Original Article

Clinical and echocardiographic predictors of outcomes in patients with peripartum cardiomyopathy: A single centre, six month follow-up study

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ABSTRACT

Introduction: Peripartum cardiomyopathy (PPCM) is an important cause of maternal mortality and morbidity. But, there is a paucity of prospective data on outcomes and prognostic markers in patients receiving contemporary evidence-based therapy, particularly in developing countries.
Methods: This was a single centre, prospective, cohort study on 43 PPCM patients who were followed for 6 months. The primary endpoint was a composite incidence of decompensation related re-hospitalization, all-cause death, and poor recovery (defined as left ventricular ejection fraction, LVEF: <45% at 6 months). Multivariate logistic regression analysis was performed to identify the independent predictors and Kaplan-Meier plots for event (re-hospitalization or death) free survival were computed at their optimal cut-offs.
Results: Mean LVEF at presentation was 34.7%. Two patients died during index hospitalization but there were no deaths during follow-up and 63.4% of patients had full LV recovery after discharge. 32.5% of the study population experienced the composite endpoint with high left atrial volume index (LAVi), and low right ventricular fractional area change (RVFAC) at presentation as independent predictors. Use of Inotropic therapy during index hospitalization (with dobutamine or levosimendan) and bromocriptine therapy were not associated with better outcome.
Conclusions: At the end of 6 months after PPCM diagnosis, about 61% of patients had full LV functional recovery with a mortality rate of 4.7%. RVFAC (<31.4% with 86% accuracy) and LAVi (>29.6 ml/m^2 with 72% accuracy) at presentation but not LVEF, predicts poor outcomes. Presence of both these risk factors at index hospitalization was associated with a significantly lower event free survival compared to patients without these predictors.

1. Introduction

Peripartum cardiomyopathy (PPCM) is a major cause of pregnancy related heart failure (HF) and is characterized by a rapid clinical course, good probability for spontaneous recovery yet with a high rate of relapse in subsequent pregnancies.[1] Despite many advances, PPCM is not a precisely defined entity. The working group on PPCM of the European Society of Cardiology (ESC) defined PPCM as cardiomyopathy with reduced left ventricular ejection fraction (LVEF usually <45%), presenting toward the end of pregnancy or in the months after delivery in a woman without previously known structural heart disease.[2] The timing of PPCM is uncertain, though National Heart, Lung, and Blood Institute defined it as idiopathic cardiomyopathy with onset between the last month of pregnancy and five months following delivery, which is not always the case.[3] The imprecise nature of the definition reflects our incomplete understanding of the patho-physiology of PPCM. Several probable mechanisms have been proposed, including viral myocarditis, nutritional deficiencies, autoimmunity, hemodynamic stresses, vascular dysfunction, hormonal insults, and genetic predisposition. Recently, a cleaved N-terminal 16-kDa prolactin fragment was

considered crucial. Because prolactin plays a central role in the pathogenesis, its inhibition by using bromocriptine, a dopamine-D2-receptor agonist showed improvement of cardiac function[4] in clinical studies. Recommended treatment for PPCM is based mainly on extrapolation from data with other forms of systolic heart failure, in accordance with current society recommendations for guideline-directed medical therapy.[5] Identifying and validating the predictors of outcomes in PPCM patients is important because, early identification of these vulnerable patients may have important clinical implications like aggressive management of heart failure, strict control of co-morbidities and rigorous follow-up, all of which would result in subsequent reduction of mortality.

