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ORIGINAL RESEARCH

# Hemodynamic Patterns and Left Ventricular Function Recovery in Peripartum Cardiomyopathy

## A Comprehensive Echocardiographic Analysis

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ABSTRACT

**BACKGROUND** The influence of hemodynamic changes at presentation on the recovery of left ventricular (LV) function in peripartum cardiomyopathy (PPCM) patients remains uncertain.

**OBJECTIVES** This study aims to identify hemodynamic patterns in individuals with PPCM.

**METHODS** This study included women with PPCM from 2 databases in Israel and Indonesia. Conventional echocardiography, 2-dimensional strain, myocardial work, and noninvasive pressure-volume loop analysis were performed with subsequent data clustering.

**RESULTS** Among 89 women (median age 32 years, IQR: 8.7 years; LV ejection fraction [EF] 36.0%, IQR: 11.5%), 63 (70.8%) experienced LV function recovery (LVEF ≥50%) during 6 months of follow-up. Gestation hypertension/pre-eclampsia and LVEF >35% and LVDD ≤55 mm at presentation were associated with LV recovery. Significant hemodynamic variability was observed, indicating a nonuniform PPCM pattern. Cluster analysis of 43 patients identified 3 hemodynamic subtypes. In cluster 1, patients exhibited the lowest rate of LV recovery (12.5%), profound contractility impairment, severe LV remodeling, and reduced cardiac output (CO). Cluster 2 showed a high LV recovery rate of 78.6%, prevalent in Southeast Asian patients with gestational hypertension. These patients displayed decreased CO and extremely elevated afterload. Load-dependent contractility indexes, like LVEF and global longitudinal strain, were markedly reduced, while load-independent end-systolic elastance remained unaffected, indicating afterload-dependent contractility impairment. All patients in cluster 3 recovered LVEF, presenting mildly reduced contractility indexes, mild ventricular dilatation, slightly increased afterload, and preserved CO.

**CONCLUSIONS** PPCM exhibits heterogeneous hemodynamic patterns, with 3 distinct phenotypes displaying varying rates of LV recovery. Understanding the heterogeneity in PPCM hemodynamic phenotypes can guide optimal treatment. (JACC Asia. 2025;5:554-564) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Peripartum cardiomyopathy (PPCM) is a significant cause of pregnancy-associated mortality and morbidity worldwide. Although PPCM generally has a higher recovery rate compared with other forms of heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF),[1,2] some young women experience persistent LV dysfunction and severe HF, necessitating advanced therapies such as durable devices or heart transplantation. According to recent data from the ESC EURObservational Research Program, up to 46% of patients with PPCM recover their LV function within 6 months.[3] However, recovery rates vary significantly among different racial groups and geographical regions.[4-8]

LVEF and left ventricular diastolic diameter (LVDD) at diagnosis are among the most reliable predictors of adverse outcomes or long-term recovery.[4,6,8,9] For instance, the Investigations of Pregnancy-Associated Cohort study found that an LVEF <30% and LVDD ≥6 cm were associated with lower recovery rates and increased risks of adverse events.[8] Nevertheless, these parameters may have limited sensitivity in predicting recovery for individual patients.[4]

In patients with PPCM, LVEF can be reduced to varying degrees at presentation, alongside either a normal-sized or significantly dilated LV. This variability does not align with a specific hemodynamic phenotype, such as dilated cardiomyopathy with HF with reduced EF, rather highlights the presence of hemodynamic heterogeneity. Therefore, a comprehensive hemodynamic analysis can provide valuable insights into the pathophysiological pathways of HF in PPCM.

This study aimed to identify distinct hemodynamic subtypes and evaluate their possible influence on LV recovery. We employed noninvasive hemodynamic assessment, including single-beat pressure-volume (PV) analysis and the recently introduced noninvasive pressure-strain-derived myocardial work (MW) analysis. Tailoring treatment based on hemodynamic patterns observed at presentation may be beneficial.

## METHODS

Using the 2 databases of patients with PPCM from Kaplan Medical Center, Israel, and Hasan Sadikin General Hospital, Indonesia, of 93 we identified 89 women (70 from Israel and 19 from Indonesia) in whom echo studies at presentation and 6-month follow-up were available. The study period extended from March 2016 to June 2021.

PPCM was defined as idiopathic cardiomyopathy diagnosed during pregnancy or within 5 months from delivery with echocardiographic LVEF <45%.[10] LV recovery was defined as LVEF ≥50% at any time during follow-up. We retrospectively analyzed clinical and echocardiographic data at presentation and at 6-month follow-up.

LV dimensions and LVEF for all patients were measured using the biplane Simpson's rule. For advanced hemodynamic assessment, 43 patients were selected based on image quality and availability for strain analysis. Raw data images were acquired using the Vivid E9 and E95 systems (GE Vingmed Ultrasound), digitally stored as DICOM cine loops, and subsequently transferred to a workstation for off-line analysis.

LV mass, and sphericity index were measured according to the American Society of Echocardiography recommendations, as well as peak velocities of early and late diastolic filling and early and late diastolic velocity by tissue Doppler imaging.[11] Both forward and total stroke volume (SV), stroke volume index (SVi), cardiac output (CO), and cardiac index were calculated. Systemic vascular resistance (SVR) (dynes·s·cm$^{-5}$) was determined as mean arterial pressure (MAP) × 80/forward CO. Total arterial compliance (TAC) was calculated as forward SV/systolic blood pressure (SBP)-diastolic blood pressure (DBP).[12]

The global longitudinal strain (GLS) was analyzed in 3 apical views and averaged. MW analysis, using estimated LV pressure from brachial artery BP and GLS, yielded the following values: Global Work Index (GWI, mm Hg %) is the total LV work during systole. Global Constructive Work (GSC, mm Hg %) includes productive work from muscle shortening during systole and lengthening during isovolumetric relaxation. Global wasted work (mm Hg %) covers nonproductive work, such as muscle lengthening during systole and shortening during isovolumetric relaxation. Global work efficiency (%) is the ratio of constructive work to the total of constructive and wasted work.[13,14]

