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**RESEARCH ARTICLE**

# A global perspective on the management and outcomes of peripartum cardiomyopathy: a systematic review and meta-analysis

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**Aims** Peripartum cardiomyopathy (PPCM) remains a major contributor to maternal morbidity and mortality worldwide. The disease is associated with various complications occurring mainly early during its course. Reported adverse outcomes include decompensated heart failure, thromboembolic complications, arrhythmias and death. We sought to systematically and comprehensively review published literature on the management and outcome of women with PPCM across different geographical regions and to identify possible predictors of adverse outcomes.

**Methods and results** We performed a comprehensive search of relevant literature (2000 to June 2021) across a number of electronic databases. Cohort, case-control and cross-sectional studies, as well as control arms of randomized controlled trials reporting on 6- and/or 12-month outcomes of PPCM were considered eligible (PROSPERO registration: CRD42021255654). Forty-seven studies (4875 patients across 60 countries) met the inclusion criteria. Haemodynamic and echocardiographic parameters were similar across all continents. All-cause mortality was 8.0% (95% confidence interval [CI] 5.5–10.8, $I^2 = 79.1\%$) at 6 months and 9.8% (95% CI 6.2–14.0, $I^2 = 80.5\%$) at 12 months. All-cause mortality was highest in Africa and Asia/Pacific. Overall, 44.1% (95% CI 36.1–52.2, $I^2 = 91.7\%$) of patients recovered their left ventricular (LV) function within 6 months and 58.7% (95% CI 48.1–68.9, $I^2 = 75.8\%$) within 12 months. Europe and North America reported the highest prevalence of LV recovery. Frequent prescription of beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and bromocriptine/cabergoline were associated with significantly lower all-cause mortality and better LV recovery.

**Conclusion** We identified significant global differences in 6- and 12-month outcomes in women with PPCM. Frequent prescription of guideline-directed heart failure therapy was associated with better LV recovery and lower all-cause mortality. Timely initiation and up-titration of heart failure therapy should therefore be strongly encouraged to improve outcome in PPCM.

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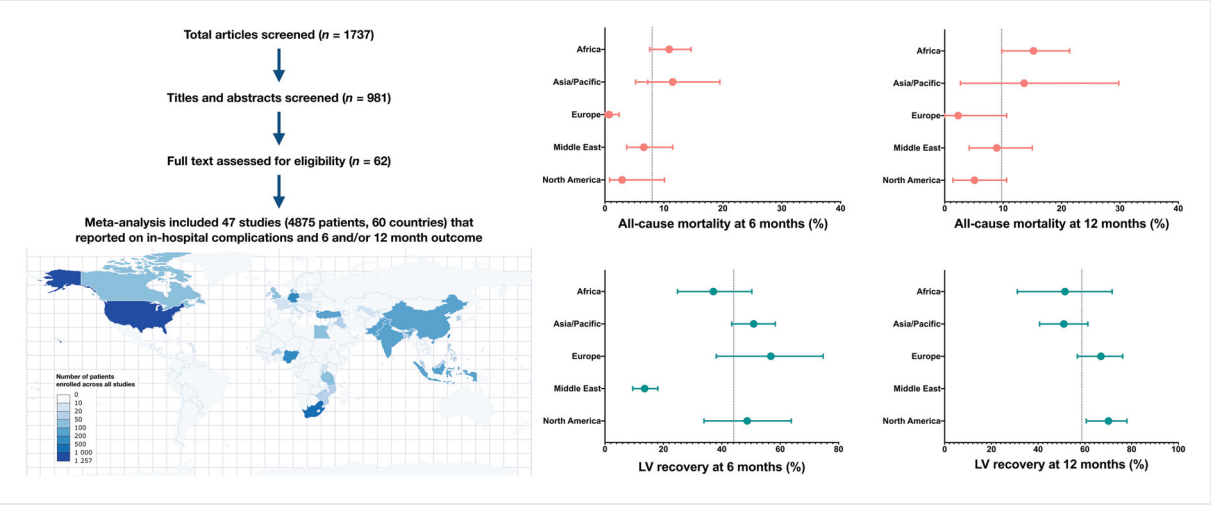
## Graphical Abstract




There are regional differences in both all-cause mortality and left ventricular (LV) recovery in peripartum cardiomyopathy. These differences may be explained by the variable prescription of guideline-directed medical therapy and access to health care services in different parts of the world. Studies that reported high prescription rates of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and bromocriptine/cabergoline were associated with better rates of LV recovery and lower all-cause mortality.

**Keywords** Peripartum cardiomyopathy • Systematic review • Meta-analysis • Complications • Outcomes • Mortality

# Introduction

Peripartum cardiomyopathy (PPCM) affects women across all continents and ethnicities, and remains a major risk factor for maternal morbidity and mortality worldwide.[1] The disease is characterized by new-onset left ventricular (LV) systolic dysfunction and dilatation that occur in previously healthy women towards the end of pregnancy and up to 5 months postpartum.[2] PPCM is associated with various complications and adverse events, which occur predominantly early during its course.

