Prognostic value of various markers in recovery from peripartum cardiomyopathy: a systematic review and meta-analysis

Alireza Hosseinpour¹, Hamidreza Hosseinpour², Fatemeh Kheshti³, Saeed Abdollahifard³,⁴ and Armin Attar¹*

¹Department of Cardiovascular Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; ²Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; ³Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran; and ⁴Research Center for Neuromodulation and Pain, Shiraz, Iran

Abstract

Aims The aetiology of peripartum cardiomyopathy (PPCM) is still not clear, and it is unknown who would recover from PPCM. In this meta-analysis, for the first time, we aimed to explore the prognostic value of potential baseline factors that may help predict recovery in patients with PPCM.

Methods A systematic approach following the Meta-analysis of Observational Studies in Epidemiology guideline was taken by using appropriate keywords in PubMed, Scopus, and Embase databases. Studies that had compared different clinical and paraclinical markers at the time of diagnosis related to cardiovascular function between recovered and non-recovered patients with PPCM were included. To find potential predictors of recovery, the odds ratio (OR) was calculated for different parameters using the random-effects model.

Results Eighteen cohort studies including 1047 patients with PPCM were enrolled. Six markers out of the 11 potentially eligible markers were associated with PPCM recovery. Baseline echocardiographic parameters [left ventricular ejection fraction (LVEF) (OR = 4.84 [2.53; 9.26]), left ventricular end-diastolic diameter (OR = 3.67 [2.58; 5.23]), left ventricular end-systolic diameter (OR = 3.99 [2.27; 7.02]), and fractional shortening (OR = 6.14 [1.81; 20.85])] were strong predictors of PPCM recovery. Systolic blood pressure (OR = 2.16 [1.38; 3.38]) and diastolic blood pressure (OR = 2.06 [1.07; 3.96]) at diagnosis were also associated with recovery.

Conclusions Patients with PPCM who have a higher baseline LVEF, lower left ventricular diameters, and higher blood pressure levels have a greater chance to recover from PPCM.

Keywords Heart failure; Left ventricular recovery; Peripartum cardiomyopathy; Predictors of recovery

Received: 26 March 2022; Revised: 9 July 2022; Accepted: 15 July 2022
*
Correspondence to: Armin Attar, MD, Department of Cardiovascular Medicine, School of Medicine, Zand Street, Shiraz University of Medical Sciences, 71344-1864 Shiraz, Iran.
Email: attar_armin@yahoo.com; attarar@sums.ac.ir

Introduction

Peripartum cardiomyopathy (PPCM) is an uncommon type of heart failure (HF) with reduced ejection fraction (EF) (HFrEF, commonly classified as a type of HF with an EF of ≤40%). PPCM is a rare type of dilated cardiomyopathy, which presents with HF associated with pregnancy that has no apparent cause and left ventricular (LV) EF (LVEF) that is nearly always below 45%.¹,² The incidence of PPCM varies markedly across different regions, with Japan having an incidence rate of six cases per 100 000 births and some other countries such as Nigeria with a high incidence rate of 995 per 100 000 live births.³ The incidence of PPCM appears to be correlated with some risk factors such as advanced maternal age, African descent, multiple-gestation pregnancy, and several comorbid conditions including pre-eclampsia (PE) and gestational hypertension.⁴ In a meta-analysis of 22 studies, the prevalence of PE in patients with PPCM was about four times higher than...
the average estimated rate in the general population (22 vs. 3–5%), suggesting a strong correlation between PE and PPCM. The definition of PPCM recovery is usually made by resolution of echocardiographic parameters, and LVEF is one of the most indicated ones. The majority of studies define recovery as LVEF reaching ≥45–55% in the follow-up echocardiography.5–8 Recovery from PPCM is more frequently achieved compared to other types of HF, and it usually occurs within 3–6 months after initial diagnosis. The recovery rate varies in different studies, ranging from 24 to 72%.10,11 Multiple factors have been associated with recovery and outcome including the baseline LVEF,10 African-American race,12 C-reactive protein (CRP) values,8 hypertension disorders,7 and the presence of an LV thrombus.13 Although studies have investigated different potential prognostic factors for recovery of patients with PPCM, the literature lacks appropriate meta-analyses evaluating predictors of PPCM recovery. In this study, we systematically reviewed the literature and sought to determine the baseline markers of PPCM patients including the baseline echocardiographic parameters, initial cardiovascular markers, and cardiovascular-related comorbidities that are associated with PPCM recovery.

Methods

For reporting the methodology and results of this systematic review and meta-analysis, we adhered to recommendations made by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.14

Eligibility criteria

Potential eligible studies were all the observational cohort ones that assessed the baseline markers and conditions related to the cardiovascular function indices including general parameters [systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)] and LV function markers measured by transthoracic echocardiography [LVEF, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and fractional shortening (FS)] in patients diagnosed with PPCM between the two groups of recovery and non-recovery. All the potentially eligible markers that were repeated in three or more studies were retrieved for meta-analysis based on a predefined criteria. PPCM was defined as the occurrence of an unexplained cardiomyopathy presenting with HFrEF in the last couple of months of pregnancy or following delivery without any recognized etiology for the HF.1 Three studies were required to divide the PPCM patients into two subgroups of recovered and non-recovered patients. Criteria for recovery from PPCM were resolution of LVEF ≥45% at the last available follow-up measurement, and LVEF values <45% were categorized into the non-recovery group. Studies that compared the markers between PPCM and control groups (normal pregnancies with cardiomyopathy) were excluded from this review. Studies that classified PPCM patients into improved vs. vs. PPCM patients [improved defined as LVEF and New York Heart Association (NYHA) functional class (FC)] improvement by 10% and 1 grade, respectively] and poor vs. good outcomes (poor outcome defined as mortality, rehospitalization, EF ≤35%, or no change in NYHA FC) were also not included in this study. Exclusion criteria for participants included patients with other comorbidities or previous history of HF, and age <18 years.