We performed noninvasive PV analysis via echocardiography and simultaneous BP measurement. End-systolic elastance (Ees) was calculated using a single-beat methodology validated against invasive

### ABBREVIATIONS AND ACRONYMS

**σES** = myocardial fiber stress at end-systole

**Ea** = effective arterial elastance

**EDP** = end-diastolic pressure

**EDPVR** = end-diastolic pressure-volume relationship

**Ees** = end-systolic elastance

**GLS** = global longitudinal strain

**MW** = myocardial work

**PV** = pressure-volume

**TAC** = total arterial compliance

**$V_{30}$** = end-diastolic volume at a pressure of 30 mm Hg

methods.[15] Effective arterial elastance (Ea) was determined as: 0.9 × SBP/total SV,[16] and ventricular-arterial coupling was assessed using the Ea/Ees ratio.

Myocardial fiber stress at end-systole $\sigma_{ES}$ (kilodynes/cm$^2$) was estimated using the formula developed by Arts et al.[17]

LV diastolic operating stiffness was assessed by the ratio of end-diastolic pressure (EDP) to end-diastolic volume (EDV), a noninvasive measurement recently validated against invasive analysis.[18] A single-beat technique was employed to estimate the end-diastolic pressure-volume relationship (EDPVR) curves, utilizing stiffness constants $\alpha$ and $\beta$.[19] EDV at a pressure of 30 mm Hg ($V_{30}$) was used to estimate ventricular capacitance.

Group-averaged PV loops were reconstructed for PPCM patients and compared with 16 age-matched healthy nonpregnant women (age 33 ± 5 years) using echocardiographic data (end-systolic, end-diastolic LV volume, calculated EDP), along with simultaneous BP measurements and EDPVR.

All echocardiographic analyses were conducted at the Kaplan Medical Center echocardiography laboratory using EchoPAC software. An experienced sonographer, blinded to clinical data, performed the evaluations, with previously reported reproducibility for GLS measurements in our laboratory.[20] The study protocol received approval from the Human Research Institutional Review Board of both medical centers.

**CLUSTERING ANALYSIS.** Cluster analysis was performed to discern hemodynamic phenotypes. The following variables at the index event were included: the patient's age, geographic origin, the number of days from onset to diagnosis, hypertension, body mass index, heart rate, SBP, DBP, MAP, grade of MR, SV, SVi, CO, cardiac index, EF, GLS, Ees, EDV, EDV index, $V_{30}$, SVR, TAC, Ea, $\sigma_{ES}$, and Ea/Ees. Following data preparation, the data set was clustered using the Simple K-Means algorithm in the Weka 3.8.5 software package. The K-means algorithm was applied with a different number of clusters on each run, ranging from 2 to 8. To determine the final number of clusters for each visit, we identified the knee points of the sum of squared errors values. We observed 3 knees corresponding to 3, 4, and 7 clusters. After analyzing each division, 3 clusters were chosen. Subsequently, we used k-means clustering, and 3 homogeneous groups of patients were recovered.[21]

**STATISTICAL ANALYSIS.** Categorical and nominal variables were reported as prevalence and percentages, whereas continuous variables were reported as mean ± SD or as median (IQR). Continuous variables of each subgroup (recovered vs not recovered LV function, and among 3 cluster groups) were tested for normality using the Shapiro-Wilk test. When an abnormal distribution was identified, nonparametric tests were applied. Wilcoxon rank sum test was used to compare 2 groups, and the Kruskal-Wallis test was employed to compare 3 groups. A Student's *t*-test was utilized for normally distributed variables. Categorical and nominal variables were analyzed using Pearson's chi-square tests or Fisher exact tests, as appropriate.

Univariate and multiple logistic regression analyses were conducted to identify predictors of LV recovery. All baseline variables available for the entire group with $P < 0.20$ in the univariate analysis were entered stepwise into the multivariate logistic regression model. Various regression models were assessed after checking for multicollinearity and considering the relatively small sample size. To determine the discriminative ability of the combination of LVEF and LVDD between patients with and without LV recovery, a receiver-operating characteristic (ROC) analysis was performed, calculating the area under the curve, *P* values and test parameters, including sensitivity, specificity, and the Youden index. Results were considered significant when the *P* value was <0.05. All statistical analyses were performed using IBM SPSS Statistics, version 27.

## RESULTS

This study included 89 women with a median age of 32 years (IQR: 8.7 years); 78.7% were from Israel and 21.3% from Indonesia. Clinical characteristics, LVEF, and LVDD are presented in **Table 1**. Hypertension (gestational/pre-eclampsia) was present in 50.6% of the participants. All women were diagnosed with PPCM postdelivery, with 28.1% experiencing a diagnosis delay of over 2 weeks. Data on medical treatment were available for 87 patients: 92% received ACE inhibitors or ARBs, 96.6% beta-blockers, 34.5% spironolactone, 89.2% furosemide, and 9% bromocriptine. Baseline LVEF was 36.0% (IQR: 11.5%) and LVDD was 53.0 mm (IQR: 7.5 mm). The median follow-up was 183 days (IQR: 34.5 days). At 6 months, 70.8% showed LV function recovery, and 29.2% had persistent LV dysfunction. Follow-up LVEF and LVDD were 55.0% (IQR: 12.0%) and 50.0 mm (IQR: 8.5 mm), respectively. The nonrecovery group had a higher body mass index (26.7 kg/m$^2$ [IQR: 12.4 kg/m$^2$] vs 23.5 kg/m$^2$ [IQR: 4.5 kg/m$^2$]; $P = 0.002$) and a higher rate of delayed diagnosis (46.2% vs 20.6%; $P = 0.01$). No other significant differences were noted between the groups.