The outcome of PPCM remains markedly heterogeneous and seems to differ significantly between countries and ethnicities. While about 50% of women recover LV function within 6 months after diagnosis, there seems, however, to be marked differences in the rate of recovery between ethnicities and provenance.[1]

We sought to systematically and comprehensively review published literature on the management, complications and outcome of women with PPCM across different geographical regions, and to identify possible predictors of adverse outcome. To the best of our knowledge, there is currently no systematic review or meta-analysis that summarizes the global differences in pooled prevalence estimates of in-hospital complications, or 6- and/or 12-month outcomes in PPCM.

The aim of this systematic review and meta-analysis was to systematically summarize, from published literature, the clinical presentation, management, complications and outcomes of women with PPCM across different geographical regions. We specifically sought to delineate regional differences and changes over time, as well as to identify possible predictors of adverse outcomes.

# Methods

## Search strategy, selection criteria and data extraction

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[3] A detailed description of the selection criteria, search strategy, as well as data extraction and analysis was published previously as a protocol (PROSPERO registration, CRD42021255654).[4]

In brief, women with a confirmed diagnosis of PPCM according to the latest European Society of Cardiology (ESC) position statement (i.e. heart failure [HF] secondary to LV systolic dysfunction with an LV ejection fraction [LVEF] <45%, which occurred towards the end of pregnancy or in the months following delivery in the absence of any other identifiable cause of HF), were considered eligible.[5] We included all cohort, case-control and cross-sectional studies, as well as control arms of randomized controlled trials that reported on in-hospital complications and 6- and/or 12-month outcomes after the diagnosis of PPCM. Women with PPCM and a subsequent pregnancy, studies in which the study population was not solely PPCM or when data could not be differentiated from other patients with HF of other

**Table 1** Key characteristics of included studies and their reported predictors of outcome

| | Country | No. of participants | Study type | Outcomes reported | | | Predictors of outcome | |
|---|---|---|---|---|---|---|---|---|
| | | | | In-hospital | 6-month | 12-month | Favourable outcome | Adverse outcome |
| Achmad *et al.*[15] | Indonesia | 54 | Prospective cohort study | | X | | Beta-blocker administration | |
| Azibani *et al.*[16] | Germany and South Africa | South Africa ($n = 72$) Germany ($n = 79$) | Prospective cohort study | X | X | | | ↑ Galectin-3, ↑ soluble ST2, ↑ OPN at baseline |
| Biteker *et al.*[17] | Turkey | 42 | Prospective cohort study | X | X | | ↑ LVEF, ↓ LVESD at baseline. | |
| Biteker *et al.*[18] | Turkey | 52 | Prospective cohort study | X | X | X | ↑ LVEF, ↓ LVESD at baseline, bromocriptine | ↑ BNP, ↑CRP at follow-up |
| Blauwet *et al.*[19] | South Africa | 176 | Prospective cohort study | X | X | | ↑ Age, ↓ LVESD. | ↑ LVESD, ↓ serum cholesterol |
| Chee *et al.*[20] | Malaysia | 12 | Retrospective case record analysis | X | | X | | |
| Cooper *et al.*[21] | United States | 39 | Prospective cohort study | | X | | | Diagnosis >120 days postpartum |
| Cuenza *et al.*[22] | The Philippines | 39 | Retrospective cohort study | X | X | | | LVEF <25%. |
| Dayoub *et al.*[23] | United States | 975 | Retrospective cohort study | | | X | | |
| Djordjevic *et al.*[24] | Multicentre | 16 | Prospective study, including patients with PPCM from EUROMACS registry | X | | X | | |
| Elkayam *et al.*[25] | United States | 100 | Retrospective case record analysis | | X | X | LVEF >30% at baseline | |
| Ersbøll *et al.*[26] | Denmark | 61 | Retrospective case record analysis | | | X | Cabergoline treatment | |
| Fatema *et al.*[27] | Bangladesh | 36 | Retrospective cohort study | X | | X | | |
| Gambahaya *et al.*[28] | Zimbabwe | 43 | Prospective cohort study | X | X | | | |
| Haghikia *et al.*[29] | Germany | 115 | Prospective cohort study | | X | | Pregnancy-induced hypertensive disorders | ↓ Baseline LVEF, ↑ LVEDD, deranged liver enzymes |
| Haghikia *et al.*[30] | Germany | 34 | Prospective cohort study | X | X | | | RV dysfunction |
| Hoevelmann *et al.*[31] | South Africa | 66 | Prospective cohort study | | X | X | Sinus arrhythmia | ↑ QTc, sinus tachycardia |
| Hoevelmann *et al.*[32] | South Africa | 35 | Prospective cohort study | | | X | | NT-proBNP ≥900 pg/ml |
| Horgan *et al.*[33] | Ireland | 12 | Retrospective cohort study | X | X | | | |
| Hu *et al.*[34] | China | 106 | Prospective cohort study | | X | | | Baseline cTnT concentration of >0.04 ng/ml |
| Karaye *et al.*[35] | Nigeria | 39 | Prospective case-control study | | X | | | |
| Karaye *et al.*[36] (A) | Nigeria | 45 | Prospective cohort study | | X | X | | |
| Karaye *et al.*[37] (B) | Nigeria | 54 | Prospective cohort study | X | X | X | | |
| Karaye *et al.*[38] | Nigeria | 244 | Prospective cohort study | X | X | X | Regular use of beta-blockers at follow-up, obesity | Age <20 years, hypotension, tachycardia, LVEF <25% |
| Laghari *et al.*[39] | Pakistan | 45 | Retrospective case record analysis | X | X | | | |