Search strategy of the literature and article identification

To find the relevant papers, we systematically searched electronic databases (PubMed, Scopus, and Embase), using a combination of the following keywords in addition to medical subject headings (MeSH): ‘peripartum cardiomyopathy’, ‘recovery’, ‘prognostic factors’, ‘predictors’, and ‘echocardiography’. The last search was run in February 2022. There were no specific restrictions on the date of publication and language. Two reviewers (AH and HH) screened the titles and/or abstracts to find the relevant articles independently. After a primary screening process, potentially eligible studies were retrieved for full-text screening eligibility by two authors (AH and AA). Any discrepancy during the screening was resolved by a group discussion. The citation list of the eligible studies was searched for possible additional relevant articles. A PRISMA flow diagram was created to illustrate the mentioned screening process.

Data extraction

Data abstraction for this review was conducted by a single author (AH) and then rechecked by a second reviewer (AA). Any discrepancy was solved through discussion between the authors. The following data were transferred into a pre-designed Excel sheet: title, first author name, publication year, study design, mean and standard deviation (SD) of the age of both groups, sample size of the recovery and non-recovery groups, values of parameters (general parameters SBP, DBP, and HR), and echocardiographic markers (LVEF, LVEDD, LVESD, and FS) for recovery and non-recovery groups. Additionally, dichotomous variables recorded in three or more studies, including data regarding the rate of hypertensive disorders of pregnancy (HDP), diabetes mellitus (DM), LV thrombus, and NYHA FC ≥III among both recovery and non-recovery groups, were also extracted for potential predictors of recovery. For serial publications with patient overlap, data were extracted only from the last published article with larger sample size.
Quality appraisal of eligible studies

For assessing the quality of eligible studies included in this systematic review, we employed the Quality in Prognostic Studies (QUIPS) tool. This quality appraisal tool assesses the risk of bias in six different domains, which may arise from the study participation, study attrition, measurement of prognostic factors, outcome measurement, potential confounding factors in the study, and statistical analyses and also an overall rating for each included study. The overall risk of bias for each study was rated as moderate or high if any domain had a moderate or high risk of bias. Two reviewers (AH and HH) performed the quality appraisal independently, and in the case of any disagreements, they were resolved through discussion.

Statistical analysis

All statistical analyses were conducted using RStudio software version 1.3.959. The mean and SD were calculated from the median and interquartile range (IQR) or median and range, using the method proposed by Wan et al. For all the analyses, the random-effects model was used for quantifying the pooled effect estimates. The inverse variance method was employed to calculate an overall mean and 95% confidence interval (CI) from the included studies for continuous outcomes. The results of the meta-analysis were presented by generating forest plots. For outcomes with dichotomous data, odds ratio (OR) and 95% CI were calculated. For continuous data, standardized mean difference (SMD) and its 95% CI were used to generate OR and 95% CI (smd2or function) with the Hasselblad and Hedges method. The mean difference (MD) and 95% CI were also calculated for continuous data. For easier interpretation of the results, ORs of recovery between 0 and 1 were reversed and the values differed significantly between the recovery and non-recovery groups in 12 studies. [One study measured EF values using cardiac magnetic resonance (CMR) and was not included for analysis of echocardiographic parameters.] Pooled analysis of LVEF at diagnosis and its 95% CI was reported in 18 studies. Settlement of values for analysis showed a high level of heterogeneity (I² = 76.5%, P < 0.001) with a high level of heterogeneity (I² = 76.5%, P < 0.001) (Figure A). After removal of the outliers, heterogeneity decreased to 95.5%, but the level of association diminished (OR = 3.10, 95% CI = [1.95, 4.93], P < 0.001). For other echocardiographic markers at baseline, a total of 14 included studies yielded 783 records. After removal of duplicates and application of the inclusion and exclusion criteria on the titles and abstracts of the remaining records, 358 studies were excluded. Full-text screening of the remaining articles led to a further exclusion of 407 records based on different reasons (130 review articles, 53 case reports, 8 practice guidelines, 17 non-human studies, 1 serial publication with patient overlap, and 198 studies failing to meet all the inclusion criteria or containing irrelevant data), and finally, 18 studies were included for systematic review and meta-analysis. Figure 1 depicts the PRISMA flow diagram for screening and inclusion process of this review.

Description of studies

A total of 1047 patients with PPCM, comprising 520 (50%) in the recovery group and 526 (50%) in the non-recovery group, from 18 studies were included. Majority of the studies were from the USA, China, South Africa, and Turkey. All eligible studies were published between 2005 and 2021. The sample size of PPCM patients ranged from 13 to 206 in the included studies. The mean age of the participants was 29.7 ± 5.9 years. There was a race diversity across studies: some studies recruited from the African race only, some had patients from different ethnicities (Caucasian and non-Caucasian), and one study had patients from rural Haiti, whereas others did not mention the proportion of different races.