**TABLE 1** Patient Characteristics and Comparison Between LV Recovery and Nonrecovery Groups

| | PPCM Patient (n = 89) | Recovered (EF ≥50%) (n = 63, 70.8%) | Nonrecovered (EF <50%) (n = 26, 29.2%) | *P* Value[a] |
|---|---|---|---|---|
| Middle East | 70 (78.7) | 48 (76.2) | 22 (84.6) | 0.378 |
| Southeast Asia | 19 (21.3) | 15 (23.8) | 4 (15.4) | |
| Age, y | 32.0 (8.7) | 31.6 (8.6) | 33.2 (9.8) | 0.400 |
| BMI, kg/m$^2$ | 24.1 (6.6) | 23.5 (4.5) | 26.7 (12.4) | 0.002 |
| Multiparity | 51 (57.3) | 35 (55.6) | 16 (61.5) | 0.604 |
| Twin pregnancy | 12 (13.5) | 8 (12.7) | 4 (15.4) | 0.740 |
| Hypertension | 45 (50.6) | 36 (57.1) | 9 (34.6) | 0.053 |
| Delay of diagnosis, d | 2 (18) | 2 (11) | 10 (60) | 0.010 |
| Delay in diagnosis >2 wks | 25 (28.1) | 13 (20.6) | 12 (46.2) | 0.010 |
| NYHA functional class | | | | |
| II | 13 (14.6) | 9 (14.3) | 4 (15.4) | 0.976 |
| III | 48 (53.9) | 34 (54.0) | 14 (53.8) | |
| IV | 28 (31.5) | 20 (31.7) | 8 (30.8) | |
| LVEF, % at presentation | 36.0 (11.5) | 38.0 (10.8) | 30.0 (10.0) | <0.001 |
| LVDD, mm at presentation | 53.0 (7.5) | 52.0 (6.0) | 57.5 (11.0) | <0.001 |
| LVEF, % at follow-up | 55.0 (12.0) | 60.0 (5.0) | 43.0 (12.2) | <0.001 |
| LVDD, mm at follow-up | 50.0 (8.5) | 46.0 (7.0) | 56.0 (8.0) | <0.001 |

Values are n (%) or median (IQR). [a]Pearson's chi-square test; Wilcoxon rank sum test; Fisher exact test.
BMI = body mass index; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

**LV FUNCTION AT THE INDEX EVENT AND RECOVERY OF LV SYSTOLIC FUNCTION AT 6 MONTHS.** At diagnosis, the nonrecovery group had a lower LVEF (30.0% [IQR: 10.0%] vs 38.0% [IQR: 10.8%]; $P < 0.001$) and larger LV size (LVDD 57.5 mm [IQR: 11.0 mm] vs 52.0 mm [IQR: 6.0 mm]; $P < 0.001$). Although LV function improved in both groups, it was less in the nonrecovery group (LVEF 43.0% [IQR: 12.2%] vs 60.0% [IQR: 5.0%]; $P < 0.001$), and LVDD remained larger (56.0 mm [IQR: 8.0 mm] vs 46.0 mm [IQR: 7.0 mm]; $P < 0.001$) (Supplemental Figure 1).

**PREDICTORS OF LV FUNCTION RECOVERY.** Univariate analysis included age, gestational hypertension, diagnosis delay, baseline LVEF >35%, LVDD ≤55 mm, and MR grade ≥3 (Table 2). Gestational hypertension/pre-eclampsia and baseline LVEF >35% with LVDD ≤55 mm were associated with LV function recovery. Multivariate analysis identified baseline LVEF >35% (HR: 6.0; 95% CI: 1.60-22.25; $P = 0.008$) and LVDD ≤55 mm (HR: 4.05; 95% CI: 1.17-14.18; $P = 0.029$) as significant predictors. Recovery probability increased 35-fold for patients with both LVDD ≤55 mm and LVEF >35% at presentation. ROC analysis (Supplemental Figure 2) showed that this combined cutoff significantly predicted LV recovery, with an area under the curve of 0.847 (95% CI: 0.754-0.940; $P < 0.001$).

**EXTENDED NONINVASIVE HEMODYNAMIC ANALYSIS.** Based on image quality and availability for strain offline analysis, 43 patients were chosen for advanced hemodynamic assessment. Table 3 presents the basic characteristics and echocardiographic data for. patients with recovered vs nonrecovered LV systolic function. Average heart rate, SBP, DBP, and MAP were similar between the 2 groups.

**GEOMETRIC CHANGES.** Nonrecovery patients showed significant LV dilatation with increased end-systolic volume (110.4 ± 28.7 mL vs 81.2 ± 19.5 mL; $P < 0.001$) and EDV (162.9 ± 45.3 mL vs 125.4 ± 23.2 mL; $P = 0.022$) compared with the recovery group. LV shape changed more in the nonrecovery group, with a pronounced increase in sphericity index.

**CARDIAC OUTPUT.** Forward SV, SVi, CO, and cardiac index were lower in the nonrecovery group, although total CO was similar between groups. Total SV and CO were slightly higher in the nonrecovery group, potentially caused by a higher proportion of patients with significant MR.

**CONTRACTILITY.** Patients with LV recovery had a higher LVEF at diagnosis (34.7% ± 7.2% vs 27.6% ± 6.6%; $P = 0.007$) and greater Ees (2.18 ± 0.55 mm Hg/mL vs 1.59 ± 0.90 mm Hg/mL; $P = 0.012$) than those with nonrecovery. No differences were found in GLS or MW indexes.

**AFTERLOAD.** Afterload was elevated in both recovery and nonrecovery patients with PPCM. The nonrecovery group had higher SVR, lower TAC, and increased wall stress caused by LV remodeling. However, Ea was similar between groups.