Numerous predictors of poor outcome among PPCM patients had been proposed; of which, most cited and discussed is degree of LV systolic dysfunction and dilatation at diagnosis. An inflammatory pathogenesis is postulated for many cases with "reversible" non-ischemic cardiomyopathy (NICM), including PPCM[4]; in which, the extent of ventricular remodelling is proportional to the degree of inflammation. Recovery in these patients usually ensues when the inflammatory event resolves which in-turn depends on the severity of inflammatory process.[6] In-fact, multicentre data suggests that, in patients with acute NICM of varied aetiology, left ventricular remodelling serves as an independent predictor of functional recovery.[7] Similarly, LVEF was considered as a most reliable predictor of adverse events or long-term recovery among PPCM patients. However, despite having severe LV dysfunction at the time of initial diagnosis, many women will eventually recover; thus, initial LVEF is less than optimal for predicting clinical events and it was proposed that additional prognostic factors had to be considered for determining an early and possible premature need for advanced therapies such as left ventricular assist device cardiac resynchronization therapy, or transplant.[8]

Role of left atrial (LA) enlargement as a predictor of adverse cardiovascular (CV) events and death is well documented in patients with heart failure irrespective of LV systolic function. Possible explanation for this observation is that, LA enlargement may represent an indicator of the combined effect over time of co-morbid conditions (hypertension, diabetes), structural defects (mitral valve disease, ventricular dilatation) and adverse cardiac hemodynamics (any condition associated with increasing LV filling pressures). In addition, LA enlargement may also contribute to CV events in a more direct fashion, by acting as a source for embolic events.[9] Despite considerable data demonstrating the utility of LA size in predicting incrementally CV events, risk stratification strategies incorporating this parameter are not fully exploited in clinical practice and in-fact no study had evaluated its prognostic significance in PPCM to date. One of the important problems in the assessment of chamber volumes is the dynamicity of their size given the rapid changes that occur after the delivery. Nevertheless, studies have shown that, indexed left atrial and left ventricular chamber volumes do not vary significantly in the 3rd trimester and post-partum period.[10,11]

RV systolic dysfunction in PPCM, is proposed as an independent predictor of adverse outcomes[8] and may indicates more severe PPCM phenotype with biventricular dysfunction. However, its prognostic significance is not uniformly documented.[12] Numerous other predictors of poor outcome among patients with PPCM proposed were presence of LV thrombus, NYHA class, delayed diagnosis, lower body mass index (BMI) and black African descent.[8] Given to the low prevalence of this disorder, there is a minimal prospective data on clinical outcomes and prognostic markers in patients with PPCM, receiving contemporary evidence-based heart failure therapy, particularly in resources limited countries. So, this study is intended to identify the clinical, demographic, and echocardiographic predictors of outcomes in Indian PPCM patients.

2. Methodology

2.1. Study design and population

This was a 42 month (with 36 months of enrolment period), single centre, prospective, cohort study conducted on patients with PPCM after an institutional ethical committee approval and adhered to the declaration of Helsinki.

2.1.1. Inclusion criteria

Patients were eligible if, at the time of presentation, they meet each of the following criteria:

(1) Heart failure (HF) secondary to left ventricular dysfunction with a LVEF <45% with its onset between the last month of pregnancy and five months following delivery
(2) >18 years of age.

2.1.2. Exclusion criteria

Patients are excluded, if at the time of presentation they meet any of the following criteria:

(1) Pre-existing known cardiac or thyroid disease or any drug abuse.
(2) Concomitant therapy for other systemic illness other than HF.
(3) Haemoglobin at the time of initiation of study was <8 gm/dl.
(4) Associated with any congenital heart defects.

2.2. Clinical course and data collection

2.2.1. In-hospital management

(1) Patients were initially stabilized, later ante-partum patients were shifted to an obstetric ward for supervised obstetric care and safe institutional delivery, whereas post-partum patients received routine heart failure-medication based care in cardiac wards. All the patients underwent standard evaluation with routine haematological and biochemical investigations, ECG, and 2D echocardiography. Echocardiographic examinations were performed by a clinician who has more than 10 years of experience in non-invasive cardiology, and image acquisition was performed as per IAE recommendations. Once stable, patients were discharged with appropriate oral medical therapy
(2) Patients were treated with evidence-based medical therapy for HF, which was appropriate in ante-partum and post-partum settings.[13] Patients were prescribed oral bromocriptine with different protocols (2.5 mg once or twice daily for varying duration from 1 week to 8 weeks) for a mean duration of 3.9 weeks. Concurrently, anticoagulation with heparin (in-hospital) and vitamin K antagonist (during follow-up) were prescribed for these patients, also in those with left ventricular (LV) thrombus and/or LV ejection fraction (LVEF) of <35%.[14]