Baseline echocardiographic parameters

Predictors of the LV function recovery differed among the included studies. Among the baseline echocardiographic parameters, initial LVEF was reported in 18 studies, and the values differed significantly between the recovery and non-recovery groups in 12 studies. (Figure A depicts the PRISMA flow diagram for screening and inclusion process of this review.)
Based on 14 studies involving 803 patients, the mean (95% CI) LVEDD was 56.28 mm (54.19–58.37) and 61.04 mm (59.01–63.06) in the recovery and non-recovery groups, respectively. The recovery group had significantly lower values of LVEDD compared to the non-recovery group (MD = −4.74 mm, 95% CI = [−5.48, −4.00], P < 0.001), and higher levels of LVEDD at baseline were associated with non-recovery of LV function (OR = 3.67, 95% CI = [2.58, 5.23], P < 0.001) (I² = 31.9%, P = 0.12) (Figure 2B).

There were six studies6,10,17,20,24,29 including 346 participants for measuring the initial LVESD between the two groups, and there was a statistical difference between the recovery and non-recovery groups in five out of the six included studies.6,10,17,20,29 The pooled mean of LVESD of the recovery and non-recovery groups was 45.84 mm (40.75–50.92) and 50.93 mm (44.22–57.64), respectively, and the recovery group had lower values of LVESD (MD = −5.30 mm, 95% CI = [−7.53, −3.08], P = 0.001). Pooled analysis of the six studies showed that higher levels of LVESD at diagnosis were associated with non-recovery from PPCM (OR = 3.99, 95% CI = [2.27, 7.02], P < 0.001) (I² = 37.9%, P = 0.15) (Figure 2C).

FS at diagnosis was reported by five studies,18,20,22,24,25 and only one study18 did not show a variation between the recovery and non-recovery groups. The mean FS of the included studies was 19.53% (17.24–21.82) and 15.29% (13.42–17.16) in the recovery and non-recovery groups, respectively. Also, the recovery group had significantly higher values of FS when compared to the non-recovery group (MD = 4.12%, 95% CI = [3.21, 5.03], P < 0.001). The pooled estimate showed a significant association between LV recovery and FS at baseline (OR = 6.14, 95% CI = [1.81, 20.85], P = 0.003) (Figure 2D), and the heterogeneity of these studies was high (I² = 76.1%, P = 0.002) with no outliers detected.

**Blood pressure and heart rate changes**

A total of five studies7,8,17,21,28 recorded the initial SBP and DBP at the time of diagnosis and compared them between the recovery and non-recovery groups. The mean values for SBP and DBP compared between recovered and non-recovered patients were 123.00 (108.12–137.86) and 80.58 (70.95–90.19) mmHg vs. 114.93 (104.17–125.68) and 74.32 (67.67–80.96) mmHg, respectively. Two studies7,28 showed a significant difference between the recovery and non-recovery groups regarding their initial measured DBP, whereas in only one study,7 SBP was significantly higher in the recovery group compared to the non-recovery one. The meta-analysis of the five studies showed that levels of SBP and DBP were significantly higher in recovered patients com-
| Study            | Publication year | Country          | Study design            | Age (mean ± SD) | Sample size (n) | Baseline LVEF (%) |
|------------------|------------------|------------------|-------------------------|-----------------|-----------------|-------------------|
| Amos et al.      | 2006             | United States    | Retrospective cohort    | 29 ± 6          | 22              | 23 ± 10           | LVEF ≥ 50%        |
| Biteker et al.   | 2018             | Turkey           | Prospective cohort      | 28 ± 5.3        | 30              | 29.7 ± 4.3        | LVEF ≥ 50% (early: at 6 months, late: after 6 months) |
| Biteker et al.   | 2018             | Turkey           | Prospective cohort      | 28 ± 5.3        | 30              | 29.7 ± 4.3        | LVEF ≥ 50% (early: at 6 months, late: after 6 months) |
| Blauwet et al.   | 2013             | South Africa     | Prospective cohort      | 30.7 ± 6.9      | 30              | 28.7 ± 8.4        | LVEF ≥ 55% at 6 months |
| Duran et al.     | 2008             | Turkey           | Prospective cohort      | 32 ± 7          | 8               | 34.5 ± 3.5        | LVEF ≥ 50% and NYHA FC I |
| Ekizler and Cay  | 2017             | Turkey           | Prospective cohort      | 29.2 ± 6        | 32              | 29.5 ± 8.5        | LVEF ≥ 55% at last available follow-up |
| Fett et al.      | 2005             | Haiti            | Prospective cohort      | 32.2 ± 6.8      | 26              | 28 ± 33.8         | LVEF ≥ 50% + NYHA FC I + LVFS ≥ 30% |
| Goland et al.    | 2011             | United States    | Retrospective cohort    | 30 ± 6          | 32              | 29.5 ± 8.5        | LVEF ≥ 55% at last available follow-up |
| Gürkan et al.    | 2017             | Turkey           | Retrospective cohort    | 30 ± 5.9        | 29              | 31 ± 10           | LVEF ≥ 50% at 6 months of follow-up |
| Hoevelmann et al.| 2021             | South Africa     | Prospective cohort      | 30 ± 5.9        | 19              | 25 ± 6.25         | LVEF ≥ 45%        |
| Liang et al.     | 2020             | China            | Prospective cohort      | 28.4 ± 5.9      | 10              | 29.3 ± 11.2       | LVEF ≥ 50% within 12 months of follow-up |
| Liu and Zeng     | 2016             | China            | Retrospective cohort    | 28 ± 4.5        | 16              | 39.1 ± 8.6        | LVEF ≥ 50% within 12 months of follow-up |
| Modi et al.      | 2009             | United States    | Retrospective cohort    | 25.2 ± 6.9      | 14              | 28.6 ± 25.7       | LVEF ≥ 50% at any follow-up visit |
| Perveen et al.   | 2016             | Pakistan         | Prospective cohort      | 27.4 ± 3.2      | 14              | 44.7 ± 2.3        | Resolution of HF symptoms and LVEF ≥ 50% at 6 months post-partum |
| Prasad et al.    | 2014             | India            | Prospective cohort      | 25.2 ± 5        | 8               | 28.7 ± 1.9        | LVEF ≥ 50% + NYHA FC I + LVFS ≥ 30% |
| Rajan et al.     | 2021             | India            | Retrospective cohort    | 27.2 ± 5        | 46              | 37.35 ± 9         | LVEF ≥ 50%         |
| Safi et al.      | 2010             | United States    | Prospective cohort      | 31.7 ± 5.7      | 43              | 29.8 ± 10.5       | LVEF ≥ 50%         |
| Li et al.        | 2015             | China            | Retrospective cohort    | 28 ± 6          | 40              | 39.5 ± 4.4        | LVEF ≥ 50%         |