**TABLE 2 Univariate Analysis of Predictors of Recovery of LV Systolic Function**

| | Recovered (EF ≥50%) (n = 63) | Nonrecovered (EF <50%) (n = 26) | OR | 95% CI | *P* Value[a] |
|---|---|---|---|---|---|
| LVDD ≤55 mm | 49 (77.8) | 9 (34.6) | 5.83 | 2.11-16.14 | <0.001 |
| EF >35% | 40 (63.5) | 5 (19.2) | 7.30 | 2.43-21.99 | <0.001 |
| MR grade ≥3 | 10 (15.9) | 8 (30.8) | 0.41 | 0.14-1.20 | 0.104 |
| Delay in diagnosis >2 wks | 13 (20.6) | 12 (46.2) | 0.28 | 0.10-0.76 | 0.012 |
| Hypertension (gestational/pre-eclampsia) | 36 (57.1) | 9 (34.6) | 2.52 | 0.97-6.51 | 0.053 |
| Age, y | 31.6 (8.6) | 33.2 (9.8) | 0.96 | 0.89-1.04 | 0.400 |

Values are n (%) or median (IQR). [a]Pearson's chi-square test; Wilcoxon rank sum test.
LVEF = left ventricular ejection fraction; LVDD = left ventricular diastolic diameter; MR = mitral regurgitation.

**PRELOAD, LV CAPACITANCE, DIASTOLIC STIFFNESS, EDP.** The nonrecovery group had greater LV capacitance compared with the recovery group ($V_{30}$: 179.9 ± 47.7 mL vs 134.6 ± 25.1 mL; $P < 0.001$). Diastolic function indexes and LV EDP did not differ between groups, although LV EDP was elevated in all PPCM patients. LV operating stiffness was significantly lower in the nonrecovery group (0.06 ± 0.02 vs 0.09 ± 0.03; $P = 0.009$). The stiffness coefficient β was similar between the groups.

**VENTRICULAR-ARTERIAL EFFICIENCY.** The ventricular-arterial efficiency, as measured by the Ea/Ees ratio, was markedly impaired in the nonrecovery group compared to the recovery group.

**CLUSTERING.** The variables used in the clustering analysis are presented in Table 4. The Central Illustration shows significant separation of these variables between at least one pair of clusters and includes schematic PV loops for each cluster compared with normal LV function in an age-matched control cohort. Figure 1 summarizes the hemodynamic trends observed within each cluster.

Patients in cluster 1 had the lowest LVEF recovery rate (12.5%) and the longest time from symptom onset to diagnosis (98 days, IQR: 138 days), compared with cluster 2 (14 days, IQR: 20 days), and cluster 3 (7 days, IQR: 18 days) ($P = 0.08$). Although the difference did not reach statistical significance, it remains meaningful from a clinical perspective. 87.5% of patients in this cluster were from the Middle East, and no cases of associated hypertension were observed. They had the lowest BP, normal total CO, and markedly decreased forward CO, EF, GLS, and the worst contractility index Ees (1.18 mm Hg/mL [IQR: 0.68 mm Hg/mL]; $P = 0.001$). LV EDV and $V_{30}$ were significantly higher in cluster 1 compared with cluster 2 (160 mL [IQR: 56 mL] vs 125 mL (IQR: 36 mL]; $P = 0.038$; 173 mL [IQR: 46 mL] vs 137 mL (IQR: 36 mL]; $P = 0.018$). Cluster 1 also had increased SVR and decreased TAC, with the highest Ea/Ees ratio among the clusters, indicating poor ventricular-arterial coupling.

Cluster 2 showed a high LV function recovery rate (78.6%) with 88% of patients from Southeast Asia and a high prevalence of gestational hypertension or pre-eclampsia (78.6%). This cluster had decreased forward and total CO, with severely reduced load-dependent contractility indexes (LVEF and GLS), although load-independent Ees was unaffected. Elevated afterload was noted with increased SVR, σES, and Ea, and decreased TAC, resulting in higher BP compared with clusters 1 and 3.

Cluster 3 had the best LV function recovery, with all patients achieving LVEF ≥50% at 6 months. Despite an initially moderately reduced LVEF of 38.0% (IQR: 5.8%), contractility indexes were only mildly reduced, preload and afterload slightly increased, and CO remained preserved.

## DISCUSSION

Our study confirms that reduced LVEF and LV dilatation are predictors of failure to recover LV function in PPCM, consistent with previous reports.[4,8,9] Gestation hypertension/pre-eclampsia and LVEF >35%, with LVDD ≤55 mm at presentation, are associated with recovery of LV function.

A comprehensive noninvasive analysis provided a more detailed assessment of cardiac function beyond LVEF and LV size, including parameters of contractility, preload, and afterload. Decreased GLS and MW were observed across all patients without significant differences between those with recovered LVEF and nonrecovered LVEF. Supporting our results, Briasoulis et al[22] did not find that GLS was an