Patients received inotropic (dobutamine, levosimendan) and/or vasorelaxing (NTG-Nitroglycerin, levosimendan) therapy for hemodynamic stabilization. Dobutamine was initially administered at an infusion rate of 5 µg/kg/min for 10 min. If no dose-limiting side effects were experienced, then infusion at 20 µg/kg/min was continued for 24 h. Patients with no contraindications had received levosimendan infusion (with-out bolus dose) at a rate of 0.05–0.1 mg/kg/min for 24 h if tolerated.[15] Since our institute is a

state-run tertiary care hospital, levosimendan use was based on drug availability and at the discretion of treating physician.

2.2.2. Follow-up

After discharge, patients were followed for six months with interim visits every four weekly. At each visit, adverse events, NYHA class, and vital signs were recorded. Physical examination was performed, compliance to medication was assessed, and the standard heart failure medications were adjusted if necessary. 2D-echocardiography was performed at the end of 6 months.

2.3. Study endpoint

Defined as a composite of re-hospitalization for HF decompensation, all-cause mortality, and poor recovery (defined as LVEF of <45% at the end of 6 months. LV-EF 45−55% and LVEF >55% at the end of 6 months were considered as partial and Full LV recovery, respectively.

2.4. Statistical analysis

Continuous and categorical variables were reported as mean- and number of observations, respectively. Multivariate logistic regression analysis was performed to determine the predictors and receiver operator characteristic (ROC) curves (with Mann−Whitney 95% confidence limits) were analysed for an optimal cut-off (defined as a value yielding maximal Youden index). Kaplan-Meier plots with log-rank test (Mantel-haenszel) for event-free survival were computed. EZR® (3.5.2, R foundation) was used for statistical analysis. A *p* value of <0.05 was considered significant statistically.

3. Results

3.1. Patient population

From October 2016 to March 2020, 48 patients were able to fulfil all the inclusion criteria, and 44 patients had completed six months follow-up. After considering exclusion criteria, 43 patients (1 patient had haemoglobin of 6.4 g/dl at presentation) were finally included (14 ante-partum) with a mean age of 25.4 years (range: 21−31 years). Breathlessness was the presenting complaint in all, and majority (72.1%) were primiparous. Postpartum PPCM patients presented with in a median time of 4.6 days after delivery (range: 0−32 days) and mean time to delivery after the diagnosis was 4.2 ± 2.9 days (range: 1−10 days) in antepartum PPCM patients' group.

3.2. Clinical course and investigatory data

3.2.1. Index hospitalization

During in-hospital stay, 32 patients received inotropes (dobutamine and/or levosimendan), and one patient had an episode of left lower limb deep vein thrombosis (DVT), which was treated with heparin. Two patients died after delivery on 6th and 11th day of hospitalization. Notably, bromocriptine was prescribed in 88.3% (38/43) of patients. Mean left ventricular ejection fraction (LV-EF), Right ventricle-fractional area change (RV-FAC), left ventricular end-diastolic volume index (LVEDVi) and Left atrial volume index (LAVi) were 34.7%, 34.1%, 52.9 ml/m^2 and 27.1 ml/m^2, respectively. The mean duration of hospital stay was 5.1 ± 2.2 days (range: 1−15 days). Table 1.

Table 1
Clinical and investigatory data of study population at presentation.

