META-ANALYSIS

Maternal-related factors associated with development and improvement of peripartum cardiomyopathy and therapeutic outcomes of bromocriptine

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ABSTRACT

Objective: This study aimed to fill the significant knowledge gap regarding peripartum cardiomyopathy (PPCM), a heart failure phenotype linked to pregnancy. The main objectives were to explore the factors influencing the development and progression of PPCM and to assess the outcomes of bromocriptine.
Materials and Methods: Systematic search across PubMed, ScienceDirect, and Cochrane Library identified studies until December 2022. This study includes non-randomized prospective and retrospective studies, as well as relevant randomized controlled trials. Risk factors were compared between the recovered and non-recovered PPCM groups, and bromocriptine therapy outcomes were evaluated against standard heart failure treatment as the primary endpoint.
Results: The analysis included 24 observational studies and 1 randomized controlled trial involving 1,651 PPCM patients; 9 studies evaluating the outcomes of bromocriptine therapy. The most prevalent factors were caesarean delivery (proportion = 53%, 95% CI = 41%-66%) and anemia (proportion = 51%, 95% CI = 38%-65%). Non-recovered patients were younger (MD=-1.04 years old, 95%CI=-1.82-(-0.27), p=0.008) and predominantly black (RR=1.82, 95% CI = 1.43-2.31, p <0.001). Hypertensive disorders and primiparity were found less among non-recovered patients (RR=0.73, 95% CI = 0.60-0.88, p=0.001; RR=0.81, 95% CI = 0.66-0.99, p=0.04, respectively). Non-recovered patients also exhibited higher baseline serum creatinine levels, lower LVEF, larger left ventricular end-systolic diameter (LVESD), larger left ventricular end-diastolic diameter (LVEDD), and lower fractional shortening (all p-values <0.05). Furthermore, bromocriptine significantly reduced major adverse cardiac events (MACE), mortality, and increased LVEF (all p-values <0.05).
Conclusion: Younger maternal age, black race, absence of hypertension, and multiparity are associated with poorer prognosis for PPCM recovery. Bromocriptine therapy demonstrates superior benefits in reducing adverse events in PPCM.

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Highlights:

Younger age, black race, normotension, and multiparity indicate a poorer prognosis for peripartum cardiomyopathy recovery, while bromocriptine therapy reduces adverse events.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurs during pregnancy or in first few months after childbirth. PPCM is diagnosed when there is unexplained onset of heart failure with a reduced left ventricular ejection fraction (LVEF) below 45% in previously healthy women.[1] Incidence of PPCM varies globally and is estimated to be 1 in 1000 pregnancies.[2] In United States, over 40% of PPCM cases are observed in women of black race.[3,4] Interestingly, although anemia is a well-established contributor to the pathophysiology of chronic heart failure, its consistency as a risk factor for PPCM has not been established.[5] However, a cohort study reported that pregnant women with anemia were five times more likely to develop PPCM.[6] Other factors that have been suggested to contribute to development of PPCM, such as history of preeclampsia/eclampsia or other hypertensive disorders, and multiple gestation, have also shown inconsistent associations with PPCM.[7] Therefore, the factors associated with the development of PPCM remain unclear.

Despite the unclear understanding of the risk factors and pathophysiology, the prognosis of PPCM appears to be improving. This is supported by the Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study, which reported a spontaneous recovery in 72% of patients, with only 13% experiencing persistent cardiomyopathy with an ejection fraction <35%.[8] The mortality rate of PPCM patients seems to be influenced by race/ethnicity and varies across geographical regions.[9] In contrast to previous studies citing mortality rates ranging from 2% to 10%, recent reports have shown a decrease in mortality to below 2%.[6,10] Recent research has revealed the involvement of the hormone prolactin in the pathogenesis of PPCM, suggesting that the inhibition of pituitary prolactin secretion through lactation cessation or the use of bromocriptine may be beneficial in PPCM treatment.[11] In a prospective observational study conducted in Germany, the use of bromocriptine demonstrated echocardiographic improvements compared to non-users.[12] However, it should be noted that bromocriptine has the side effect of suppressing lactation.[13] Since previous studies have reported spontaneous recovery of PPCM without the use of bromocriptine,[8,14–16] the administration of bromocriptine should be selective for patients who have a lower likelihood of recovery to balance the risks and benefits of this therapy.

Due to the substantial knowledge gap surrounding PPCM, systematic review and meta-analysis are necessary to provide a holistic assessment of various aspects, including risk factors, factors associated with recovery, and the outcomes of bromocriptine therapy. Such an analysis would contribute to the refinement of clinical management strategies for PPCM by providing robust evidence. The aims of study are to evaluate factors associated with development, recovery, and poor outcomes of PPCM and to assess outcomes of bromocriptine therapy.

MATERIALS AND METHODS

This meta-analysis strictly following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[17] The protocol was registered in international prospective register of systematic reviews (PROSPERO) under the registration code of CRD42023435415.

Search strategies

Comprehensive literature search conducted in MEDLINE (Medical Literature Analysis and Retrieval System Online) via PubMed, ScienceDirect, and the Cochrane Library. The search was performed from the beginning of the databases until December 2022, without any language restrictions. The following search string was used: ((Peripartum Cardiomyopathy) OR (PPCM)) AND ((Recovery) OR (Bromocriptine) OR (Prolactin)). Five authors (I.G.B.M.A.P, G.N.P.J, I.B.S.W, F.D, I.W.A.S.P) oversaw the entire process, from conducting the literature search to data extraction and bias assessment. Any discrepancies or uncertainties regarding study eligibility were thoughtfully resolved through consensus, involving an additional author (R.S.M) in the decision-making process.

Study selection

Identified studies were initially screened based on title and abstract. Studies met the criteria were included in this analysis. Population of study consists of all patients diagnosed with PPCM defined as signs and symptoms of left ventricular systolic dysfunction occurring towards the end of pregnancy or in the months following delivery, without the possibility of another identified cause of heart failure. Inclusion criteria for this study encompassed non-randomized two-arm prospective studies, two-arm retrospective studies, and randomized controlled trials. We excluded studies falling into the following categories: experimental animal models/basic science, review/meta-analysis, secondary research papers, case reports, and case series, as well as those involving duplicate populations. The search strategy included both Medical Subject Headings (MeSH) terms and relevant free-text keywords pertinent to the subject of inquiry. From the initial pool of 2,233 retrieved manuscripts, a total of 25 met the predefined inclusion criteria, as delineated in the PRISMA flowchart (Figure 1).