**TABLE 3 Extended Hemodynamic Data in Patients With Recovered and Nonrecovered LV Systolic Function**

| | PPCM Patients (n = 43) | Recovered (EF ≥50%) (n = 32) | Nonrecovered (EF <50%) (n = 11) | *P* Value[a] |
|---|---|---|---|---|
| Heart rate, beats/min | 94.2 ± 18.2 | 94.8 ± 17.2 | 92.4 ± 21.7 | 0.720 |
| PASP, mm Hg | 37.2 ± 11.5 | 38.9 ± 11.3 | 31.4 ± 10.9 | 0.106 |
| MR grade ≥3 | 8 (18.6) | 5 (15.6) | 3 (27.3) | 0.392 |
| Forward cardiac output | | | | |
| SV, mL | 44.3 ± 12.5 | 47.0 ± 11.5 | 36.2 ± 12.2 | 0.016 |
| SVi, mL/m$^2$ | 26.9 ± 8.1 | 29.2 ± 7.4 | 19.8 ± 5.9 | <0.001 |
| CO, L/min | 4.04 ± 1.11 | 4.31 ± 0.90 | 3.22 ± 1.32 | 0.006 |
| Cardiac index, L/min/m$^2$ | 2.46 ± 0.75 | 2.69 ± 0.65 | 1.76 ± 0.61 | <0.001 |
| Total cardiac output | | | | |
| SV, mL | 46.3 ± 15.7 | 44.2 ± 14.0 | 52.6 ± 19.2 | 0.130 |
| SVi, mL/m$^2$ | 27.4 ± 7.2 | 27.2 ± 7.5 | 28.3 ± 6.7 | 0.649 |
| CO, L/min | 4.20 ± 1.30 | 4.03 ± 0.88 | 4.83 ± 2.01 | 0.075 |
| Cardiac index, L/min/m$^2$ | 2.56 ± 0.60 | 2.49 ± 0.51 | 2.62 ± 0.89 | 0.656 |
| Contractility indexes | | | | |
| EF, % | 32.9 ± 7.6 | 34.7 ± 7.2 | 27.6 ± 6.6 | 0.007 |
| Ees, mm Hg/mL | 2.03 ± 0.70 | 2.18 ± 0.55 | 1.59 ± 0.90 | 0.012 |
| GLS, % | −10.8 ± 3.2 | −11.1 ± 3.2 | −9.9 ± 3.1 | 0.266 |
| MW | | | | |
| GWE, | 0.88 (0.08) | 0.87 (0.09) | 0.89 (0.06) | 1.000 |
| GWI, mm Hg | 1,061 (542) | 1,113 (387) | 847 (411) | 0.200 |
| GCW, mm Hg | 1,200 (395) | 1,211 (315) | 1,032 (424) | 0.286 |
| GWW, mm Hg | 130.0 (94.0) | 136 (91) | 110 (178) | 0.468 |
| LV volume, mass and geometry | | | | |
| ESV/BSA, mL/m$^2$ | 52.7 ± 12.1 | 50.1 ± 11.9 | 60.4 ± 9.6 | 0.014 |
| EDV/BSA, mL/m$^2$ | 80.2 ± 13.4 | 77.2 ± 12.5 | 88.7 ± 12.8 | 0.013 |
| LVDD, mm | 54.6 ± 6.5 | 52.8 ± 5.1 | 59.8 ± 7.7 | 0.001 |
| $V_{30}$, mL | 146.5 ± 37.7 | 134.6 ± 25.1 | 179.9 ± 47.7 | <0.001 |
| LVMi, g/m$^2$ | 101.6 ± 21.9 | 102.4 ± 24.3 | 99.2 ± 13.0 | 0.700 |
| SpI diast | 0.47 (0.13) | 0.47 (0.14) | 0.43 (0.09) | 0.794 |
| Afterload | | | | |
| SBP, mm Hg | 126.8 ± 20.7 | 126.4 ± 20.4 | 127.9 ± 22.6 | 0.835 |
| DBP, mm Hg | 80.0 ± 17.4 | 81.7 ± 16.6 | 74.8 ± 19.6 | 0.262 |
| MAP, mm Hg | 95.6 ± 17.5 | 96.6 ± 16.9 | 92.5 ± 19.6 | 0.510 |
| SVR, dynes·s·cm$^{-5}$ | 2,067 ± 742 | 1,904 ± 590 | 2,555 ± 954 | 0.014 |
| TAC, mL/mm Hg | 0.97 ± 0.30 | 1.10 ± 0.32 | 0.71 ± 0.25 | 0.001 |
| Ea, mm Hg/mL | 2.41 (1.64) | 2.67 (1.6) | 2.20 (0.97) | 0.200 |
| $\sigma_{ES}$, kilodynes/cm$^2$ | 440.3 ± 81.4 | 424.3 ± 80.3 | 486.8 ± 68.1 | 0.026 |
| Ventricular-arterial interaction | | | | |
| Ees/Ea | 1.42 (0.61) | 1.28 (0.55) | 1.63 (0.39) | 0.011 |
| LV diastolic function and filing pressure | | | | |
| E, cm/s | 85.6 ± 28.2 | 85.7 ± 26.0 | 85.3 ± 35.7 | 0.971 |
| A, cm/s | 58.0 ± 22.1 | 61.6 ± 23.9 | 48.2 ± 12.5 | 0.100 |
| E/e' | 12.6 ± 3.5 | 12.9 ± 3.3 | 11.9 ± 3.9 | 0.442 |
| EDP, mm Hg | 18.3 ± 1.8 | 18.4 ± 1.7 | 18.1 ± 2.2 | 0.597 |
| LV diastolic stiffness | | | | |
| LV operating stiffness, mL$^{-1}$ | 0.08 ± 0.03 | 0.09 ± 0.03 | 0.06 ± 0.02 | 0.009 |
| α, mm Hg | $1.23\times10^{-12}$ ($3.35\times10^{-12}$) | $2.32\times10^{-12}$ ($3.26\times10^{-12}$) | $4.74\times10^{-13}$ ($5.11\times10^{-13}$) | 0.044 |
| β | 6.18 (0.17) | 6.19 (0.18) | 6.13 (0.20) | 0.404 |

Values are mean ± SD or median (IQR). α, β = stiffness constants. [a]Wilcoxon rank sum test; Wilcoxon rank sum exact test; 2-sample Student's *t*-test.

BSA = body surface area; CO = cardiac output; DBP = diastolic blood pressure; E = peak velocities of early and late (A) diastolic filling; e' = and early and late (a') diastolic velocity by tissue Doppler imaging; Ea = effective arterial elastance; EDP = end-diastolic pressure; EDV = end-diastolic volume; Ees = end-systolic elastance; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; GSC = global constructive work; GWE = global work efficiency; GWI = global work index; GWW = global wasted work; LV = left ventricular; LVDD = left ventricular diastolic diameter; LVMi = left ventricular mass index; MAP = mean arterial pressure; MR = mitral regurgitation; MW = myocardial work; PASP = pulmonary artery systolic pressure; PPCM = peripartum cardiomyopathy; SBP = systolic blood pressure; SpI = sphericity index; SV = stroke volume; SVi = stroke volume index; SVR = systemic vascular resistance; TAC = total arterial compliance; $V_{30}$ = end-diastolic volume at a pressure of 30 mm Hg; $\sigma_{ES}$ = myocardial fiber stress at end-systole.