**Table 1 (Continued)**

| | Country | No. of participants | Study type | Outcomes reported | | | Predictors of outcome | |
|---|---|---|---|---|---|---|---|---|
| | | | | In-hospital | 6-month | 12-month | Favourable outcome | Adverse outcome |
| Libhaber *et al.*[40] | South Africa | 206 | Prospective cohort study | | X | | | SBP <110 mmHg, tachycardia, ↑ LVESD at baseline |
| Lim *et al.*[41] | Malaysia | 11 | Retrospective cohort study | X | X | | | |
| Lindley *et al.*[42] | United States | 39 | Retrospective cohort study | | | X | Concomitant pre-eclampsia is associated with better LV recovery | Concomitant pre-eclampsia is associated with increased mortality and morbidity |
| Lu *et al.*[43] | Taiwan | 391 | Retrospective case record analysis | X | | X | | |
| Maro *et al.*[44] | Tanzania | 64 | Prospective cohort study | X | X | X | | LVEF <30%, LVEDD ≥60 mm |
| McNamara *et al.*[45] | United States | 100 | Prospective cohort study | X | X | X | Ancillary studies: RVFAC,[46] ↑ relaxin-2[47] | Initial LVEF <30%, LVEDD ≥60 mm, black race, presentation after 6 weeks post-partum. Ancillary studies: LAE on ECG,[48] ↑ sFlt1,[47] ↓ speckle-tracking GLS, GCS,[49] GNB3 TT genotype[50] |
| Moulig *et al.*[51] | Germany | 67 | Prospective cohort study | X | X | X | | |
| Perveen *et al.*[52] | Pakistan | 22 | Prospective cohort study | | X | | | Baseline LVEF <35%, FS <20% |
| Ravi Kiran *et al.*[53] | India | 43 | Prospective cohort study | X | X | | | RVFAC <31.4%, LAVi >29.6 ml/m$^2$ |
| Ricke-Hoch *et al.*[54] | Germany | 64 | Prospective cohort study, with age-matched healthy controls | | X | | | |
| Salam *et al.*[55] | Seven Middle Eastern countries | 64 | Prospective cohort study, including patients with PPCM from Gulf CARE registry | X | | X | | |
| Sarojini *et al.*[56] | India | 46 | Prospective case-control study | X | X | | | ↑ CRP, ↑ IL-6, TNF-α, ↑ NYHA FC at baseline |
| Shaikh *et al.*[57] | Pakistan | 25 | Observational study* | X | X | | | ↑ Age |
| Sharieff *et al.*[58] | Pakistan | 35 | Prospective cohort study | | X | | | Age >30 years, ↑ LVEDD, ↓ LVEF |
| Sliwa *et al.*[59] | South Africa | 29 | Prospective cohort study | X | X | | ↑ LVEF. | ↑ Fas/APO-1 |

**Table 1 (Continued)**

| | Country | No. of participants | Study type | Outcomes reported | | | Predictors of outcome | |
|---|---|---|---|---|---|---|---|---|
| | | | | In-hospital | 6-month | 12-month | Favourable outcome | Adverse outcome |
| Sliwa *et al.*[60] | South Africa | 100 | Prospective cohort study | X | X | | | ↑ Fas/APO-1, ↑ NYHA FC at baseline |
| Sliwa *et al.*[61] | South Africa | 10 | Randomized controlled trial (control group) | X | X | | | |
| Sliwa *et al.*[62] | South Africa | 80 | Prospective cohort study | | X | X | | |
| Sliwa *et al.*[1] | Multi-national | 739 | Prospective cohort study | X | X | | | |
| Tremblay-Gravel *et al.*[63] | Canada | 68 | Retrospective cohort study | X | X | | Bromocriptine | |
| Yang *et al.*[64] | Republic of Korea | 21 | Prospective cohort study | | | X | | |
| Zhu *et al.*[65] | China | 60 | Prospective cohort study | X | X | | | AKI, LVEF <40% at baseline |

AKI, acute kidney injury; BNP, B-type natriuretic peptide; CRP, C-reactive protein; cTnT, cardiac troponin T; ECG, electrocardiogram; FS, fractional shortening; GCS, global circumferential strain; GLS, global longitudinal strain; IL, interleukin; LAE, left atrial enlargement; LAVi, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; OPN, osteopontin; PPCM, peripartum cardiomyopathy; QTc, corrected QT interval; RV right ventricular; RVFAC, right ventricular fractional area change; SBP, systolic blood pressure; sFlt1, soluble fms-like tyrosine kinase 1; ST2, interleukin 1 receptor-like 1; TNF, tumour necrosis factor.
*Not specified whether performed prospectively or retrospectively.

aetiologies, or studies with a variable follow-up that did not include objective outcomes or complications reported for 6 months and/or 12 months, were excluded.