HF, heart failure; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; NYHA FC, New York Heart Association functional class.
Figure 2. Forest plots of the correlation between echocardiographic parameters [(A) LVEF, (B) LVEDD, (C) LVESD, and (D) FS] and peripartum cardiomyopathy recovery (LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; FS, fractional shortening). The mentioned forest plots were reversed to the odds ratio of the non-recovery group for easier interpretation.
pared to non-recovered patients (SBP: MD = 6.64 mmHg, 95% CI = [0.14, 13.14], P = 0.04; DBP: MD = 5.01 mmHg, 95% CI = [−2.55, 12.58], P = 0.14). The pooled estimate for the baseline SBP and DBP showed that higher levels of SBP and DBP were associated with recovery [SBP: OR = 2.16, 95% CI = [1.38, 3.38], P < 0.001 (Figure 3A), DBP: OR = 2.06, 95% CI = [1.07, 3.96], P = 0.03 (Figure 3B)]. The level of heterogeneity for SBP and DBP was low (I² = 2.6%, P = 0.39) and moderate (I² = 50.7%, P = 0.08), respectively. There were four studies7,8,21,28 that retrieved the baseline HR in the two studied groups [mean HR = 88.98 (79.95–97.99) and 91.93 (80.88–102.98) in the recovered and non-recovered patients, respectively], and no study showed a variation between the baseline levels of HR between the groups. HR values were not significantly different among the groups (MD = −2.33, 95% CI = [−11.06, 6.40], P = 0.46). The overall estimate also showed no difference between the groups regarding their baseline HR values (OR = 1.31, 95% CI = [0.77, 2.24], P = 0.32), and minimal heterogeneity was observed (I² = 3.8%, P = 0.37) (Figure 3C).

Cardiovascular-related comorbidities and New York Heart Association functional class comparison

The included studies were analysed regarding the status of participants on HDP, DM, presence of LV thrombus, and

---

Figure 3  Forest plots of the correlation between baseline blood pressure and heart rates ([A] SBP, [B] DBP, and [C] heart rate) and peripartum cardiomyopathy recovery (SBP, systolic blood pressure; and DBP, diastolic blood pressure). *The mentioned forest plots were reversed to the odds ratio of the non-recovery group for easier interpretation.*
NYHA FC. Eleven studies\textsuperscript{6–8,10,13,19,20,22,23,26,29} compared the status of HDP in the recovery vs. non-recovery groups, and only one study\textsuperscript{7} showed a significantly higher rate of HDP among the patients recovered from PPCM. Pooled analysis did not show a difference between the two groups regarding the rates of HDP (OR = 1.44, 95% CI = [0.78, 2.65], \(P = 0.21\).

Figure 4  Forest plots of the correlation between (A) hypertensive disorders, (B) diabetes mellitus,\textsuperscript{8} (C) LV thrombus,\textsuperscript{8} and (D) NYHA FC\textsuperscript{9} and peripartum cardiomyopathy recovery (LV thrombus, left ventricular thrombus; and NYHA FC, New York Heart Association functional class). The mentioned forest plots were reversed to the odds ratio of the non-recovery group for easier interpretation.
was recorded in among the recovered and non-recovered PPCM patients lower in the recovered patients. However, a higher prevalence of NYHA FC ≥ III at diagnosis was statistically lower in the recovered patients. However, a higher prevalence of NYHA FC ≥ III was not associated with long-term non-recovery (OR = 1.92, 95% CI = [0.84, 4.36], P = 0.09, I^2 = 0.0%, P = 0.64) (Figure 4D). Table 2 summarizes the OR of PPCM recovery based on different parameters at diagnosis.