**TABLE 4 Comparative Analysis of Clusters**

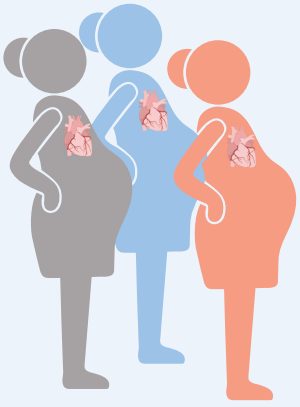
| | Cluster | | | |
|---|---|---|---|---|
| | 1 (n = 8, 20%) | 2 (n = 14, 35%) | 3 (n = 18, 45%) | *P* Value[a] |
| Middle East | 7 (87.5) | 2 (14.3) | 12 (66.7) | <0.001 |
| Southeast Asia | 1 (12.5) | 12 (85.7) | 6 (33.3) | |
| Time from symptom onset to diagnosis, d | 98 (138) | 14 (20) | 7 (18) | 0.08 |
| Pre-eclampsia/gestational hypertension | 0 (0) | 11 (78.6) | 9 (50) | 0.002 |
| MR grade ≥3 | 4 (50) | 1 (7.1) | 1 (5.6) | 0.014 |
| Forward cardiac output | | | | |
| SV, mL | 40.2 (12.9) | 36.5 (10.0) | 53.8 (7.8) | <0.001 |
| SVi, mL/m$^2$ | 20.9 (9.4) | 21.6 (6.1) | 33.6 (7.1) | <0.001 |
| CO, L/min | 3.01 (1.59) | 3.49 (0.73) | 4.58 (1.11) | <0.001 |
| Cardiac index, L/min/m$^2$ | 1.57 (0.62) | 2.22 (0.58) | 2.85 (0.87) | <0.001 |
| Total cardiac output | | | | |
| SV, mL | 51.5 (12.0) | 32.0 (6.2) | 51.5 (10.0) | <0.001 |
| SVi, mL/m$^2$ | 30.8 (6.7) | 21.5 (3.2) | 31.1 (7.2) | <0.001 |
| CO, L/min | 4.59 (2.63) | 3.29 (0.58) | 4.67 (0.76) | <0.001 |
| Cardiac index, L/min/m$^2$ | 2.51 (1.1) | 2.04 (0.47) | 2.76 (0.41) | <0.001 |
| Left ventricular contractility | | | | |
| EF, % | 29.0 (10.1) | 28.8 (9.4) | 38.0 (5.8) | <0.001 |
| GLS, % | −10.7 (5.2) | −8.26 (2.0) | −13.5 (3.26) | <0.001 |
| Ees, mm Hg/mL | 1.18 (0.68) | 2.58 (0.82) | 1.95 (0.78) | <0.001 |
| Preload | | | | |
| EDV, mL | 160 (59) | 125 (36) | 129 (38) | 0.038 |
| EDVi, mL/m$^2$ | 92.5 (23.1) | 80.8 (12.6) | 83.2 (19.7) | 0.189 |
| $V_{30}$, mL | 173 (46) | 137 (36) | 136 (40) | 0.018 |
| Afterload | | | | |
| SBP, mm Hg | 115 (18) | 140 (30) | 120 (33) | 0.017 |
| DBP, mm Hg | 66 (18) | 90 (10) | 80 (21) | <0.001 |
| MAP, mm Hg | 80 (13) | 108 (20) | 95 (23) | 0.002 |
| SVR, dynes•s•cm$^{-5}$ | 2515 (1469) | 2444 (608) | 1540 (450) | <0.001 |
| TAC, mL/mm Hg | 0.78 (0.44) | 0.77 (0.35) | 1.23 (0.42) | <0.001 |
| Ea, mm Hg/mL | 2.01 (0.71) | 3.94 (1.15) | 2.21 (0.94) | <0.001 |
| $\sigma_{ES}$, kilodynes/cm$^2$ | 438 (96) | 479 (103) | 403 (64) | 0.013 |
| Ventricular-arterial interaction | | | | |
| Ea/Ees | 1.61 (0.58) | 1.59 (0.35) | 1.05 (0.43) | 0.003 |
| LVEF at 6-month follow-up | | | | |
| EF, % | 39.5 (13.8) | 57.5 (11.5) | 59.0 (5.0) | <0.001 |
| Number of patients with EF ≥50% | 1 (12.5) | 11 (78.6) | 18 (100) | <0.001 |

Values are n (%) or median (IQR). [a]Fisher exact test; Kruskal-Wallis rank sum test.
Abbreviations as in Table 3.