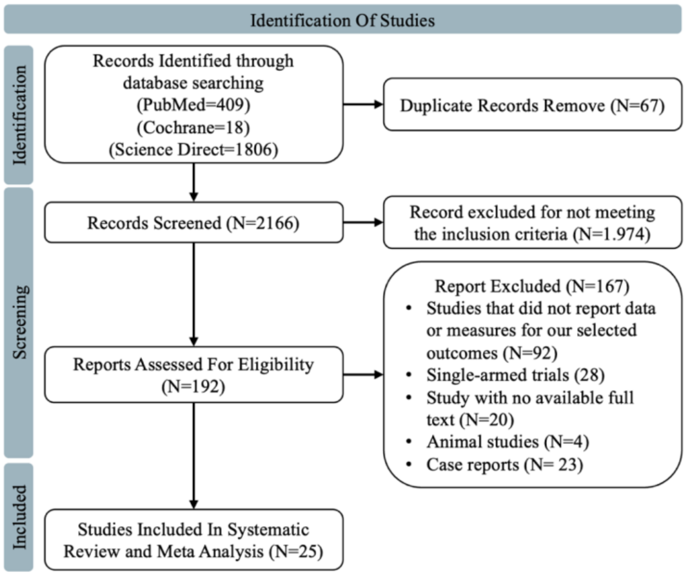

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Data extraction

A systematic data extraction process was carried out to assemble comprehensive demographic, baseline characteristics, and outcome-related data derived from the studies included in the analysis. Data extraction was conducted independently by five researchers (I.G.B.M.A.P, G.N.P.J, I.B.S.W, J.C.S, B.G.D.L). Standard forms were utilized to extract the relevant information. The extracted data included the baseline characteristics and demographic patients in each study, such as study design, sample size, definition of PPCM, number of patients who recovered from PPCM, criteria for recovery, number of patients treated with bromocriptine, dosage of bromocriptine, follow-up duration, mean age, and other key variables. The research aimed to evaluate factors associated with development, recovery, and poor outcomes of PPCM and to assess outcomes of bromocriptine therapy. Thus, the data for analysis focused primarily on the specified outcomes of interest. These outcomes included factors related to the recovery of PPCM, such as hypertensive disorders, preeclampsia/eclampsia, primiparity, multiple gestations, caesarean delivery, gestational diabetes, race/ethnicity, baseline New York Heart Association (NYHA) functional class >3, baseline age, baseline serum creatinine, baseline C-reactive protein (CRP), baseline prolactin, baseline LVEF, baseline left ventricular end-systolic diameter (LVESD) baseline left ventricular end-diastolic diameter (LVEDD), baseline fractional shortening (FS), and baseline brain natriuretic peptide (BNP). Outcomes of bromocriptine therapy included major adverse cardiac events (MACE), mortality, PPCM recovery, and change in LVEF.

Quality and risk-of-bias assessment

Following data extraction, the systematic quality assessment of the included studies was independently performed by the five reviewers. Newcastle-Ottawa Scale (NOS) were performed for assessing the quality of observational studies, which comprises eight items categorized into three domains. Based on the total score, if the score ranged from 7 to 9 was classifies as good, score ranged from 4 to 6 as moderate and otherwise as poor, and the Cochrane Risk of Bias tool (RoB) were used for randomized controlled trial (RCT) studies,[18,19] which evaluated the possible risk of bias in various domains. The judgments for each domain were categorized as "low risk," "unclear," or "high risk" of bias.

Outcome measurement

This meta-analysis encompasses three primary outcomes, namely the proportion of baseline risk factors among PPCM patients, the differences in baseline characteristics of PPCM patients who achieved recovery and those who did not, and the outcomes of bromocriptine therapy. We conducted a comparative analysis of each risk factor between recovered and non-recovered PPCM patients, as well as a comparison of the outcomes between bromocriptine and standard heart failure (HF) treatment, which served as the endpoint of our study. Data synthesis and Analysis Quality Assessment Review Manager Software (RevMan 5.4.1) was utilized for conducting the analysis. Continuous data were presented as mean difference (MD) with standard error, along with 95% confidence intervals.

Dichotomous outcomes were expressed as percentages and totals. Inconsistency among studies was assessed using the I-square test (I2) and the P-value of the x2 test.[20] The overall proportion of risk factors for PPCM development was analyzed using a random-effects model of proportional meta-analysis through RStudio (version 4.1.3).

RESULTS AND DISCUSSION

Study selection and study characteristics

Study selection process is summarized in the PRISMA flow diagram shown in Figure 1. The initial search yielded 2,223 studies, and after removing duplicates, 2,166 studies were independently screened by five researchers. A total of 192 potentially relevant studies underwent full-text review. Ultimately, this meta-analysis included 25 studies with 1,651 PPCM patients.[12,14–16,21–41] Among these studies, only one was a RCT.[28] The characteristics of included studies, including methodology, endpoints, and demographic data, are presented in Table 1. Of the total population, 703 patients recovered from PPCM, while 948 patients did not. Regarding the definition of PPCM, which has been explained above. There were variations in the criteria for recovery, considering clinical improvement and an increase in ejection fraction. Only seven studies administered bromocriptine therapy, with daily doses ranging from 2.5 to 5 mg.[12,16,28,29,32,39,41] The follow-up duration for patients varied from 6 to 45 months.

Table 1. Baseline summary of study characteristics

No	Study ID, Year	Country	Study Design	Sample Size	Recovery Patients	Recovery Criteria	Bromocriptine Use	Bromocriptine Dosage
1	Amos, 2006	USA	Cohort Retrospective, Single Center	49	27	Recovery of LV function was defined as an improvement in absolute EF of 50%.	NA	NA
2	Azibani, 2020	South Africa and Germany	Cohort Prospective, Multi Center	151	105	Gain of 10% in LVEF and, LVEF ≥35% at 6 months of follow-up; full left ventricular recovery was defined as LVEF ≥50% at 6 months of follow-up.	97	NA
3	Biteker, 2018	Turkey	Cohort Prospective, Single Center	52	30	Resolution of heart failure symptoms or signs and normalization of LVEF (ejection fraction >50 %)	15	2.5 mg b.i.d for 2 weeks, followed by 2.5 mg o.d for 6 weeks.
4	Blauwet, 2014	South Africa	Cohort Prospective, Single Center	176	30	LVEF ≥55% at 6 months.	NA	NA
5	Duran, 2007	Turkey	Cohort Retrospective, Single Center	33	8	NYHA FC I (New York Heart Association Functional Class) and LVEF above 50%.	NA	NA
6	Ekizler, 2019	Turkey	Cohort Retrospective, Single Center	64	29	Presence of LV ejection fraction (LV EF) >45%.	NA	NA
7	Ersbøll, 2017	Denmark	Cohort Retrospective, Single Center	61	32	LVEF ≥55% after 12 months or at last available follow-up before 12 months	NA	NA
8	Fett, 2005	Haiti	Cohort Prospective, Single Center	98	26	LVEF of 50% or higher, a LVFS of 30% or higher, and NYHA class I, with or without continuation of medications related to HF.	NA	NA
9	Goland, 2011	USA	Cohort Retrospective, Multi Center	187	115	LVEF ≥50% at ≥6 months after the diagnosis.	NA	NA
10	Gürkan, 2017	Turkey	Cohort Retrospective, Single Center	40	19	LV ejection fraction (EF) >45%	NA	NA
11	Haghikia, 2013	Germany	Cohort Prospective, Single Center	115	45	Reaching an LVEF of 55 % and NYHA class I to II.	64	2.5-5mg o.d. for 4 weeks