A comprehensive search for all articles that were published between 2000 (the year in which the first universal definition of PPCM was used)[6] and 1 June 2021 was performed on PubMed/MEDLINE, Web of Science, Scopus and EBSCO Host, including Academic Search Premier, Africa-Wide Information, Cumulative Index to Nursing and Allied Health Literature (CINAHL), with the help of an expert librarian. Detailed search terms are outlined in online supplementary *Table S1*. After removal of duplicates, two reviewers (J.H. and E.M.) screened all abstracts independently for eligibility. Subsequently, two reviewers (J.H. and E.M.) independently reviewed full-text articles in duplicate. Where necessary, a third reviewer (C.V.) was consulted to resolve any disagreements by consensus.

## Data extraction and analysis

Data were extracted using a standardized electronic data collection form on Research Electronic Data Capture (REDCap),[7] a secure online database manager hosted at the University of Cape Town. As elaborated in the study protocol,[4] data extracted included study characteristics, clinical characteristics as well as in-hospital complications and reported outcomes at 6- and/or 12-month follow-up (all-cause mortality, all-cause readmission to hospital, LV non-recovery [persistent LV dilatation and/or LVEF <50%], arrhythmias [e.g. atrial fibrillation, ventricular tachycardia] or thromboembolism [e.g. deep vein thrombosis, pulmonary embolism, LV thrombus, stroke, arterial embolism]). Whenever more than one article was found to report on the same cohort, we used the article with the most complete dataset for data extraction. The main findings of duplicate publications are described in online supplementary *Table S2*. Data from multinational studies were extracted according to the geographical region.

The primary outcome of our meta-analysis was to describe the pooled prevalence estimates and their 95% confidence intervals (CI) of all-cause mortality and LV recovery at the time of diagnosis as well as at 6 and/or 12 months. We identified predictors of outcome based on the studies included in the systematic review, which were used in the meta-analysis to determine associations with all-cause mortality and LV recovery.

## Risk of bias assessment

Two researchers (J.H. and C.V.) reviewed all included studies and graded their risk of bias, using the tool recommended by Hoy *et al.*[8] for the assessment of methodological quality of non-randomized studies.

## Statistical analysis

Where data were available and amendable for meta-analysis, we calculated pooled prevalence estimates using the Freeman–Tukey double arcsine transformation method to stabilize the variance of proportion within the Metaprop package in Stata (V.17). We evaluated heterogeneity using the Cochran's $\chi^2$ test (significant if $p < 0.10$) and the $I^2$ statistic test (>50% indicative of substantial heterogeneity).[9] We used a random-effects model due to the considerable heterogeneity across studies in both all-cause mortality and LV recovery. For sub-analyses on echocardiographic features at time of diagnosis, we dichotomized studies using the median values of LVEF, LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) reported across all studies. For sub-analyses on treatment, we dichotomized studies according to more or less than 80% reported use of the