Cardiovascular parameters associated with mortality

The rate of mortality differed in the included studies, with some studies carrying a mortality rate from 3.3% (2/61 patients) to 30% (10/33 patients) (highest)10; some reported no cases of deaths within the follow-up period.13,22 Nine studies6,10,17,18,27,28,29–32 compared different parameters between the deceased and surviving patients. Mortality in PPCM patients was mostly associated with higher values of LVEF,6,10,17,29–32 and LVEDD10,17,29–32 and lower initial SV,30,32 in echocardiography. Lower initial SBP,30,31 and NYHA FC17,30,32 were also correlated with mortality in four studies. Other factors that could predict mortality included lower pulmonary artery systolic pressure (PASP),10 QRS duration,10 body mass index (BMI),17,31 dosage of the beta-blocker agent,31 need for mechanical ventilation,29 inotropic use,29 LVEF increase at the final follow-up,27 and higher log BNP level 6 months after diagnosis.6 One study did not find any marker (only measured echocardiographic markers) associated with mortality.18

Occurrence of major adverse events

The rates of mortality and non-recovery from PPCM have been discussed above. Other major adverse events included cardiac transplantation, embolic events, acute renal failure, deep vein thrombosis (DVT), and pulmonary oedema. Based on the data provided by four studies, the highest rate of PPCM patients requiring cardiac transplantation following persistent ventricular dysfunction was 10% (5/51).13 One study stated that 8.2% of the included patients needed mechanical circulation support and/or heart transplantation,7 and the other two studies reported transplantation in one of their participants.8,20 Four studies8,13,20,22 reported the rate of thromboembolic events [including one embolic myocardial infarction,15 two acute pulmonary embolisms,22 two DVTs,22 and other non-specified thromboembolic events8,20]. Seven cases of multiorgan failure and two ventricular arrhythmias leading to death were reported in a study.20 Acute renal failure happened as a complication of PPCM in four patients in one study.22 Also, two studies8,20 reported the number of patients who needed implantable cardioverter-defibrillator (ICD) implantation, in one of which,8 out of the total 20 patients receiving ICD, 15 had been assigned to the non-recovery group and five belonged to the recovery group.

Baseline treatment and recovery from peripartum cardiomyopathy

Data from eight studies were available regarding the applied treatment at diagnosis for recovered and non-recovered patients with PPCM.6–8,10,21,22,28,29 The baseline treatment was generally similar among the studies and included beta-blockers, diuretics, renin–angiotensin system inhibitors [angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB)], and inotropic agents (including dobutamine, digoxin, levosimendan, and milrinone). Only

Table 2  Odds ratio of peripartum cardiomyopathy recovery based on baseline echocardiographic parameters and clinical and paraclinical markers

| Markers                          | Odds ratio (95% CI) | P-value |
|----------------------------------|--------------------|---------|
| Left ventricular ejection fraction | 4.84 (2.53–9.26)   | <0.001  |
| Left ventricular end-diastolic diameter | 3.67 (2.58–5.23) a | <0.001  |
| Left ventricular end-systolic diameter | 3.99 (2.27–7.02) a | <0.001  |
| Fractional shortening            | 6.14 (1.81–20.85)  | 0.003   |
| Systolic blood pressure          | 2.16 (1.38–3.38)   | <0.001  |
| Diastolic blood pressure         | 2.06 (1.07–3.96)   | 0.03    |
| Heart rate                       | 1.31 (0.77–2.24) a | 0.32    |
| Hypertensive disorders           | 1.44 (0.78–2.65)   | 0.22    |
| Diabetes mellitus                | 1.26 (0.48–3.36) a | 0.56    |
| Left ventricular thrombus        | 3.06 (0.52–583.27) a | 0.46    |
| NYHA functional class            | 1.92 (0.84–4.36) a | 0.09    |

NYHA, New York Heart Association.

The mentioned values were reversed to the odds ratio (OR) of peripartum cardiomyopathy (PPCM) non-recovery for easier interpretation of data.
two studies\textsuperscript{6,21} reported data on the use of mineralocorticoid receptor antagonists (MRA), and three studies\textsuperscript{6,7,21} on the use of bromocriptine. One study\textsuperscript{6} reported the number of patients having an intra-aortic balloon pump, and another study\textsuperscript{7} had data on mechanical circulatory support use. Also, a study reported a significant correlation between ICD implantation and non-recovery from PPCM.\textsuperscript{8} The pooled meta-analysis on the different baseline treatments did not vary significantly between the two groups of recovery and non-recovery (Supporting Information, Figure S1).

\section*{Risk of bias in the studies}

Eighteen included studies used the process of quality appraisal using the QUIPS tool, seven trials were considered to have a low risk of bias, five studies were considered to be at moderate risk of bias, and five others were at high risk of bias (Table 3). All the studies with moderate and high risk were included for quantitative synthesis.

\section*{Publication bias and sensitivity analysis}

For LVEF, visual inspection of the funnel plot suggested asymmetrical distribution of the studies (Supporting Information, Figure S2), and for other parameters, the studies had a relatively symmetrical distribution around the mean. Egger’s test did not suggest publication bias, indicating no small-study effect in the parameters ($P > 0.05$) except for LVEF ($P = 0.04$) and LV thrombus ($P = 0.0009$). Thus, the trim-and-fill method was used for the mentioned markers. For LVEF, with two studies being added, a new OR of 3.72 (95% CI [1.68; 8.23], $P = 0.001$) was calculated. For LV thrombus, two studies were added during the trim-and-fill method, and an OR of 0.44 (95% CI [0.01; 30.33], $P = 0.62$) was achieved. For sensitivity analysis, we removed each single study from all the analyses to see their impact on the summary of results, and no significant change was observed for all the markers.