Variable	N(%)	Variable	Mean (SD)
Diagnosis after delivery	29 (67.4%)	Age (years)	25.4 (2.9)
received inotropes	32 (74.4%)	Parity	1.4 (0.8)
Risk factors		**Haematological**	
HTN-CP	8 (18.6%)	Haemoglobin (g/dl)	10.9 (1.9)
Tocolysis	2 (4.6%)	Serum creatinine (mg/dl)	1.0 (0.12)
Other risk factors*	2 (4.6%)	Serum bilirubin (mg/dl)	0.7 (0.1)
Discharged with	41	**Echocardiographic**	
Furosemide	39 (95.1%)	LV-EDVi (ml/m^2)^	52.9 (4.2)
Spironolactone	39 (95.1%)	LV-ESVi (ml/m^2)^	34.5 (3.5)
ACEi/ARB	41 (100%)	LVEF (%)	34.7 (3.2)
Beta blocker (M)	41 (100%)	Mitral E/A	1.5 (0.7)
Bromocriptine#	35 (85.3%)	LAVi (ml/m^2)^	27.1 (2.3)
iron folic acid	34 (83%)	RVFAC (%)	34.1 (4.9)

ACEi: ACE inhibitors (Enalapril); Angiotensin II receptor blockers (Losartan); M: Metoprolol extended release. LV: Left ventricular; EDVi: End Diastolic Volume index; ESVi: End Systolic Volume index; EF: Ejection fraction; LAVi: left atrial volume index; RVFAC: RV fractional area change; * twin pregnancy (1), past H/O PPCM (1). HTN-CP: Hypertensive disorders complications pregnancy. #: 3 patients completed 1 week therapy with-in hospital (so a total of 38 patients were prescribed with bromocriptine). ^ by biplane simpson method.

3.2.2. Follow-up data

No patients were lost in follow-up and mean time for last follow up being 185.7 days (ranges from 177 to 194 days) since diagnosis. Patient-reported drug compliance rates were almost 100% except with bromocriptine (54%) and were mainly due to financial and personal reasons. No thrombo-embolic or bleeding episodes were reported during these six months. Mean LV-EF, RV-FAC, LV-EDVi, LAVi were 50.3%, 42.2%, 44.4 ml/m^2, and 22.7 ml/m^2 respectively, at the end of follow period.

3.3. Study end-point

Incidence of study end-point was 32.5% (14) with 4 patients needing decompensation related re-hospitalization(s) and 2 in-hospital deaths at index-hospitalization. Among discharged patients, full and poor LV recovery were seen in 26 (63.4%) and 11 (26.8%) patients, respectively, and remaining have partial LV recovery.

On multivariate regression analysis, only LAVi and RV-FAC at presentation were found as independent predictors of the primary out-come. Inotropic therapy at index presentation and bromocriptine use were not associated with the primary end-point. Besides, we found that LVEDVi do not predict recovery. Table 2.

Optimal cut-offs, sensitivity, specificity and overall diagnostic accuracy for LAVi (AUROC:, 0.72, 95% CI 0.54−0.90; *p*: 0.014) and RVFAC (AUROC: 0.82, 95% CI 0.68−0.96; *p*: <0.01) were >29.6, 57.1%, 79.3%, 72.1% and <31.4%, 71.4%, 93.1%, 86% respectively (Fig. 1). Kaplan Meier event curve analysis suggests that, the presence of both the risk factors (i.e. LAVi >29.1% and RVFAC <31.4%) at index presentation was associated with a significantly lower event (re-hospitalization or death) free survival compared to the patients without these predictors (i.e. LAVi <29.1% and RVFAC >31.4%) at the end of 6 months (Fig. 2).

4. Discussion

This is the first study to the best of our knowledge that assessed the prognostic impact of left atrial volume in PPCM and one of the few studies reporting the impact of bromocriptine and inotropic therapy on the clinical outcomes of patients with PPCM. Due to financial and logistic reasons, cardiac MRI was not performed in all; but due to its wide availability, echocardiography was used for

Table 2
Follow-up data, outcomes and predictors.