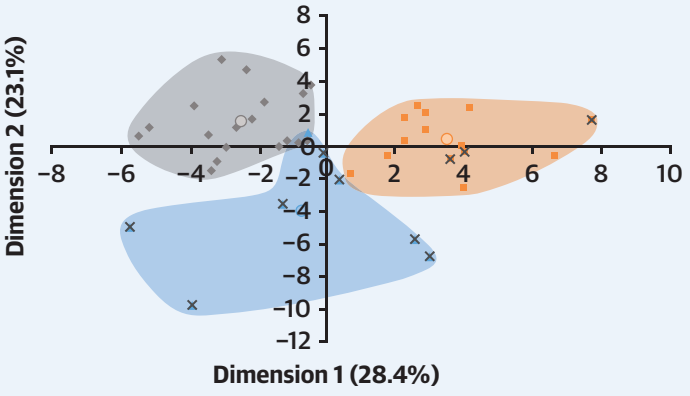
independent predictor of all-cause mortality, rehospitalization, or lack of LVEF recovery. Conversely, Sugahara et al[23] demonstrated that a low GLS (cutoff of 10.6%) at presentation was associated with death, transplantation, LV assist device implantation, or persistent LV dysfunction. These differences could be attributable to the larger sample size and higher prevalence of Black patients in their PPCM cohort. GLS reduction may indicate direct damage to the heart muscle or be influenced by high heart rates, volume overload, and elevated afterload. Averaging GLS across the entire group might obscure critical differences, leading us to identify specific hemodynamic patterns. Considering the recognized limitations of MW assessment principles, including the disregard for LV size, wall thickness, and wall stress, there is a potential for MW to be underestimated in dilated ventricles, where wall stress is higher.[24] This could explain the absence of differences in MW between patients with subsequent LV recovery and those with persistent LV dysfunction. Indeed, the latter group had more dilated ventricles and higher wall stress. In the nonrecovery group, we observed increased LV volume and ventricular capacitance,

**CENTRAL ILLUSTRATION** **Distinct Hemodynamic Clusters in Peripartum Cardiomyopathy**

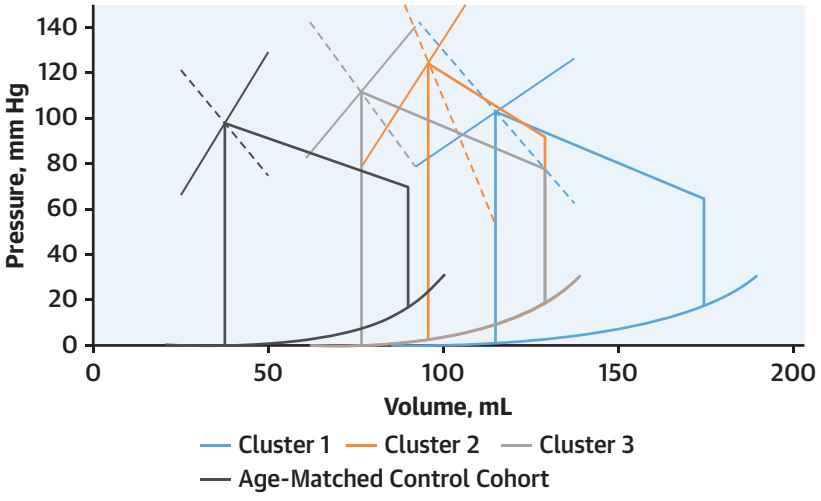
## Clustering Analysis of Clinical and Hemodynamic Parameters Identified 3 Homogeneous Groups With a Notable Separation of the Variables



The variability in hemodynamic parameters suggests a nonuniform pattern of peripartum cardiomyopathy




## Schematic Pressure-Volume Loops in 3 Clusters Compared With Age-Matched Normal Controls




## The Key Characteristics of Clusters

### Cluster 1

Profound contractility impairment, left ventricular (LV) remodeling, secondary mitral regurgitation, and reduced forward cardiac output (CO).
**The LV function recovery rate is 12.5%**

### Cluster 2

Extremely elevated afterload, reduced load-dependent contractility indexes, and total CO. There is a high prevalence of patients of Southeast Asian descent with gestational hypertensive disorders.
**The LV function recovery rate is 78.6%**

### Cluster 3

Mildly reduced contractility indexes, mild ventricular dilatation, slightly increased afterload, and preserved CO.
**The LV function recovery rate is 100%**

**Meledin V, et al. JACC Asia. 2025;5(4):554–564.**

Hemodynamic heterogeneity was observed in peripartum cardiomyopathy patients (upper left). Cluster analysis identified 3 homogeneous groups (upper right). Schematic pressure-volume loops in 3 clusters compared with age-matched normal controls (lower left). The key characteristics of clusters (lower right). Thick solid lines = pressure-volume (PV) loops and estimated end-diastolic PV relationship; thin solid lines = end-systolic elastance (Ees); thin dotted line = effective arterial elastance (Ea). CO = cardiac output; EF = ejection fraction; LV = left ventricular.

**FIGURE 1 Cluster-Specific Hemodynamic Patterns**

| Clusters (LV function recovery rate, %) | Total CO | Forward CO | Contractility | Preload | Afterload | MR | Energetic efficiency |
|---|---|---|---|---|---|---|---|
| Cluster 1 (12.5%) | ↔ | ↓↓↓ | ↓↓↓ | ↑↑↑ | ↑↑ | ↑↑ | ↓↓↓ |
| Cluster 2 (78.6%) | ↓↓↓ | ↓↓↓ | ↓↓ | ↑↑ | ↑↑↑ | ↑ | ↓↓ |
| Cluster 3 (100%) | ↔ | ↔ | ↓ | ↑ | ↑ | ↑ | ↓ |

Hemodynamic phenotypes of peripartum cardiomyopathy identified through cluster analysis. Cluster 1 is characterized by markedly reduced forward cardiac output (CO), a high prevalence of high-grade mitral regurgitation (MR), severely reduced contractility, left ventricular (LV) dilatation, increased preload, and severe ventricular-arterial decoupling. Cluster 2 features reduced forward and total CO, decreased load-dependent contractility indexes but preserved load-independent indexes, and extremely increased afterload. In Cluster 3, contractility indexes are mildly reduced, with slight increases in preload and afterload, and preserved CO. 1 to 3 arrows indicate slight, moderate, or severe changes in the corresponding parameter, while ↔ denotes no or nonsignificant changes.

suggesting ventricular remodeling, and reduced LV stiffness. Transitioning to low stiffness, as shown in the study of Chaturvedi et al., may indicate irreversible dilatation.[25]