12	Hilfiker-Kleiner, 2017 (a)	Germany	Randomized Multicenter Clinical Trial	63	NA	NA	31	2.5 mg b.i.d. for the first 2 weeks and 2.5 mg o.d. for another 6 weeks
13	Hilfiker-Kleiner, 2017 (b)	South Africa, Germany, Scotland	Cohort Prospective, Multi Center	34	18	LVEF ≥50% were classified as fully recovered	21	2.5-5mg o.d. (For four weeks)
14	Hoevelmann, 2018	South Africa	Cohort Prospective, Single Center	66	21	LVEF ≥50% was regarded as a full recovery of LV function	19	NA
15	Hoevelmann, 2021	South Africa	Cohort Prospective, Single Center	35	18	LVEDD <55 mm and LVEF ≥ 50% within the 12-month follow-up period	NA	NA
16	Kurbanov, 2020	Republic of Uzbekistan	Cohort Retrospective, Single Center	43	18	Full recovery of LV function (LVEF >55%) and significant regression of CHF symptoms	21	2.5 mg b.i.d for 2 weeks, followed by a decrease to 2.5 mg per day for another 2 weeks
17	Li, 2015	China	Cohort Retrospective, Single Center	71	40	Presence of LVEF >50%	NA	NA
18	Liang, 2020	China	Cohort Retrospective, Single Center	21	10	LVEF ≥50% over at least 6 months' follow-up.	NA	NA
19	Mahowald, 2019	USA	Cohort Retrospective, Single Center	59	22	LVEF ≥55% at the conclusion of follow-up	2	NA
20	Modi, 2009	USA	Cohort Retrospective, Single Center	44	14	LV function recovery as the presence of LVEF of 50% or higher at any follow-up visit after the diagnosis	NA	NA
21	Perveen, 2016	Pakistan	Cohort Prospective, Single Center	22	14	Resolution of HF symptoms and signs and normalization of left ventricular systolic function (LVSF) (EF >50%) and persistent left ventricular dysfunction (PLVD) (EF<50%) at 6 months postpartum.	NA	NA
22	Prasad, 2014	India	Cohort Prospective, Single Center	16	13	LVEF of 50%, LV fractional shortening of 30% or higher and NYHA functional class I with or without continuation of medication related to heart failure.	NA	NA
23	Safirstein, 2012	USA	Cohort Prospective, Single Center	55	43	LVEF ≥50% at the conclusion of follow-up	NA	NA
24	Silwa, 2010	South Africa	Cohort Prospective, Single Center	20	16	NYHA functional class III/IV, or LVEF 35% at 6 months as death, NYHA functional class III/IV, or LVEF 35% at 6 months as previously described.	10	2.5 b.i.d for 2 weeks followed by 2.5 mg daily for 6 weeks in addition to standard heart failure therapy.
25	Tremblay, 2019	Canada	Cohort Prospective, Multi Center	76	NA	NA	8	2.5 mg b.i.d for 2 weeks followed by 2.5 mg daily for 6 weeks

Table 2. Risk of bias assessment of observational studies included in the meta-analysis according to the Newcastle-Ottawa Scale

No	Author, years	Selection				Comparability	Outcome			Overall score	Quality of study
		Representative-ness exposed cohort	Selection of non-exposed cohort	Ascer-tainment of exposure	Outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assess-ment of outcome	Enough follow up time	Adequacy of follow up of cohorts		
1	Amos, 2006	*	*	*	*	**	*	*	*	9	Good
2	Azibani, 2020	*	*		*	*	*	*	*	7	Good
3	Biteker, 2018	*	*		*	*	*	*	*	7	Good
4	Blauwet, 2014	*	*	*	*	*	*	*	*	8	Good
5	Duran, 2007	*	*	*		*	*	*	*	7	Good
6	Ekizler, 2019	*	*	*	*	**	*	*	*	9	Good
7	Ersbøll, 2017	*	*	*	*	**	*	*	*	9	Good
8	Fett, 2005	*	*	*	*	*	*	*	*	8	Good
9	Goland, 2011	*		*	*	*	*	*	*	7	Good
10	Gürkan, 2017	*	*	*	*	*	*	*	*	8	Good
11	Haghikia, 2013	*	*		*	*	*	*	*	7	Good
12	Hilfiker-Kleiner, 2017 (b)	*		*	*	**	*	*	*	8	Good
13	Hoevelmann, 2018	*	*		*	*	*	*	*	7	Good
14	Hoevelmann, 2021	*	*		*	**	*	*	*	8	Good
15	Kurbanov, 2020	*	*	*		**	*	*	*	8	Good
16	Li, 2015	*	*	*	*	**	*	*	*	9	Good
17	Liang, 2020	*	*	*	*	*	*	*	*	8	Good
18	Mahowald, 2019	*	*		*	*	*	*	*	7	Good
19	Modi, 2009	*	*	*	*	*	*	*	*	8	Good
20	Perveen, 2016	*	*		*	**	*	*	*	8	Good
21	Prasad, 2014	*	*		*	**	*	*	*	8	Good
22	Safirstein, 2012	*	*	*	*	**	*	*	*	9	Good
23	Silwa, 2010	*	*	*	*	**	*	*	*	9	Good
24	Tremblay, 2019	*	*	*	*	*	*	*	*	8	Good

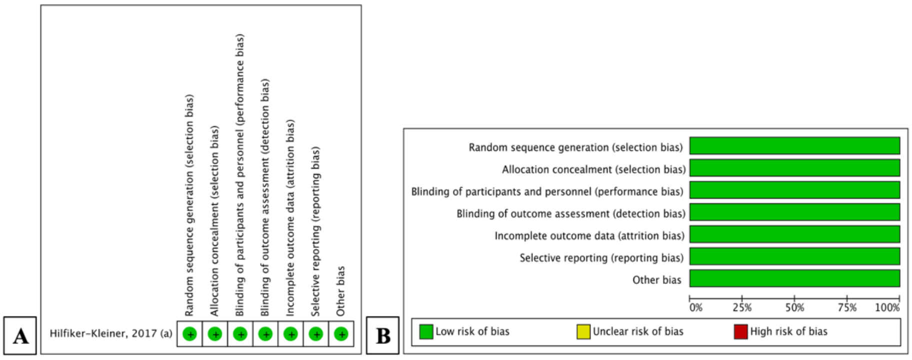

Figure 2. Quality assessment of RCT. (A) Risk of potential bias of individual RCT studies. (B) Risk of bias summary of all RCT studies. RCT: Randomized controlled trial.

Risk-of-bias of included studies

Regarding the quality assessment of the studies using the Cochrane RoB tool, it was observed that 1studies exhibited a low risk of bias, as presented in Figure 2. The quality of included observational studies were all deemed ‘Good’ with NOS values ranging from 7 to 9. However, two studies did not include elaboration regarding the selection of non-exposed cohort, 9 studies did not include ascertainment of exposure, and 2 studies did not evaluate presence of the outcome at start of study, as presented in Table 2.