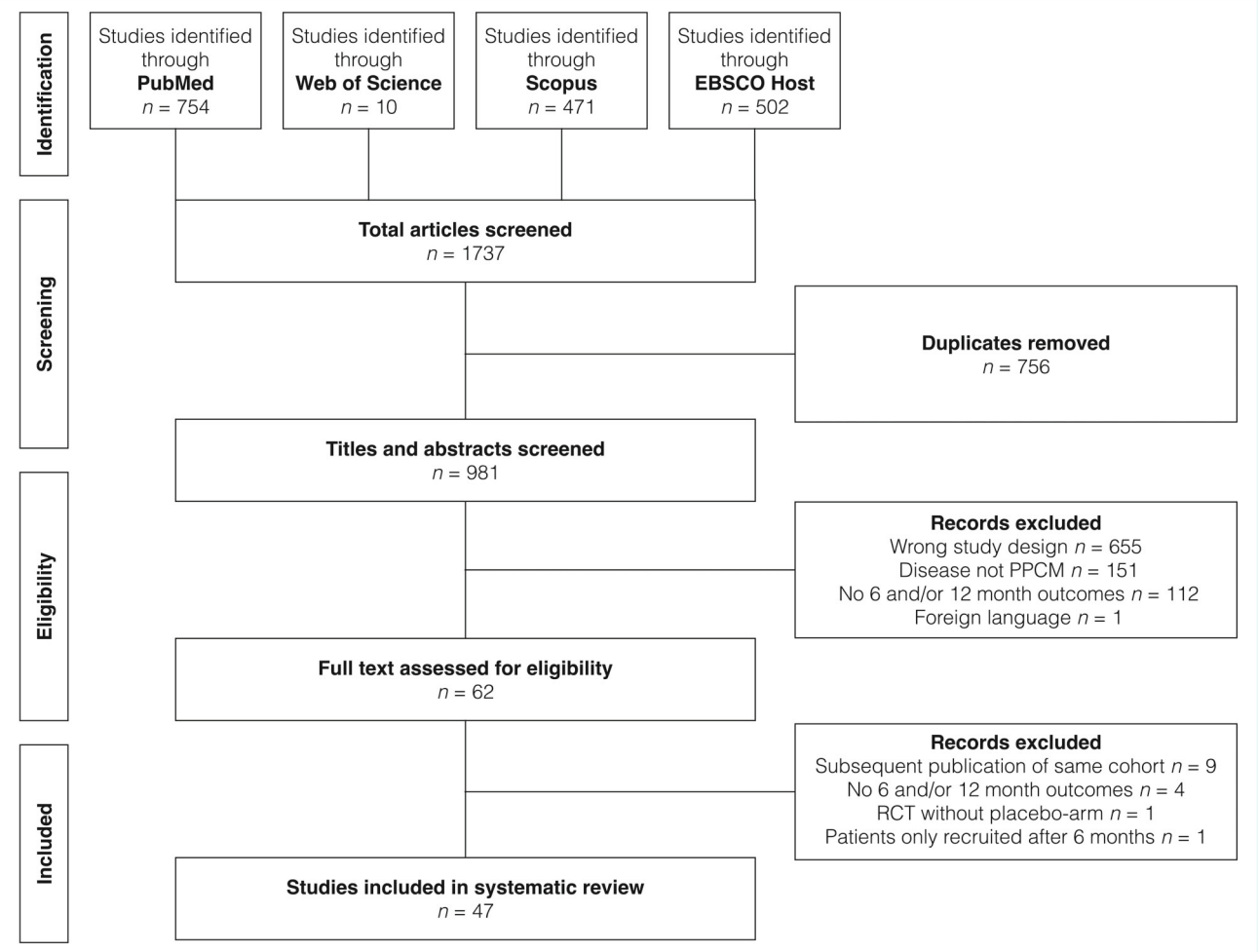



**Figure 1** Study selection diagram. PPCM, peripartum cardiomyopathy; RCT, randomized controlled trial.

relevant drug, based on the commonly used threshold to describe adherence to HF therapy.[10–12] We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation-Guideline Development Tool (GRADEpro).[13,14]

# Results

Following the removal of duplicates, our search strategy identified 981 publications. Forty-seven studies, comprising 4875 patients across 60 countries, were considered eligible and were included in the systematic review (*Table 1*).[1,15–65] A list of excluded studies, with reasons for exclusion, is provided in online supplementary *Table S2*.

Results of study identification, screening, eligibility, and inclusion are outlined in the study selection diagram (*Figure 1*). Studies included participants predominantly from Africa ($n$ = 1476, 16 studies), Asia/Pacific ($n$ = 1059, 16 studies), North America ($n$ = 1321, 6 studies), Europe ($n$ = 695, 9 studies), and the Middle East ($n$ = 324, 4 studies). A world map of included participants in this systematic review is presented in online supplementary *Figure S1*.

Twenty-nine studies (2773 patients) reported on in-hospital complications, 37 studies (3225 patients) and 20 studies (2522 patients) on 6- and 12-month outcomes, respectively. The most commonly reported predictors of outcome were baseline LVEF, LVEDD, LVESD, sinus tachycardia, New York Heart Association functional class (NYHA FC) or bromocriptine/cabergoline treatment (*Table 1*). A more detailed description of the included studies is provided in online supplementary *Table S3*.

## Regional differences in presentation and management

*Table 2* depicts the clinical characteristics, investigations, treatment, in-hospital complications, as well as 6- and 12-month outcomes. The mean age of patients included in this cohort was 30.1 years (range 21.0–34.7) with a mean body mass index of 24.9 kg/m$^2$ (range 19.9–27.2) and 70.1% (95% CI 62.9–76.8%) presented with a NYHA FC III/IV. Studies from Asia/Pacific and the Middle East reported the highest incidence of antepartum onset of PPCM. Studies from Africa and the Middle East included the most multiparous (≥2 pregnancies) women. Comorbid pre-eclampsia

**Table 2 Geographical comparison of clinical characteristics, prescribed treatment, as well as in-hospital, 6- and 12-month outcomes**