\section*{Discussion}

In this systematic review and meta-analysis, we investigated if baseline values of echocardiographic parameters and clinical and paraclinical markers can predict recovery in patients diagnosed with PPCM. Although multiple studies have aimed to detect the potential predictors of recovery, results have appeared to be contradictory. In the majority of studies, baseline LVEF was statistically associated with recovery, suggesting a potential predictor of outcome in PPCM; however, in some other studies,\textsuperscript{13,17,18,21,26,29} the initial EF was not statistically different in the two groups. Also, the values of LVEF 2–3 months after diagnosis were able to predict recovery.\textsuperscript{13,24} Follow-up values of LVEF after 6 months were remarkably higher in the recovered patients than in the non-recovered patients. This is expected because most cases of recovery happen up to 6 months after delivery. According to our results, pooled data of baseline LVEF from 17 studies and 1025 patients showed that higher baseline levels of LVEF were greatly correlated with LV recovery (OR = 4.84). Notably, among echocardiographic parameters, the initial FS had the largest magnitude of association with PPCM recovery, although FS had a wide CI, and this may be due to

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
Study & Participation & Attrition & Prognostic factor measurement & Outcome measurement & Confounding & Statistical analysis and reporting & Overall rating \\
\hline
Amos et al.\textsuperscript{13} & Low & Moderate & Low & Low & Low & Low & Moderate \\
Biteker et al.\textsuperscript{6} & Low & Low & Low & Low & Low & Low & Low \\
Blauwet et al.\textsuperscript{17} & Low & Moderate & Low & Low & Low & Low & Moderate \\
Duran et al.\textsuperscript{10} & Low & Low & Low & Low & Low & Low & Low \\
Ekizler and Cay\textsuperscript{8} & Low & Low & Low & Low & Low & Low & Low \\
Ersbell et al.\textsuperscript{7} & Low & Low & Low & Low & Low & Low & Low \\
Fett et al.\textsuperscript{18} & Low & Low & Moderate & Low & Low & Low & Moderate \\
Goland et al.\textsuperscript{19} & Moderate & High & Low & Low & Low & Low & High \\
Gürkan et al.\textsuperscript{20} & Low & Low & Low & Low & Low & Low & Low \\
Hoevelmann et al.\textsuperscript{21} & Low & Low & Low & Low & Low & Low & Low \\
Liu and Zeng\textsuperscript{5} & Moderate & High & Low & Low & Low & Low & High \\
Perveen et al.\textsuperscript{24} & High & Low & Moderate & Low & Low & Low & High \\
Prasad et al.\textsuperscript{25} & Low & Moderate & Low & Moderate & Low & Moderate & Moderate \\
Safirstein et al.\textsuperscript{26} & Low & High & Low & Low & Low & Low & High \\
Li et al.\textsuperscript{22} & Low & Low & Low & Low & Low & Low & Low \\
Liang et al.\textsuperscript{28} & Moderate & Low & Low & Low & Low & Low & Moderate \\
Rajan et al.\textsuperscript{29} & High & Low & Low & Low & Low & Low & High \\
Modi et al.\textsuperscript{27} & Low & Moderate & Low & Low & Low & Low & Moderate \\
\hline
\end{tabular}
\caption{Quality appraisal of the included studies using the Quality in Prognostic Studies tool}
\end{table}

\textsuperscript{ESC Heart Failure} 2022; 9: 3483–3495
DOI: 10.1002/ehf2.14085
heterogeneity between the studies. On top of that, other baseline echocardiographic parameters including end-diastolic diameter (EDD) and end-systolic diameter (ESD) of the left ventricle could also distinguish the recovered from the non-recovered patients because they both were statistically lower in the recovered group (EDD: OR = 3.67 and ESD: OR = 3.99). We should mention that some markers such as LVEF and FS had a wide CI and that this may be due to heterogeneity between the studies, and after excluding the outliers for LVEF, the CI was narrowed, although the level of correlation decreased. These results point out that baseline echocardiographic parameters can be employed in predicting recovery with FS and LVEF, having the strongest correlation with PPCM recovery.

Furthermore, the results of another analysis in the present study found a correlation between higher SBP and DBP at baseline and recovery, although diastolic values barely reached the significance level. It has been shown that higher levels of BP at diagnosis could be associated with recovery, and in one study, DBP could predict the LV recovery (OR = 1.145). However, baseline HR values did not differ between the two studied groups. Similar to our results, no study had found that HR is a predictor of recovery.

We performed additional analyses on the potential impact of cardiovascular-related comorbid conditions on PPCM recovery. Previous studies have reported that the incidence of PPCM is correlated with HDP, including gestational hypertension, PE, and eclampsia. In a study by Afana et al., all the incidence of HDP was remarkably higher in PPCM patients than in normal pregnancies. In some studies, PPCM patients were more likely to recover if they had HDP, although there was no correlation between hypertension and recovery rate in some other studies. HDP include four main categories of chronic hypertension (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg before 20 weeks of pregnancy), gestational hypertension (BP ≥ 140/90 mmHg after 20 weeks), PE–eclampsia, and chronic hypertension with superimposed PE. Although the main causes of a better prognosis of PPCM in patients with HDP are poorly explained, it has been hypothesized that besides the HDP itself, the early beta-blockade in patients with HDP during pregnancy may contribute to better results of PPCM. It is noteworthy that our results suggested that HDP were not associated with PPCM recovery (OR = 1.44). Contrary to the non-significant correlation of HDP with PPCM recovery, our results have revealed that higher BP values within the normal reference range at presentation (mean baseline BP values in the recovery group: 123/80 mmHg vs. in the non-recovery group: 114/74 mmHg) can predict recovery, and this should not be mixed up with HDP. Even though baseline BP values were considered as predictors of recovery, the BP values between the two groups differed slightly, and it may be challenging to deploy the information clinically. Thus, the clinical importance of this finding should be discussed with caution. The presence of LV thrombus in the echocardiogram has been listed as one of the other factors that were observed more frequently in the recovered patients, although our pooled analysis showed no link between LV thrombus and recovery. Moreover, Hoevelmann et al. have found that non-recovered patients were more likely to present with higher NYHA FC (III/IV). Based on our findings, higher FCs of NYHA at the time of diagnosis were not associated with recovery. Another comorbid condition was diabetes, and, as expected, pooled estimates did not show any variation when the two groups were compared.