Synthesis of results

Proportion of risk factors of PPCM

Figure 3 presents the ten risk factors for PPCM discussed in this study, including smoking habits, history of preeclampsia/eclampsia, hypertension disorder, caesarean delivery, gestational diabetes, anemia during pregnancy, multiple gestations, primiparity, age >30 years, and race/ethnicity. The risk factor with the highest proportion was a history of caesarean delivery (Proportion = 53%, 95%CI = 41%-66%), followed by anemia during pregnancy as the second highest and age >30 years as the third highest (Proportion = 51%, 95%CI = 38%-65%, and Proportion = 45%, 95%CI = 33%-57%, respectively). On the other hand, the risk factor with the lowest proportion was a history of gestational diabetes (Proportion = 6%, 95%CI = 9%-12%). Meanwhile, the proportions for a history of hypertension disorder and preeclampsia/eclampsia were (Proportion = 32%, 95%CI = 22%-41%, and Proportion = 24%, 95%CI = 15%-34%, respectively).

Maternal factors associated with recovery of PPCM

In terms of the factors associated with recovery from PPCM, the comparison was made between the recovered and non-recovered groups. It was found that African descent/Black race population is associated with an increased risk of non-recovery (RR= 1.82, [1.43-2.31], p <0.001) as shown in Figure 4. Conversely, primiparity (Figure 6) and hypertension (Figure 5) is associated with a decreased risk of non-recovery (RR= 0.81, [0.66–0.99], p=0.04 and RR= 0.73, [0.60–0.88], p=0.001). Additionally, Figure 5 shows that significantly younger age is correlated with an increased risk of non-recovery (MD= -1.04, [-1.82-(-0.27), p= 0.008). Although no significant associations were observed for other parameters, Figure 5 presents a trend towards an increased risk of non-recovery was observed in patients with a history of preeclampsia/eclampsia (RR=1.01) baseline NYHA >3 (RR= 1.08) (all p-values >0.05), and gestational diabetes (RR= 1.71) as presented in Figure 4.

In the comparison of baseline laboratory examinations and echocardiography parameters between the recovered and non-recovered groups, it was found that non-recovered PPCM patients had higher baseline values of serum creatinine (MD= 8.93, [3.67–14.19], p= 0.001), LVEDD (MD= 4.70, [3.70–5.70], p <0.001), and LVESD (MD= 5.29, [3.90-6.67], p <0.001) all shown in Figure 7. Additionally, non-recovered PPCM patients had lower baseline values of LVEF (Figure 7) and FS (Figure 8) (MD= -6.81, [-7.66-(-5.97)], p <0.001 and MD= -4.13, [-5.12-(-3.14)], p <0.001, respectively).