| Variable | All | Africa | Asia/Pacific | Europe | Middle East | North America | $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| Age (years) | 30.1 (28.4–31.8) | 28.8 (25.5–32.1) | 29.5 (26.6–32.3) | 33.5 (29.5–37.5) | 29.3 (23.7–34.9) | 40.2 (24.8–35.5) | 0.0 |
| BMI (kg/m$^2$) | 24.9 (22.5–27.4) | 24.2 (20.9–27.5) | 25.3 (20.9–29.7) | 27.0 (17.2–36.8) | 27.2 (17.4–37.0) | – | 0.0 |
| Multiparity (≥2 pregnancies) | 62.4 (55.4–69.2) | 74.8 (71.2–78.2) | 54.1 (41.6–66.3) | 61.1 (45.9–75.4) | 82.0 (75.5–87.1) | 46.7 (39.1–54.3) | 86.7 |
| Caesarean section | 47.3 (36.0–58.8) | 20.2 (10.4–32.1) | 49.3 (23.1–75.7) | 68.4 (64.5–72.2) | 47.0 (39.6–54.6) | 44.8 (36.6–53.3) | 95.1 |
| NYHA FC III/IV | 70.1 (62.9–76.8) | 61.6 (50.3–72.2) | 86.6 (71.7–96.7) | 78.0 (63.4–89.9) | 78.1 (69.2–85.9) | 50.6 (24.4–76.7) | 93.6 |
| Antepartum onset | 19.3 (12.0–27.8) | 4.5 (0–17.9) | 33.2 (21.4–46.1) | 11.3 (0.3–33.3) | 34.2 (22.7–46.7) | 14.3 (8.1–21.8) | 93.6 |
| Postpartum onset | 82.4 (74.5–89.1) | 95.6 (82.1–100) | 75.4 (61.5–87.2) | 88.7 (66.7–99.7) | 65.8 (53.3–77.3) | 85.7 (78.2–91.9) | 93.7 |
| Hypertension/hypertensive disorders of pregnancy | 28.1 (22.6–34.0) | 25.4 (14.3–38.3) | 31.3 (15.9–48.9) | 35.6 (28.3–43.2) | 19.0 (9.1–31-2) | 27.3 (13.7–43.5) | 92.5 |
| Pre-eclampsia | 22.5 (16.6–28.9) | 19.2 (15.7–22.9) | 21.6 (8.3–38.6) | 31.5 (10.2–57.6) | 19.0 (13.8–25.6) | 26.0 (17.1–37.5) | 81.1 |
| **Clinical investigations** | | | | | | | |
| SBP (mmHg) | 113.9 (107.9–120.0) | 111.5 (103.9–119.1) | 117.1 (101.1–133.2) | 117.3 (90.9–135.7) | 125.5 (69.1–182.0) | 120.2 (100.8–139.5) | 0.0 |
| DBP (mmHg) | 75.5 (70.1–80.8) | 73.8 (65.5–82.1) | 75.8 (65.2–86.3) | 76.1(63.1–89.2) | 83.4 (42.2–124.6) | 78.1 (63.9–92.2) | 0.0 |
| Heart rate (bpm) | 95.3 (88.9–101.8) | 99.2 (89.5–108.8) | 104.2 (85.7–122.8) | 90.2 (76.5–103.9) | 83.6 (64.6–102.6) | 91.7 (70.6–112.9) | 0.0 |
| LVEF (%) | 29.1 (26.8–31.3) | 29.3 (24.7–33.9) | 31.6 (28.0–35.2) | 23.5 (18.1–28.9) | 28.1 (20.8–35.3) | 29.3 (21.0–37.6) | 0.0 |
| LVEDD (mm) | 57.8 (55.6–60.0) | 56.1 (51.7–60.6) | 57.9 (54.1–61.6) | 59.8 (53.2–66.4) | 64.8 (58.0–71.6) | 56.6 (48.8–64.5) | 0.0 |
| LVESD (mm) | 51.1 (46.9–55.2) | 51.1 (45.6–56.7) | 49.1 (40.9–57.4) | 49.0 (29.4–68.6) | 54.7 (43.9–65.6) | - | 0.0 |
| **Treatment** | | | | | | | |
| Beta-blocker | 76.7 (64.7–87.0) | 60.0 (38.4–79.9) | 87.8 (46.6–100) | 89.4 (80.4–96.0) | 86.4 (74.2–95.3) | 85.2 (80.4–89.5) | 97.5 |
| ACE-I/ARB | 82.5 (73.4–90.1) | 75.3 (59.7–88.2) | 88.0 (50.0–100) | 93.8 (86.3–98.7) | 77.9 (71.0–84.2) | 84.3 (79.4–88.7) | 96.4 |
| MRA | 56.4 (38.3–73.7) | 74.4 (57.0–88.7) | 39.1 (1.8–87.2) | 72.6 (56.9–85.9) | 50.8 (41.7–60.0) | 16.0 (10.3–22.6) | 97.8 |