Echo data - 6 months		Univariate regression^			Multivariate regression^		
Variable	mean (SD)	β	OR (95% CI)	P	β	OR (95% CI)	p
LV-EDVi*	44.4 (4.1)	0.18	1.2 (1−1.4)	**<0.01**	0.08	1.05 (0.7−1.2)	0.12
LV-ESVi*	22.1 (3.8)	0.13	1.1 (1−1.6)	**0.01**	0.05	1.02 (0.4−1.5)	0.23
LAVi*	22.7 (2.7)	0.23	1.3 (1.1−1.5)	**<0.01**	0.12	1.18 (1.1−1.9)	**0.04**
LVEF (%)	50.3 (4.5)	−0.36	0.7 (0.5−0.9)	**<0.01**	−0.15	0.8 (0.6−1.1)	0.09
Mitral E/A	1.6 (0.3)	−0.35	0.7 (0.2−1.8)	0.46			
RVFAC (%)	42.2 (3.5)	−0.29	0.7 (0.6−0.9)	**<0.01**	−0.21	0.7 (0.5−0.9)	**0.02**
Outcomes		Univariate regression					
Endpoints	N (%)	Variable		β	OR (95% CI)		p
Death	2 (4.7%)	Bromocriptine (yes = 1)#		−0.49	0.6 (0.1−2.2)		0.44
poor LV recovery	11 (25.6%)	postpartum Δ (yes = 1)		0.27	1.3 (0.3−5.3)		0.70
re-hospitalization	4 (9.3%)	Age (1unit = 1)		0.08	1.1 (0.8−1.4)		0.56
Composite	**14 (32.5%)**	HTN-CD (yes = 1)		1.24	3.4 (0.7−15.9)		0.10
Full LV recovery	26 (60.5%)	Inotropic therapy (yes: 1)		0.82	2.2 (0.4−12.5)		0.31
Partial LV recovery	4 (9.3%)	Parity		−0.03	0.9 (0.4−2.1)		0.93

*in ml/m^2; ^ with at presentation data; Δ: diagnosis; # of 35 patients discharged with bromocriptine only 19 patients used the drug for >/ = 1 week (54% adherence) and remaining (16/35) did-not used bromocriptine though prescribed; so, these 16 patients (prescribed but not used) and 5 patients (not prescribed) were taken as control (total = 21 [No = 0]) and remaining patients (19: during follow-up and 3: within hospital) were regarded as study group (total = 22 [Yes = 1]: mean duration of use - 2.2 weeks).
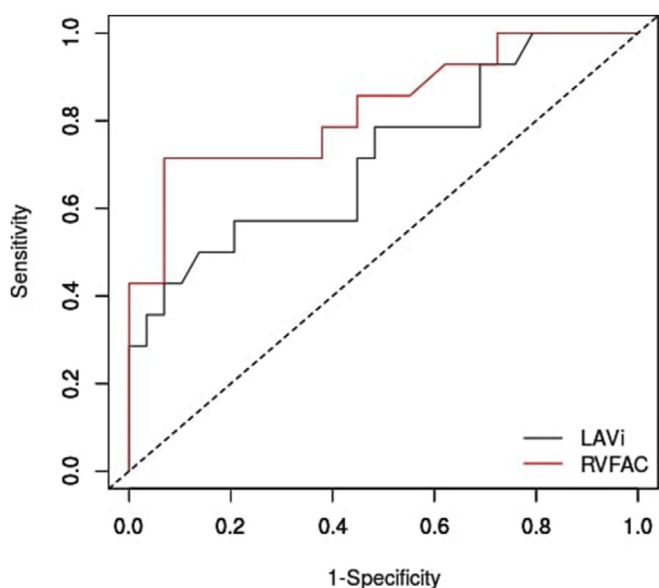