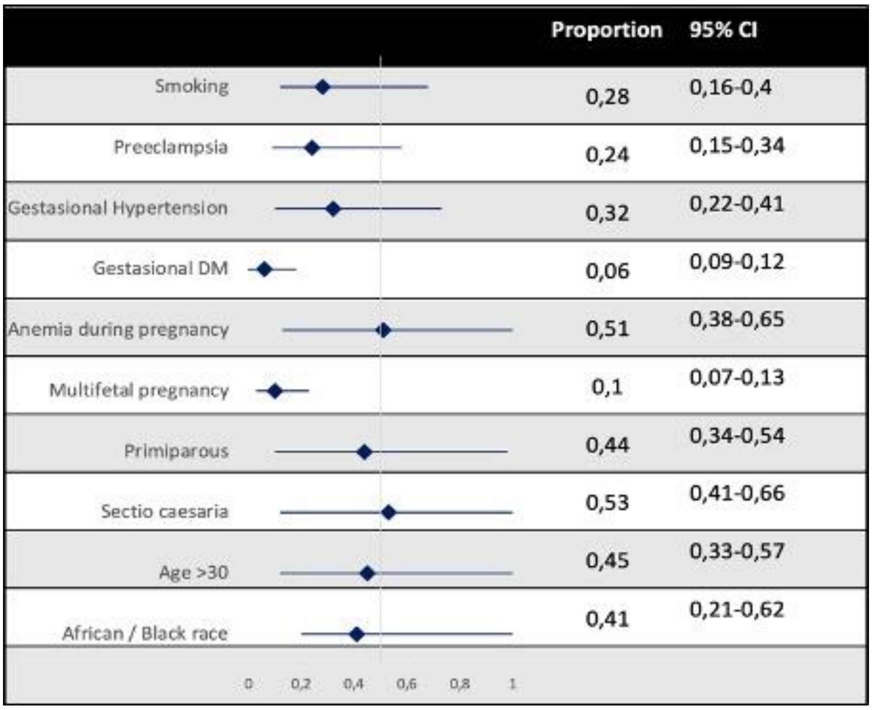

Figure 3. Single-arm forest plot for proportion of risk factors of PPCM

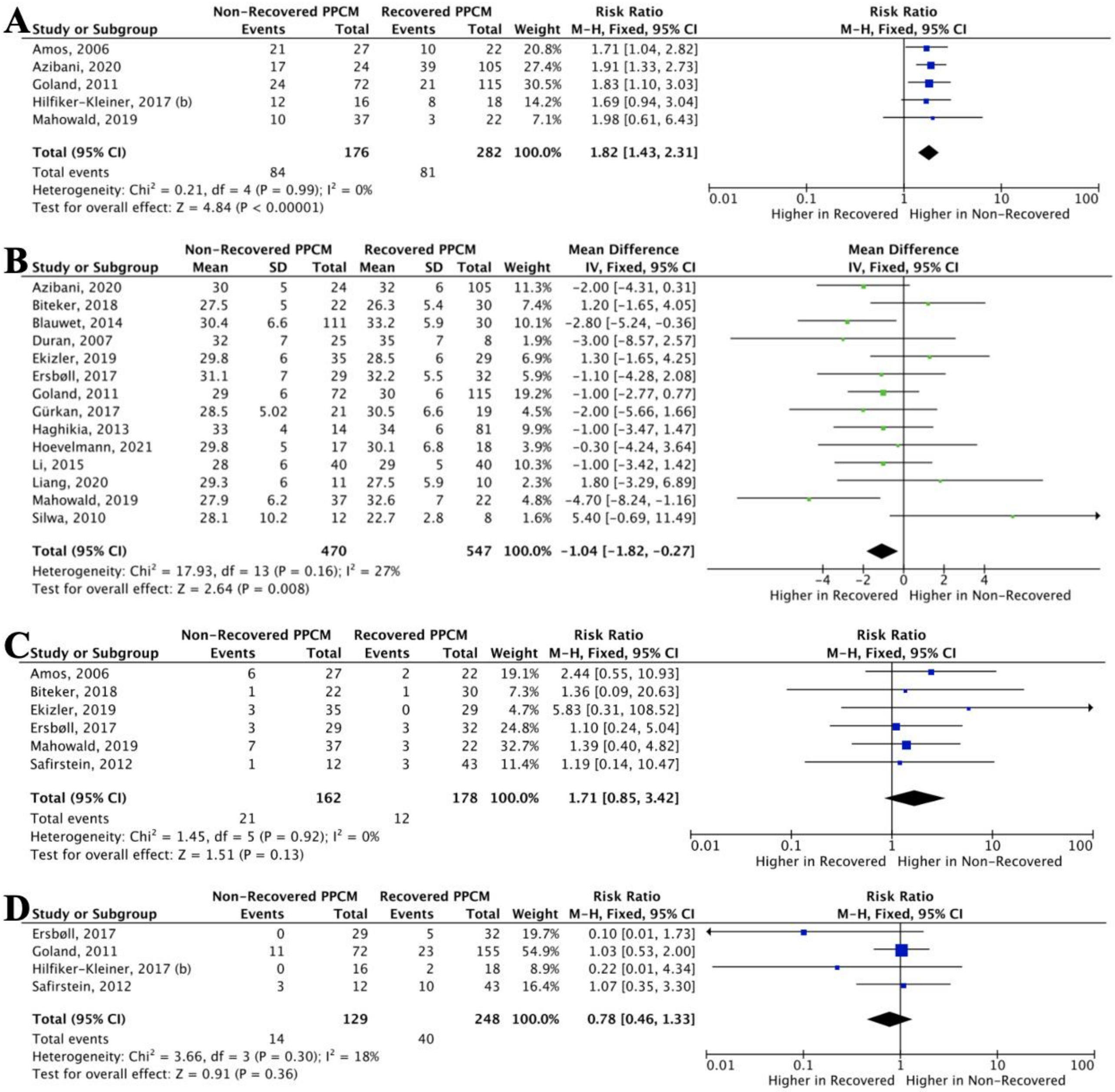

Figure 4. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of African ethnicity or black race. Test for overall effect: Z= 4.84 (p <0.001). heterogeneity: I2 = 0%. (B) Risk ratio off baseline age. Test for overall effect: Z= 2.64 (p=0.008). heterogeneity: I2 = 27%. (C) Risk ratio off history of gestational diabetes. Test for overall effect: Z= 1.51 (p=0.13). heterogeneity: I2 = 0%. (D) Risk ratio off multiple gestation. Test for overall effect: Z= 0.91 (p=0.36). heterogeneity: I2 = 18%.

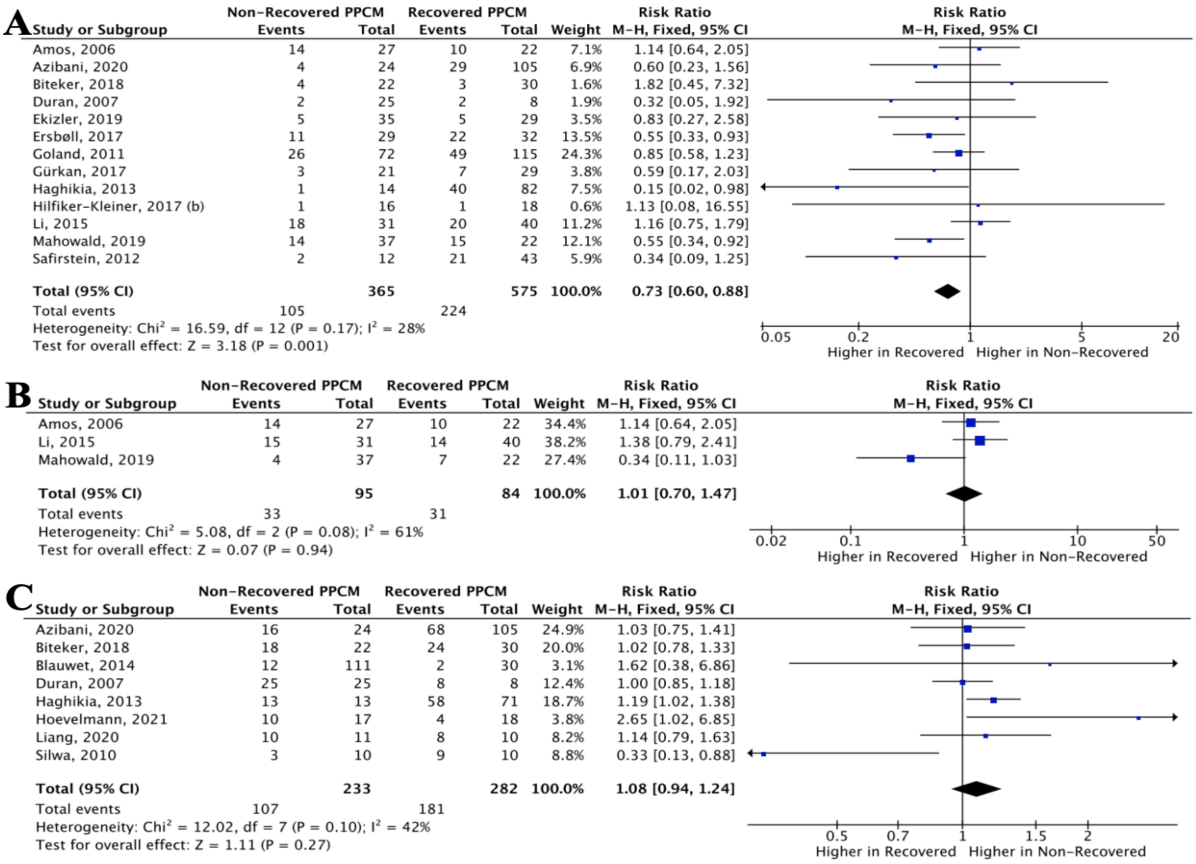

Figure 5. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of hypertension disorder. Test for overall effect: Z= 3.18 (p=0.001). heterogeneity: I2 = 28%. (B) Risk ratio off history of preeclampsia or eclampsia. Test for overall effect: Z= 0.07 (p=0.94). heterogeneity: I2 = 61%. (C) Risk ratio off baseline NYHA $\geq$ 3. Test for overall effect: Z= 1.11 (p=0.27). heterogeneity: I2 = 42%. NYHA: New York Heart Association

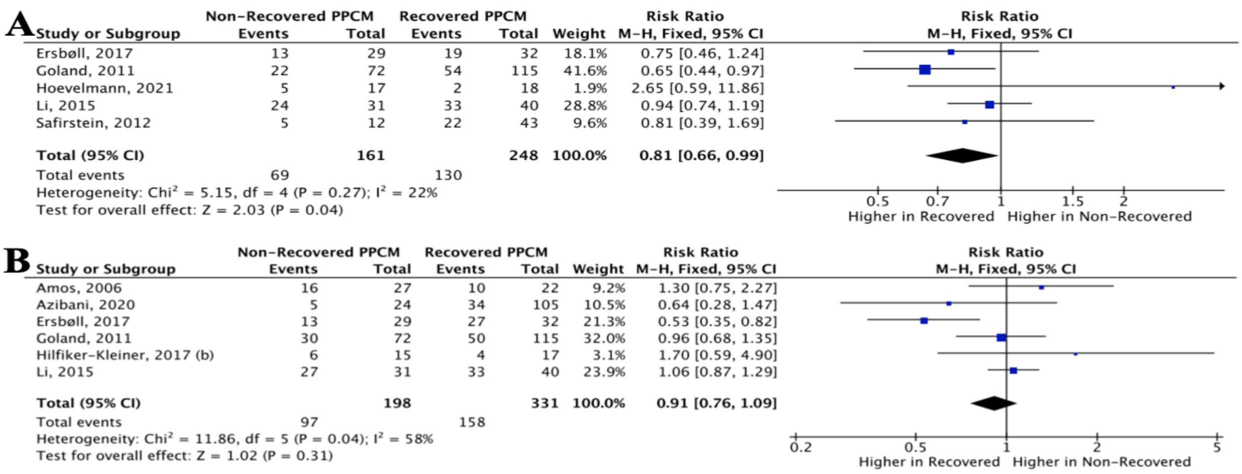

Figure 6. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of primiparity. Test for overall effect: Z= 2.03 (p=0.004). heterogeneity: I2 = 22%. (B) Risk ratio off history of caesarean delivery. Test for overall effect: Z= 1.02 (p=0.31). heterogeneity: I2 = 58%.