| Diuretics | 92.2 (86.1–96.8) | 94.9 (91.2–97.8) | 94.6 (65.0–100) | 82.9 (74.9–89.8) | 98.5 (95.6–100) | 69.2 (61.4–76.6) | 94.1 |
| Digoxin/digitoxin | 55.8 (39.7–71.4) | 84.9 (71.9–94.5) | 36.7 (32.3–41.2) | 6.8 (3.5–11.0) | 35.1 (25.6–45.1) | 18.2 (11.3–26.2) | 97.6 |
| Bromocriptine/cabergoline | 47.2 (20.7–74.6) | 28.3 (13.5–45.8) | 85.3 (71.9–93.0) | 87.5 (58.2–100) | 28.8 (18.3–42.2) | 0 (0–5.4) | 97.9 |
| Warfarin | 11.2 (5.8–17.8) | 5.2 (3.7–8.0) | 5.7 (3.7–8.1) | 20.1 (12.1–29.5) | – | 26.4 (18.3–35.3) | 84.6 |
| **In-hospital outcomes** | | | | | | | |
| All-cause mortality | 1.9 (0.5–4.0) | 0 (0–0.7) | 3.7 (0.3–9.3) | 1.2 (0–5.4) | 3.3 (1.2–6.2) | – | 62.6 |
| Invasive ventilation | 9.8 (3.0–19.2) | – | 5.3 (0.7–12.7) | 12.6 (5.9–21.1) | 4.7 (1.6–12.9) | – | 67.3 |
| Inotropic support | 21.5 (7.9–39.0) | – | 29.7 (0–81.7) | 9.0 (4.2–18.2) | 20.4 (13.4–28.4) | 15.0 (9.3–23.3) | 91.1 |
| Mechanical support | 3.1 (2.0–4.4) | 0 (0–5.1) | 3.1 (1.6–4.9) | 4.8 (2.7–7.5) | 3.5 (1.0–7.3) | 2.0 (0.6–7.0) | 10.3 |
| LV thrombus | 9.0 (6.5–11.9) | 9.8 (5.7–14.7) | 9.2 (5.3–13.9) | 2.9 (0.5–14.9) | 9.6 (4.2–16.6) | – | 46.1 |
| Stroke | 2.2 (0.7–4.3) | 1.5 (0.6–2.9) | 3.8 (0–15.7) | 2.8 (1.4–5.7) | 2.4 (0.9–6.0) | – | 68.5 |
| Arterial embolism | 1.5 (0.3–3.3) | 0.9 (0.3–3.4) | 0.3 (0–2.4) | 2.4 (1.1–5.2) | 3.0 (1.3–6.9) | – | 53.9 |
| Thromboembolism | 4.5 (2.8–6.5) | 2.4 (0.8–4.7) | 2.7 (0.9–7.5) | 6.5 (4.0–9.6) | 4.2 (4.1–17.9) | 8.8 (4.1–17.9) | 38.8 |
| All-cause embolic event | 6.1 (3.8–8.9) | 3.1 (1.7–4.9) | 5.6 (1.5–11.6) | 10.7 (7.5–14.4) | 9.6 (6.0–15.1) | 8.8 (4.1–17.9) | 66.3 |
| **6-month outcomes** | | | | | | | |
| All-cause mortality | 8.0 (5.5–10.8) | 10.9 (7.6–14.6) | 11.5 (5.2–19.5) | 0.7 (0–2.4) | 6.6 (3.7–11.5) | 2.9 (0.8–10.1) | 79.1 |
| All-cause readmission | 8.1 (6.4–10.1) | 9.5 (6.2–13.3) | 6.8 (3.2–11.5) | 9.7 (6.6–14.1) | 5.4 (2.9–10.0) | 8.8 (4.1–17.9) | 0.0 |
| Change in LVEF from baseline to 6 months | 17.7 (15.7–19.6) | 15.4 (14.1–16.7) | 21.4 (16.4–26.3) | 21.1 (18.6–23.6) | – | 16.1 (14.1–18.1) | 85.0 |
| Recovered LVEF (≥50%) at 6 months | 44.4 (36.2–52.8) | 37.1 (24.8–50.3) | 52.5 (44.9–60.0) | 56.8 (38.1–74.7) | 13.6 (9.5–18.1) | 48.7 (33.9–63.8) | 91.4 |
| **12-month outcomes** | | | | | | | |
| All-cause mortality | 9.8 (6.2–14.0) | 15.2 (9.8–21.4) | 13.6 (2.7–29.8) | 2.3 (0–10.6) | 8.9 (4.2–15.0) | 5.1 (1.4–10.6) | 80.5 |
| All-cause readmission | 13.4 (8.2–19.6) | 16.7 (9.6–27.4) | – | – | 14.1 (7.6–24.6) | 12.7 (5.8–21.7) | 73.1 |
| Change in LVEF from baseline to 12 months | 18.7 (15.7–21.6) | 17.3 (14.3–20.2) | 15.0 (8.4–21.7) | 26.0 (22.7–29.3) | – | 18.3 (15.9–20.8) | 73.2 |
| Recovered LVEF (≥50%) at 12 months | 58.7 (48.1–68.9) | 51.5 (31.1–71.7) | 51.0 (40.6–61.3) | 66.9 (56.8–76.2) | – | 70.1 (61.6–78.0) | 75.8 |