By examining individual hemodynamic patterns, we found a diversity in parameters of CO, contractility, preload, and afterload. We used cluster analysis to define the hemodynamic phenotypes and their association with subsequent LV function recovery. This is the first study that identified 3 distinct phenotypes associated with different LV function recovery (**Central Illustration**). Women in cluster 1 had the worst rate of LVEF recovery and presented with the lowest BP. They had vastly decreased forward but preserved total CO, apparently caused by a high incidence of significant MR. LVEF and GLS were significantly reduced, and Ees was extremely low, indicating severe contractility impairment. An additional feature of cluster 1 was LV remodeling, manifested by a pronounced increase in ventricular capacitance, LV volume, and reshaping with increased sphericity. LV remodeling is usually associated with altered energy metabolism and a subsequent energy deficit.[26] In fact, cluster 1 patients had the highest Ea/Ees ratio, which has been shown to denote an unfavorable energetic efficiency state.[27] Increased wasted work observed in these patients adds to the metabolic burden. Such metabolic/energy changes may contribute to adverse remodeling[13] and attenuate reverse remodeling and recovery of the LV systolic function, causing the lowest recovery rate observed in this cluster. Our analysis showed that a combination of severe contractility impairment, LV remodeling, and an unfavorable energetic efficiency state at presentation predicts a lack of recovery in women with PPCM.

In contrast, over two-thirds of patients in cluster 2 recovered LV function. Their hemodynamic phenotype featured low cardiac output and high afterload, which can depress LV contraction,[28] evidenced by low GLS and EF. Because both GLS and EF are highly afterload dependent, reduced GLS and EF do not always imply reduced contractility.[29] The load-independent index Ees was within the normal range in cluster 2, indicating preserved intrinsic contractility. Therefore, while LV performance can be significantly affected by loading conditions, myocardial contractility remains relatively intact. This phenomenon illustrates the dissociation between cardiac performance and myocardial contractility.[30] The high prevalence of Southeast Asian patients in this cluster, exhibiting good recovery rates, aligns with ESC EORP PPCM Registry, which reported higher recovery rates in Asia-Pacific regions (77.5%) compared with the Middle East (32.7%).[31] Consistent with our findings, Jackson et al[2] demonstrated that women with PPCM and hypertensive disorders, including pre-eclampsia, were more likely to achieve LV recovery compared with those with PPCM alone. This improved outcome may be attributed to earlier diagnosis and treatment,

and better baseline cardiac function in patients with hypertensive disorders.

Additionally, longer time from symptom onset to diagnosis in cluster 1 is associated with prolonged cardiac damage, leading to hemodynamic issues such as LV remodeling and a higher incidence of secondary MR. This delay increases the risk of complications, reduces treatment effectiveness, and worsens cardiac function and recovery prospects. Poorer outcomes have been reported in women with a delayed diagnosis of PPCM.[9] In contrast, earlier diagnosed patients in cluster 2 experience acutely increased afterload.

All patients in cluster 3 experienced LV recovery. These patients are characterized by only mildly reduced contractility indexes, mildly dilated ventricles, no significant changes in afterload, and normal CO.

Excluding cluster 3, which represents "mild disease" with subtle myocardial injury, both clusters 1 and 2 present significant clinical challenges caused by their severe low cardiac output states and heart failure symptoms. Our study highlights the heterogeneous hemodynamic patterns in PPCM. This raises the question of whether these clusters should be considered distinct disease entities with different causes of pregnancy-associated heart failure or as subtypes of the same disease. The pathophysiology of PPCM involves both cardio-depressive and vascular components. Cardio-depressive mechanisms primarily include oxidative stress and metabolic disruptions within cardiomyocytes. In contrast, the vascular mechanisms are characterized by anti-angiogenic effects and endothelial cell dysfunction, exacerbated by factors like the 16-kDa prolactin fragment and elevated sFLT1 levels.[32] We believe that the cardiotoxic component predominates in cluster 1, leading to its distinct hemodynamic pattern. Conversely, cluster 2 appears to be predominantly influenced by vascular mechanisms, which contribute to its specific hemodynamic subtype. The different hemodynamic patterns described in our study represent subtypes of PPCM within the concept of "one disease." As noted in the editorial by Elkayam et al[33] on the paper by Sliwa et al,[3] "one disease with many faces" is supported by similar presentations across global populations, in terms of timing, mean age of patients, EF at presentation, and associations with older age, hypertension, preeclampsia, and multifetal pregnancies. The differences observed primarily relate to rates of complications and recovery.

Understanding the hemodynamic pattern at presentation in patients with PPCM may guide therapeutic efforts to correct the predominant pathophysiological abnormalities. Thus, in patients in cluster 1, the focus should be on enhancing the contractile function using positive inotropes. Levosimendan treatment, successfully used in PPCM women with severe heart failure, may be a viable option. Alternatively, temporary mechanical circulatory support could also be considered.[34,35] For patients in cluster 2, the emphasis should be on aggressive afterload reduction, addressing the underlying causes of reduced LV performance and depressed EF and GLS. These patients, with preserved intrinsic contractility and high afterload, can generally tolerate optimal heart failure therapies.

**STUDY LIMITATIONS.** The primary limitation of this study is the relatively small number of patients included in the cluster analysis. Despite this constraint, the analysis effectively demonstrated robust separation between clusters, allowing for the differentiation of hemodynamic subtypes in PPCM.

It is important to recognize that the meaningful differences in the time from symptom onset to diagnosis across clusters may impact the interpretation of hemodynamic changes between them.

Additionally, the inclusion of only patients from Israel and Indonesia limits the generalizability of the findings. Validation in a larger, more diverse cohort is necessary to confirm these results.

## CONCLUSIONS

The hemodynamic pattern of PPCM physiology is heterogeneous. Recognition of the hemodynamic phenotype of HF in women with PPCM at presentation can predict LV function recovery and assist in optimizing treatment.

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**KEY WORDS** hemodynamic phenotypes, LV recovery, peripartum cardiomyopathy

**APPENDIX** For supplemental figures, please see the online version of this paper.


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