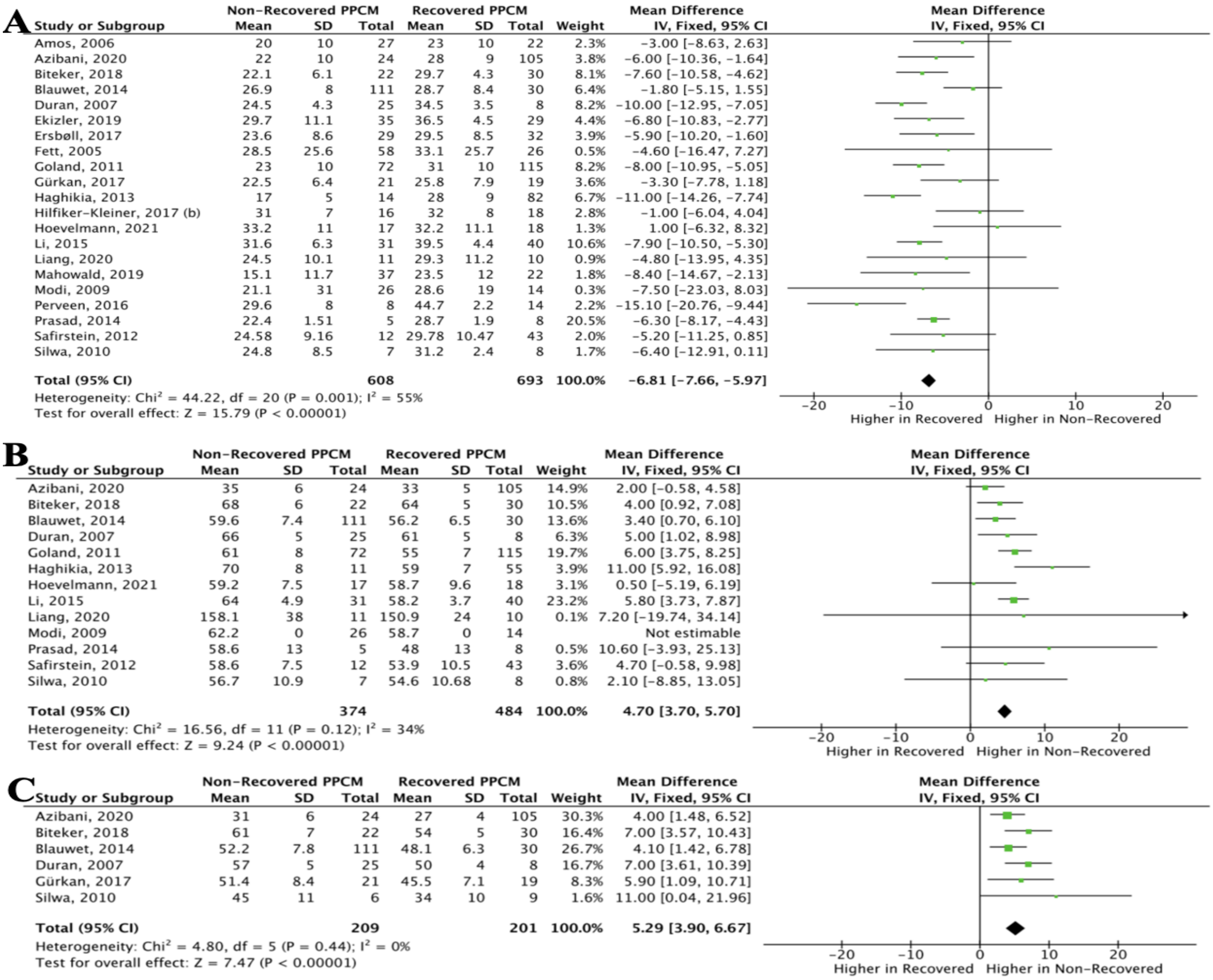

Figure 7. Forest plot of maternal factors associated with recovery PPCM. (A) Mean difference of baseline LVEF. Test for overall effect: Z= 15.79 (p <0.001). heterogeneity: I2 = 55%. (B) Mean difference of baseline LVEDD. Test for overall effect: Z= 9.24 (p <0.001). heterogeneity: I2 = 34%. (C) Mean difference of baseline LVESD. Test for overall effect: Z= 7.47 (p <0.001). heterogeneity: I2 = 0%.

Bromocriptine therapy outcomes

The use of bromocriptine in PPCM patients yielded favorable outcomes (Figure 9), as evidenced by a significant reduction in the risk of non-recovered PPCM (RR= 0.70, [0.55-0.90], p= 0.005), MACE (RR= 0.38, [0.22-0.65], p= 0.0004), and all-cause mortality (RR= 0.32, [0.15-0.66], p= 0.002). Furthermore, a significant increase in LVEF was observed in the group receiving bromocriptine therapy (MD=5.52, [1.48-9.57], p=0.007).

This study included twenty-four observational studies and one RCT. The key findings of this study revealed that the highest proportion of risk factors for PPCM was a history of caesarean delivery and anemia during pregnancy, while a history of gestational diabetes was the least commonly encountered risk factor in PPCM patients. As expected, African/Black ethnicity increased the risk of non-recovery in PPCM patients, whereas primiparity decreased the risk of non-recovery. Interestingly, a history of hypertension disorder was found to decrease risk of non-recovery in PPCM.

Thus far, pathogenesis of PPCM remains a subject of controversy, with various theories proposed encompassing genetic influences, nutritional deficiencies, hemodynamic responses to pregnancy, inflammatory processes, and heightened oxidative stress.[1,16,26] Noteworthy risk factors implicated in PPCM development include maternal age exceeding 30 years, African/Black ethnicity, multiple gestations, as well as a history of preeclampsia and hypertension.[7] Remarkably, PPCM patients exhibit a higher rate of recovery compared to other forms of heart failure characterized by reduced LVEF, typically manifesting within the initial 3-6 months postpartum.[42]

Caesarean delivery emerges as the highest proportionate risk factor in this study, likely attributable to the escalating global incidence of this procedure. The World Health Organization (WHO) reports the current rate of caesarean delivery to be 1 in 5 of all childbirths, with projections indicating a continued upward trend in