Although most of the cases with PPCM recover within a short period of time, some cases are left with persistent long-term systolic dysfunction. It has been shown that non-recovered patients will present with major adverse events such as thromboembolic events and pulmonary oedema more frequently than the recovered cases. They may also need to receive ICDs or undergo cardiac transplantation in the long term. Thus, finding patients who are more susceptible to lack of recovery from PPCM should be of great importance because they may need more intensive therapy and closer observations; also, they may be considered for possible future heart transplantation. In this meta-analysis, our main goal was to find the baseline clinical and paraclinical markers of PPCM patients associated with recovery. We found that echocardiographic parameters (LVEF, LVEDD, LVESD, and FS) could be employed in predicting recovery because they were statistically different between the recovery and non-recovery patients. According to our results, SBP and DBP at the time of diagnosis also correlated with recovery. Contrary to some individual studies, such factors as LV thrombus, NYHA FC ≥ III, DM, and hypertensive disorders (chronic hypertension, gestational hypertension, PE–eclampsia, and chronic hypertension with superimposed PE) were not associated with recovery.

This meta-analysis included some limitations. Because we aimed to find the baseline predictors associated with recovery, we were unable to include the studies that only compared PPCM patients with normal pregnancies. Moreover, the criteria for recovery from PPCM varied widely in different studies. Some studies considered factors such as FS and EDD as variables for resolution of PPCM. Some studies classified PPCM patients into two groups with and without major adverse events (hospitalization, mortality, NYHA FC ≥ III, and EF ≥ 35%) or improved vs. non-improved (improvement was defined as an increase of EF by 10% or NYHA class by one class), and including these studies in our analysis could result in inconsistency. Therefore, we decided to only include the studies that defined recovery as the resolution of EF ≥ 45% because the majority of studies lie within the scope of this criterion for recovery. We were also unable to measure the pooled estimate of the comparison of some biomarkers such as NT-proBNP and BNP between the recovery and non-recovery groups. Studies that compared these two
markers were limited, some used logarithmic values of these factors, and hence, they were not combinable.

Conclusions

In the present meta-analysis, baseline echocardiographic parameters (LVEF, LVEDD, LVEDS, and FS) and BP values appeared to be potential predictors of PPCM recovery. Because echocardiography and BP measurement are easily accessible, they can be employed to improve our capabilities in predicting LV recovery in patients with PPCM. These data highlight the importance of the need to closely observe and determine the baseline parameters of these patients. Our findings should motivate future meta-analyses with individual participant data to provide a cut-off value of recovery for echocardiographic markers such as LVEF, which could help distinguish the recovered from non-recovered patients of PPCM.

Acknowledgements

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and also the Center for Development of Clinical Research of Nemazee Hospital and Dr Nasrin Shokrpour for editorial assistance.

Conflict of interest

None declared.

Funding

This study did not receive any specific grant from funding agencies.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The comparison of baseline treatment between recovery and non-recovery group (A: β-blockers, B: Renin-angiotensin system inhibitors, C: Diuretics, D: Inotropes, E: Mineralocorticoid receptor antagonists, F: Bromocriptine) (ACEi: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, MRAs: mineralocorticoid receptor antagonists).

Figure S2. Odds ratio of LVEF funnel plot analysis.

References

1. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkhayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology working group on peripartum cardiomyopathy. *Eur J Heart Fail*. 2010; 12: 767–776.
2. van der Meer P, Gaggin HK, Dec GW. ACC/AHA versus ESC guidelines on heart failure: JACC guideline comparison. *J Am Coll Cardiol*. 2019; 73: 2756–2768.
3. Isogai T, Kamiya CA. Worldwide incidence of peripartum cardiomyopathy and overall maternal mortality. *Int Heart J*. 2019; 60: 503–511.
4. Arany Z, Elkhayam U. Peripartum cardiomyopathy. *Circulation*. 2016; 133: 1397–1409.
5. Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2013; 62: 1715–1723.
6. Biterke M, Özlek B, Özlek E, Çig C, Çelik O, Doğan V, Başaran Ö. Predictors of early and delayed recovery in peripartum cardiomyopathy: a prospective study of 52 patients. *J Matern Fetal Neonatal Med*. 2020; 33: 390–397.
7. Erbøll AS, Johansen M, Damm P, Rasmussen S, Vejlstrup NG, Gustafsson F. Peripartum cardiomyopathy in Denmark: a retrospective, population-based study of incidence, management and outcome. *Eur J Heart Fail*. 2017; 19: 1712–1720.
8. Ekkizler FA, Cay S. A novel marker of persistent left ventricular systolic dysfunction in patients with peripartum cardiomyopathy: monocyte count-to-HDL cholesterol ratio. *BMC Cardiovasc Disord*. 2019; 19: 114.
9. Davis MB, Arany Z, McNamara DM, Golan S, Elkhayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020; 75: 207–221.
10. Duran N, Günes H, Duran I, Biterke M, Ozkan M. Predictors of prognosis in patients with peripartum cardiomyopathy. *Int J Gynaecol Obstet*. 2008; 101: 137–140.
11. McNamara DM, Elkhayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexi JD, Ramani GV, Semigran MJ, Haythe J, Markham DW, Marek, Gorcsan J III, Wu WC, Lin Y, Halder I, Pisarcik J, Cooper LT, Fett JD. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol*. 2015; 66: 905–914.
12. Irizarry OC, Levine LD, LeweyJ, Boyer T, Riis V, Elovitz MA, Arany Z. Comparison of clinical characteristics and outcomes of peripartum cardiomyopathy between African American and non-African American women. *JAMA Cardiol*. 2017; 2: 1256–1260.
13. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J*. 2006; 152: 509–512.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000; 283: 2008–2012.
Prognostic value of various markers in recovery from peripartum cardiomyopathy: a systematic review and meta-analysis