Fig. 1. Receiver-Operator Characteristics (ROC) curve demonstrating the predictive ability of RVFAC and LAVi for the study end-point.
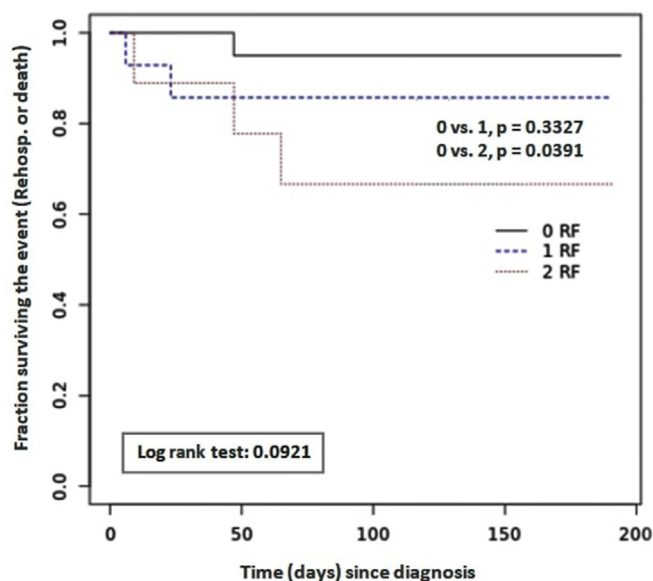

Fig. 2. Kaplan-Meier curves showing probability of event-free (re-hospitalization and death) survival in study population based on presence or absence of risk factors (RF: high LAVi, >29.6 ml/m^2 and low RVFAC, <31.4%).

evaluating cardiac function and size. The mean age of our study population was 25.4 (+/−2.9) years, comparable to studies from developing countries.[16]

Advanced maternal age,[17] post-partum timing[18] and history of hypertension[19] were found as predictors of adverse outcomes in few PPCM studies. However, similar results were not seen in our study population. Small studies had suggested the prognostic significance of serum C-reactive protein (CRP), brain natriuretic peptide (BNP) and Troponin T (Trop-T) levels[8] in predicting recovery but, due to non-availability of quantitative Trop-T and CRP round-the-clock at our centre, their clinical significance was not evaluated.

Bromocriptine is a new therapeutic agent showing promise in treating PPCM patients, but available literature has two important limitations. Firstly, most of its evidence comes from observational data. In-fact, in both German randomized trials, which proved that the rates of full ventricular functional recovery with 1-week

bromocriptine is equivalent to 8-week therapy did not have a control/placebo arm and hence cannot provide evidence for the drug benefit.[20,21] Secondly, majority of studies that showed the clinical usefulness of bromocriptine in PPCM did not used hard end-points like mortality and re-hospitalizations; this is important because, in BRO-HF study[22] though bromocriptine use was associated with significant LVEF recovery it failed to reduce the combined occurrence of all-cause death and HF events. Our practice of prescribing bromocriptine for varying duration in PPCM patients was based on patient preference, low birth weight of new-born child, and availability of new clinical evidence. Adherence rate was lower in our study with only 54% (19/35) of prescribed patients used this drug for more than or equal to 1 week and around 50% (21/43) did not used this drug for various reasons. This study results suggest that, bromocriptine had no impact on clinical outcomes,

but this was based on only 6-month observational data and also duration of the bromocriptine used was variable (1—8 weeks) thus affecting the robustness of the conclusion made. Though 2018 ESC guidelines include a weak recommendation (Class IIb, Level of Evidence: B) for the use of bromocriptine in PPCM,[2] placebo-controlled adequate sampled randomized studies like REBIRTH (Randomized Evaluation of Bromocriptine In Myocardial Recovery Therapy) are needed to truly uncover the impact of this drug on outcomes like mortality in PPCM.[8]

There is a limited data on the impact of inotropic therapy on the natural history of PPCM. Experience with levosimendan in patients with PPCM is less, with few case reports and studies indicating its beneficial effect on in-hospital outcome[23] but no effect on out-of-hospital short term follow-up outcomes.[24] In our study use of inotropic agents (dobutamine or levosimendan) was not associated with better 6-months outcomes. However, large scale metanalytic data suggests that, compared to dobutamine, levosimendan results in significantly improved survival and RV function in patients with acute decompensated heart failure.[25,26] But, due to smaller sample size, sub-group analysis was not done and impact of levosimendan in PPCM needs further study with adequate sample size.