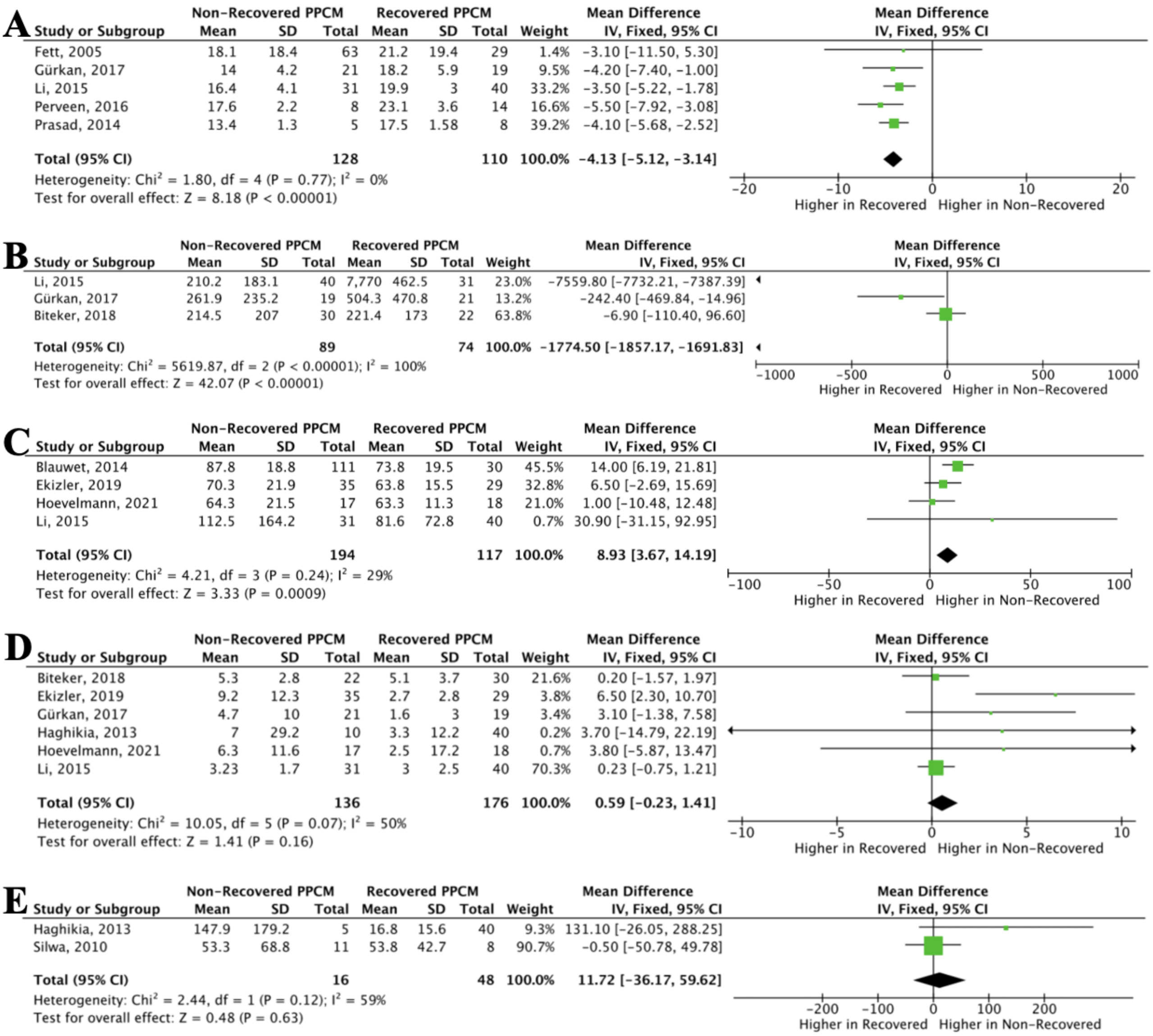

Figure 8. Forest plot of maternal factors associated with recovery PPCM. (A) Mean difference of baseline FS. Test for overall effect: Z= 8.18 (p <0.001). heterogeneity: I2 = 0%. (B) Mean difference of baseline BNP. Test for overall effect: Z= 42.07 (p <0.001). heterogeneity: I2 = 100%. (C) Mean difference of baseline creatinine serum. Test for overall effect: Z= 3.33 (p=0.0009). heterogeneity: I2 = 29%. (D) Mean difference of baseline CRP. Test for overall effect: Z= 1.41 (p=0.16). heterogeneity: I2 = 50%. (E) Mean difference of baseline prolactin. Test for overall effect: Z= 0.48 (p=0.63). heterogeneity: I2 = 59%. CRP: C-reactive protein.

the coming decades.[43] Furthermore, the heightened incidence of PPCM following caesarean delivery may be attributed to immunological reactions triggered by this surgical intervention, involving a higher degree of cellular interaction between the mother and the baby.[12] In addition to caesarean delivery, anemia during pregnancy also presents as a significant risk factor with a proportion exceeding 50%. The underlying mechanism behind this association lies in the increased heart rate and stroke volume observed in cases of anemia, leading to cardiac remodeling characterized by left ventricular hypertrophy and dilation as a compensatory response to the augmented cardiac workload.[44]

The findings of this study reveal that individuals of African/black ethnicity are at an increased risk of non-recovery in PPCM cases. The reasons underlying the disparity in recovery outcomes between black women and white women remain unclear and may be influenced by genetic factors or lower social and economic conditions.[45] Another contributing factor is that black patients are more likely to exhibit eccentric hypertrophy compared to concentric hypertrophy, which is associated with inflammation, cardiomyocyte death, and replacement fibrosis. Consequently, the difference in recovery rates may be attributed to a greater extent of cardiac tissue loss and replacement fibrosis among individuals of African/black ethnicity.[22]