15. Hayden JA, van der Windt DA, Cartwright JI, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013; 158: 280–286.

16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14: 135.

17. Blauwet LA, Libhaber E, Förster O, Tibazarwa K, Mebazaa A, Hilfiker-Kleiner D, Sliwa K. Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. Heart. 2013; 99: 308–313.

18. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc. 2005; 80: 1602–1606.

19. Goland S, Bitar F, Modi K, Safrin J, Ro A, Mirocha J, Khatri N, Ellayam U. Evaluation of the clinical relevance of baseline left ventricular ejection fraction as a predictor of recovery or persistence of severe dysfunction in women in the United States with peripartum cardiomyopathy. J Card Fail. 2011; 17: 426–430.

20. Gürkan U, Akgöz H, Aksoy Ş, Can Gürkan O, Ösk sen A, Unal Dayı S, Oz D, Hacı R. Value of the neutrophil-to-lymphocyte ratio in predicting left ventricular recovery in patients with peripartum cardiomyopathy. Wien Klin Wochenschr. 2017; 129: 893–899.

21. Hoevelmann J, Muller E, Azibani F, Kraus S, Cirota J, Briton O, Ntsekhe M, Ntusi NAB, Sliwa K, Viljoen CA. Prognostic value of NT-proBNP for myocardial recovery in peripartum cardiomyopathy (PPCM). Clin Res Cardiol. 2021; 110: 1259–1269.

22. Li W, Li H, Long Y. Clinical characteristics and long-term predictors of persistent left ventricular systolic dysfunction in peripartum cardiomyopathy. Can J Cardiol. 2016; 32: 362–368.

23. Liu Y, Zeng Y. Clinical characteristics and prognosis of peripartum cardiomyopathy in 28 patients. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2016; 38: 78–82.

24. Perverse S, Auuudden J, Jabbab S, Soomro K, Ali A. Peripartum cardiomyopathy: frequency and predictors and indicators of clinical outcome. J Pak Med Assoc. 2016; 66: 1517–1521.

25. Prasad GS, Bhupali A, Prasad S, Patil AN, Deka Y. Peripartum cardiomyopathy—case series. Indian Heart J. 2014; 66: 223–226.

26. Safrin JG, Ro AS, Grandhi S, Wang L, Fett JD, Staniloae C. Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet. Int J Cardiol. 2012; 154: 27–31.

27. Modi KA, Illum S, Jariatul K, Caldito G, Reddy PC. Poor outcome of indigent patients with peripartum cardiomyopathy in the United States. Am J Obstet Gynecol. 2009; 201: 171.e1–171.e5.

28. Liang YD, Xu YW, Li WH, Wan K, Sun JY, Lin JY, Zhang Q, Zhou XY, Chen YC. Left ventricular function recovery in peripartum cardiomyopathy: a cardiovascular magnetic resonance study by myocardial T1 and T2 mapping. J Cardiovasc Magn Reson. 2020; 22: 2.

29. Rajan S, Jha N, Jha AK. Clinical characteristics, predictors and pregnancy outcomes in Indian women with peripartum cardiomyopathy. Obstet Med. 2021; 1753495X211051253.

30. Sliwa K, Förster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, Ansari AA. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J. 2006; 27: 441–446.

31. Libhaber E, Sliwa K, Bachelier K, Lamont K, Böhm M. Low systolic blood pressure and high resting heart rate as predictors of outcome in patients with peripartum cardiomyopathy. Int J Cardiol. 2015; 190: 376–382.

32. Sarojini A, Sai Ravi Shanker A, Anitha M. Inflammatory markers serum level of C-reactive protein, tumor necrotic factor-α, and interleukin-6 as predictors of outcome for peripartum cardiomyopathy. J Obstet Gynaecol India. 2013; 63: 234–239.

33. Afana M, Brinjikji W, Kao D, Jackson E, Maddox TM, Childers D, Eagle KA, Davis MB. Characteristics and in-hospital outcomes of peripartum cardiomyopathy diagnosed during delivery in the United States from the nationwide inpatient sample (NIS) database. J Card Fail. 2016; 22: 512–519.

34. Khedagi AM, Bello NA. Hypertensive disorders of pregnancy. Cardiol Clin. 2021; 39: 77–90.