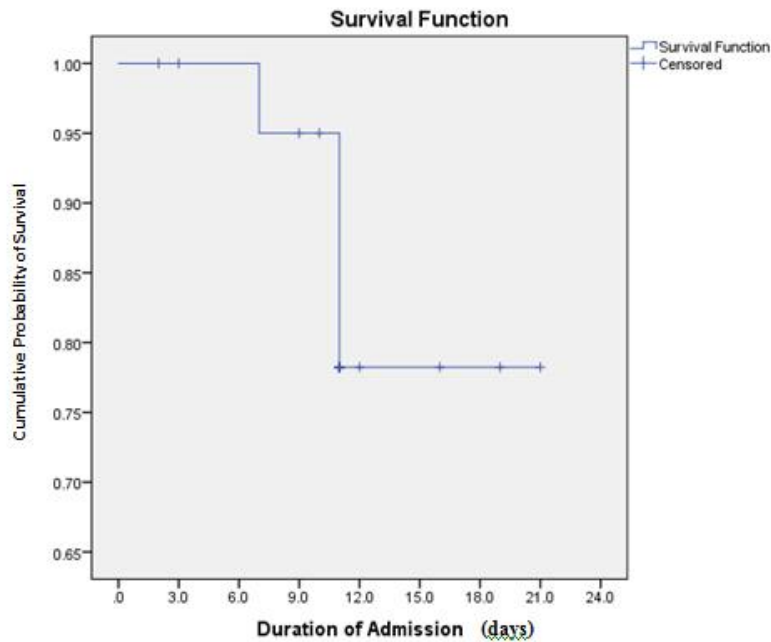


Fig. 2. Kaplan-meier survival curve showing the rate of mortality of the subjects

4. DISCUSSION

The outcome of PPCM is highly variable and the disease has high morbidity and mortality rates [3]. Specifically, environmental, socio-economic and racial differences in patient characteristics have been noted among PPCM patients living within the same country [8,17,18]. These factors have been observed to affect their disease outcomes [17,19]. This underscores the importance of studying sub-populations of PPCM patients for improved understanding of the disease and its short-term outcomes. Also, while the global epidemiology of the disease is now better understood renewed interest has been generated around its pathophysiology and intra-hospital outcomes as part of the general inquiry into the current concepts of the disease [20,21].

The mean age of our patients was similar to that observed in the Peripartum Cardiomyopathy in Nigeria (PEACE) nationwide registry of Nigerian PPCM patients [8]. Our patients are however older than patients managed in an earlier cohort in the Northwestern part of the country by Isezuo and Abubakar where the incidence of PPCM is the highest in the world [22,23]. Our patients are however younger than patients reported from Turkey and USA [18,24] and have a lower mean age than that reported in the Global registry of

PPCM patients by Sliwa et al. [25]. Variations in age of PPCM patients is likely accounted for by differences in such population variables as literacy rate, prevalence of higher education among women and cultural preferences for early or late marriage.

The intra-hospital mortality rate reported among our patients is similar to reports by Ntusi et al in South Africa [26]. Isezuo et al. [22] had also earlier reported a lower mortality rate of 12.3%. The fact that mortality rates from sub-saharan Africa are generally higher than 10% whereas figures as low as 1.4% and 1.8% have been reported in Japan [27] and the USA [19] reflects significant regional variations in patient outcomes. The relatively high mortality rate among our patients may be related to the fact that majority of our patients presented in NYHA IV. When left untreated - frequently due to late recognition- PPCM symptoms progress rapidly. Also in our environment, late presentation to specialist care by patients with chronic illnesses is relatively common due to weak referral systems within the health system as a whole and this contributes to disease mortality. The lower mortality recorded in the high income countries is no doubt also related to the availability of more advanced modalities of care for PPCM patients which includes adjunctive non-pharmacological

therapies such as implantable cardiac devices which may be indicated in cases with severe LV dysfunction, life-threatening arrhythmias or other complications of heart failure.

The factors associated with mortality in our patients were laboratory parameters serum sodium, and eGFR and echocardiography parameters LVEF and FS. Gheorghide et al. [28] showed that hyponatremia predicted poor prognosis in patients with HF. Abebe et al. [29] also reported similarly that patients with hyponatremia were four times less likely to survive intra-hospital admission than patients with normal serum sodium levels. Hyponatremia occurs in HF as a diuretic drug side-effect and as a sequelae of the action of vasopressin produced as one of the compensatory mechanisms triggered by a failing heart. The echocardiography findings associated with patient mortality are indices of cardiac systolic function. LVEF and FS were significantly lower among patients who died than among those who survived and this observation was also made by Blauwet et al. who even found them as predictors of mortality and poor clinical outcomes [13]. Poor LV systolic function is an indicator of severe disease and when initial HF compensatory mechanisms fail, it results into the reduction in cardiac output and in reduced renal perfusion. This precedes a decline in the eGFR among other sequelae.

The observation in this study that eGFR was associated with intra-hospital survival is similar to reports by Makubi et al. [30] in Tanzania. Declining eGFR results in renal dysfunction. This leads to further exacerbation of the HF through worsening of fluid retention and congestion resulting in increased potential for an adverse outcome.

The small sample size is a limitation of this study. However, the relatively low prevalence of PPCM and its being a disease exclusive to women limits the number of patients that will be seen in any hospital. Likewise, among the general population of HF patients, PPCM still ranks lower in the order of prevalence than hypertensive heart disease, cardiomyopathies, ischemic heart disease and – in the Sub-saharan African setting - rheumatic heart disease [31]. In the PEACE nationwide Registry of Nigeria, only 25 PPCM patients were seen and recruited from the three participating centres in our geo-political zone during the study period. Some zones even had as few as 13 patients recruited [8]. Moreover,

single-centre reports will better illustrate the local clinical peculiarities of PPCM patients keeping in mind that disease prevalence rate, patients' socio-economic, clinical and disease characteristics vary widely even within the same country. Our study's strength is that the cohort was recruited from a tertiary care hospital which also receives referrals from other centres making the data generalisable to a large regional population. Multicentre collaborations however remain the next focus of our team for the purpose of better studying other aspects of the disease.

5. CONCLUSION

In conclusion, our study shows that majority of our patients present with advanced stages of HF and the intra-hospital mortality is high compared to centres outside the sub-saharan African setting. The importance of biochemical variables such as serum sodium and eGFR, and echocardiographic parameters EF and FS as factors associated with mortality defines patient sub-groups requiring greater attention and targeted interventions.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Ethical approval for the study was obtained from the Ethical Research Committee of the UIH and informed consent was taken from the patients. The study conformed to the ethical guidelines of the Declaration of Helsinki on the principles for medical research involving human subjects.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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