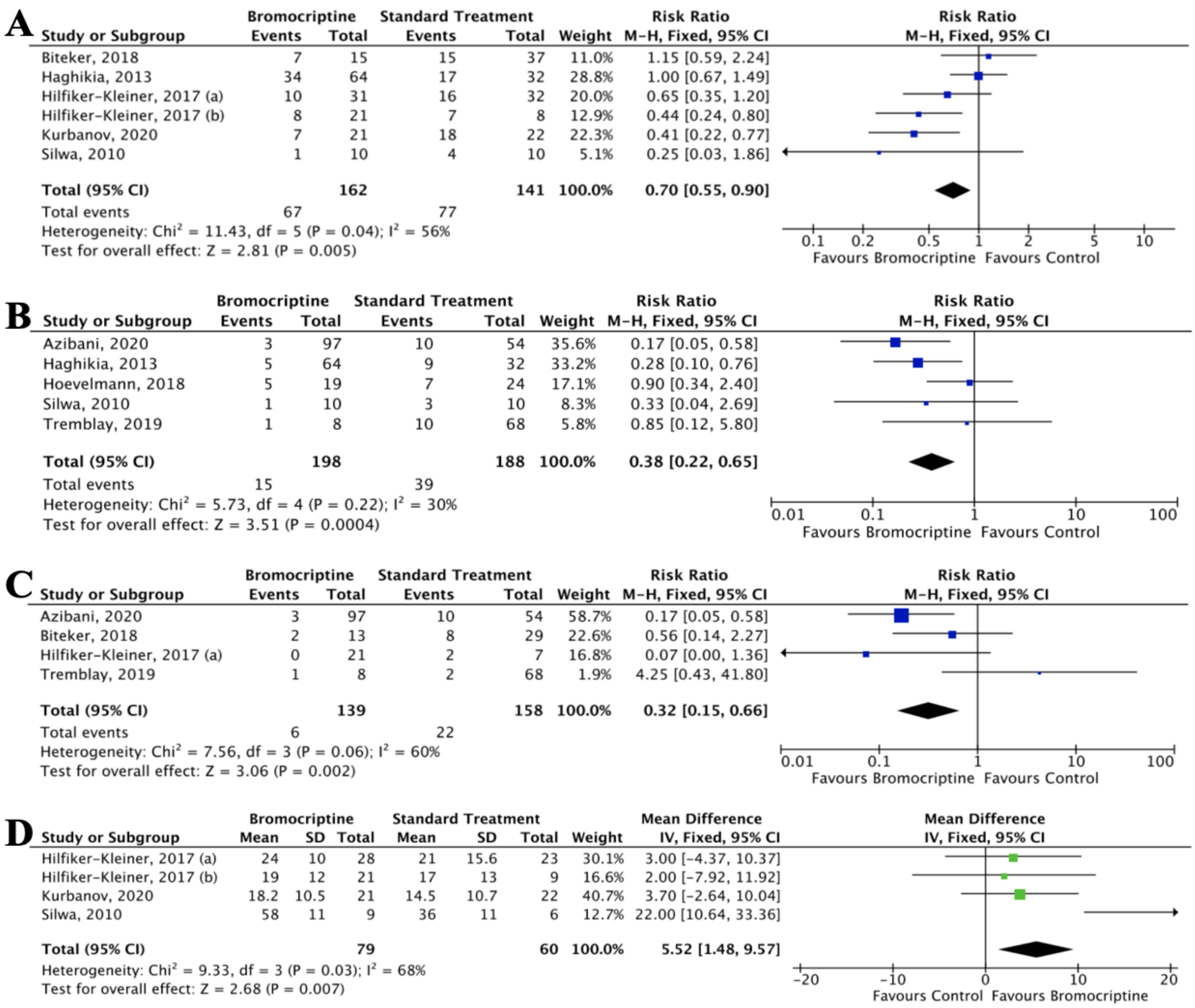

Figure 9. Forest plot of outcome of bromocriptine therapy. (A) Risk ratio of PPCM recovery. Test for overall effect: Z= 2.81 (p=0.005). heterogeneity: I2 = 56%. (B) Risk ratio off major adverse cardiac outcome. Test for overall effect: Z= 3.51 (p=0.0004). heterogeneity: I2 = 30%. (C) Risk ratio off all-cause mortality. Test for overall effect: Z= 3.06 (p=0.002). heterogeneity: I2 = 60%. (D) Mean difference of change value of LVEF. Test for overall effect: Z= 2.68 (p=0.007). heterogeneity: I2 = 68%.

On the contrary, hypertension disorder actually increases the risk of recovery in PPCM patients, and the early administration of beta-blockers is suspected to play a role in this condition.[25] Furthermore, this study found that being over the age of 30 increases the risk of recovery in PPCM patients. To date, age has rarely been reported as a factor influencing recovery in PPCM patients, as the theories supporting this claim are still unclear. However, it is possible that a more severe immune response in younger individuals leads to more extensive myocardial damage in PPCM patients.[15]

The observed significance of echocardiography parameters in relation to non-recovery in this study is not unexpected, as it aligns with the underlying pathophysiological mechanisms. The deteriorated values of LVEF, FS, LVESD, and LVEDD reflect the extent of cardiac remodeling in the studied population, indicative of more advanced disease progression.[46] These findings suggest that this particular population may require an extended duration to achieve favorable improvements in LVEF. Moreover, the correlation between increased LVEDD and major adverse cardiac events identified in follow-up echocardiography of other heart failure conditions further supports the clinical relevance of these parameters.[47] Despite optimal medical therapy, the presence of persistently high LVESD as independent predictor of ongoing LVEF impairment in context of transitioning from heart failure with reduced ejection fraction (HFrEF) to heart failure with improved ejection fraction (HFimpEF), underscores the prognostic value of echocardiographic assessments in assessing disease progression and response to treatment. These insights shed light on the intricate interplay between cardiac structural alterations and functional recovery in heart failure patients.[48]

The utilization of bromocriptine as an adjunct therapy in this study demonstrated superior outcomes compared to those receiving standard HF therapy alone. Bromocriptine is known to suppress prolactin secretion and prevent cardiac myocyte apoptosis. One of the underlying mechanisms of PPCM involves an increased oxidative stress leading to the activation of cathepsin D, which subsequently cleaves prolactin into a 16 kDa anti-angiogenic and pro-apoptotic form. This form is believed to induce endothelial inflammation, disrupt cardiomyocyte metabolism, and impair myocardial contractility, ultimately contributing to the development of PPCM. Therefore, the use of bromocriptine emerges as a potential treatment modality in PPCM patients, as it can counteract these pathological processes. By targeting the prolactin-related cascade, bromocriptine holds promise in mitigating the progression of PPCM and improving patient outcomes.[40]

Strengths and limitations

In our study, we conducted a comprehensive analysis involving echocardiography and laboratory parameters in PPCM patients. Additionally, in order to circumvent the detrimental impact of breastfeeding restriction on newborns, we included factors associated with non-recovery with the outcomes of bromocriptine therapy, enabling a more selective selection of suitable patients for the administration of bromocriptine. However, our study also has inherent limitations. Limitations of our study include the absence of separate analysis based on study types, as there was only one RCT included. Furthermore, there were limited number of studies regarding certain outcomes, resulting in lower statistical power. There was also no long-term analysis of the side effects of bromocriptine on patients or newborns. Furthermore, dosage variations among the included studies hinder the determination of the optimal dosage for PPCM therapy.

CONCLUSION

The study revealed significant associations between particular demographic and clinical factors and the prognosis of PPCM. Younger age at pregnancy, absence of hypertension, black race/ethnicity, and multiparity are key determinants to indicate a less favorable prognosis for recovery from PPCM. Additionally, bromocriptine therapy demonstrates notable benefits in mitigating adverse events in PPCM patients. By identifying the proportion of risk factors associated with the development of PPCM, it is hoped that primary prevention, such as avoiding anemia, considering alternatives to general anesthesia, limiting excessive fluid infusion in pregnant women, as well as increasing awareness through tighter monitoring in groups with unavoidable risk factors is crucial. The results of this meta-analysis, which discovered factors linked to recovery and assessed the validity of bromocriptine outcomes, can serve as a guide in identifying patients requiring bromocriptine therapy and, with the results of the discovery of factors associated with recovery and validity of bromocriptine outcomes, this meta-analysis can be used as a consideration to sort out which patients need bromocriptine treatment therapy and populations that can pursue regular heart failure therapy without bromocriptine. This consideration is important due to the potential side effects of bromocriptine, including restrictions on breast milk production, which may be detrimental to the growth and development of infants. To further understand the underlying mechanisms and strengthen therapeutic approaches, future research should concentrate on verifying and expanding upon these findings.

DISCLOSURES

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Conflict of interest

The authors report no conflict of interest.

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Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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