There is a robust data on prognostic impact of LAVi in patients with heart failure,[27] but no study to date assessed its significance in PPCM. Mean left atrial volume index in our study was 27.1 ml/m^2 and the normal range of LAVi in Indian women was reported to be 15.7—23.3 ml/m^2 (mean: 19.5 ml/m^2).[28] LAVi at presentation was independently associated with the study end-point even after correction for LVEDVi and LVEF with an optimal cut-off of 29.6 ml/m^2. This superior ability of LAVi might be due to the facts that it is independently determined by LV filling pressures (function of systolic and diastolic function) and mitral regurgitation, which in turn are the predictors of adverse clinical outcomes in heart failure.[29—31] Our results support the notion that LAVi should be incorporated into the risk stratification and decision-making strategies in patients with PPCM.

Large scale observational studies had suggested that LV-EF of <30—35% and LV end-diastolic diameter (LVEDD) > 5.5—6 cm at presentation as important predictors of short and long-term outcomes in PPCM,[32,33] however, similar results did not replicated in our study after adjusting for other variables. Possible reasons could be small sample size; almost 100% reported drug adherence with the anti-remodelling agents; importantly LAVi was included in the analysis - which is a marker of combined systolic and diastolic dysfunction, and parallels LV dilatation.[34] Few well conducted studies showed that, though LVEF is a risk factor for poor recovery, it is unable to predict individually who would eventually recover due to its poor sensitivity with low overall accuracy[35] and some even failed to show its prognostic significance.[36]

Recently, right ventricular (RV) dysfunction at presentation was also found to be an independent predictor of poor outcomes and was proposed to represent a severe form of PPCM,[37,38] in fact some studies suggested that the prognostic ability of RV-FAC is even superior to LVEF.[37] Consistent with previous data, RV function was found as an independent risk factor for poor outcomes. Quantitative assessment of the RV function with RV-FAC improves the risk stratification beyond provided by LAVi, and a cut-off of 31.4% was found to be optimal.

In-hospital mortality in our study was 4.7%, which is higher than the western studies but comparable to studies that involved the Asian women.[39,40] This disparity of higher mortality rates in Asians might be due to various factors like delayed presentation, associated anaemia, or infections and since the Asian females are more vulnerable to death from PPCM.[41] At the end of 6 months, 60.5% of study population had a full recovery. A systematic review of data on the natural history of treated PPCM patients suggests that at the

end of 6 months 40—50% of patients recover [42,43] with 10—12% mortality [42,43]. However, in most studies recovery (defined as, a LVEF ≥50—55%) at 6—12 months follow up ranged between 14% and 85%, and mortality rates ranged from 0% to 16%. Differences in recovery and mortality rates may be explained by different selection criteria, socio-demographic and genetic variations, patient risk factors, and improvements in heart failure management. No mortality was recorded during follow-up in our population; it might be due to stronger follow-up, evidence-based treatment, good drug compliance, and probably a lower threshold for hospitalization by treating physicians.

Our Study has five main limitations. This was a single-centre study that may affect the generalizability of results and includes a small sample population thus affecting its validity. Second, patients were followed for only a short period (6 months), and long-term follow-up throws more in-sight into the natural history of treated PPCM patients. Another limitation is that there was no proper control group for assessing the impact of bromocriptine and levosimendan. Fourth, prognostic significance of blood biomarkers like BNP, CRP were not evaluated and finally an important clinical question relevant to resource-limited settings, new-borns' outcomes due to lactation suppression, was left unanswered.

5. Conclusions

With contemporary evidence-based management, about 61% of PPCM patients will have full LV functional recovery by the end of 6 months after diagnosis. Inotropic therapy at index hospitalization (dobutamine and/or levosimendan) did not result in better outcomes. Low RV fractional area change (RVFAC <31.4%, with 86% accuracy) and high left atrial volume index (LAVi >29.6 ml/m^2, with 72% accuracy) at presentation are independent predictors of adverse events. Suppression of lactation with bromocriptine was not associated with better recovery.

Declaration of competing interest

All authors have none to declare.

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