Values are reported as mean (95% confidence interval), or % (95% confidence interval).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; NYHA FC, New York Heart Association functional class; SBP, systolic blood pressure.

was most prevalent in European and North American studies. Women from Europe, Asia/Pacific and the Middle East presented more frequently with advanced HF (NYHA FC III/IV) (*Table 2*). However, haemodynamic and echocardiographic parameters were similar across all continents. There were marked differences in treatment prescription across different continents. The highest reported prescription of contemporary guideline-directed HF therapy was reported for studies conducted in Europe and North America.

## Differences in outcome

As outlined in *Table 2*, in-hospital mortality was estimated to be 1.9% (95% CI 0.5–4.0) across all regions. About 10% of patients

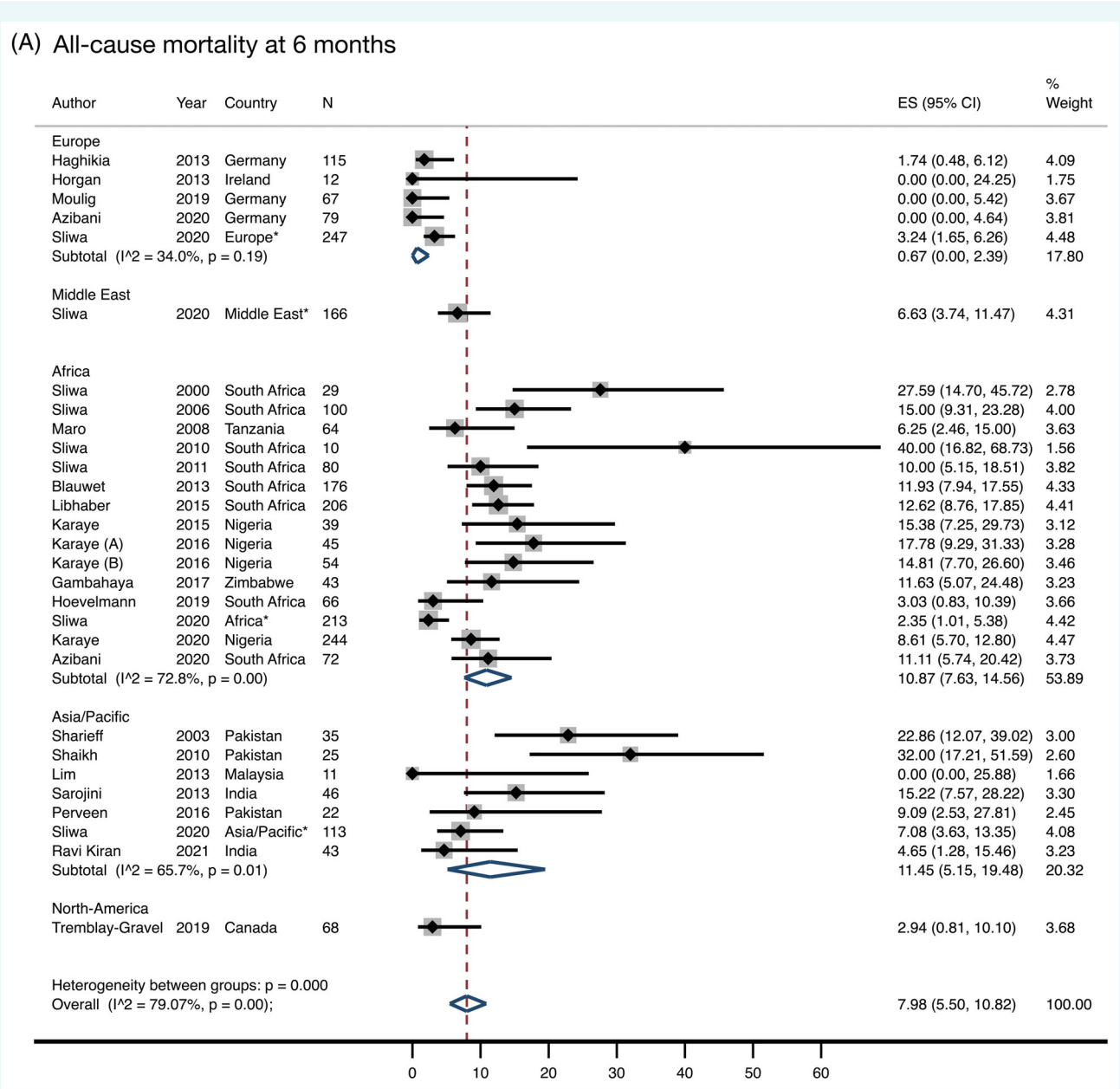



**Figure 2** All-cause mortality (*A*, *B*) and recovered left ventricular (LV) systolic function (*C*, *D*) at 6 and 12 months, respectively, across different continents. CI, confidence interval; ES, effect size.

received invasive ventilation, whereas 21.5% and 3.1% received inotropic and mechanical support, respectively. LV thrombus complicated 9.0% (95% CI 6.5–11.9) of patients and all-cause embolic events (i.e. stroke, arterial embolism, deep vein thrombosis, pulmonary embolism) occurred in 6.1% (95% CI 3.8–8.9).

All-cause mortality at 6 months was 8.0% (95% CI 5.5–10.8, 29 studies, $I^2$ = 79.1%) with significant differences between continents (*Figure 2A* and online supplementary *Figure S2A*). The highest 6-month all-cause mortality rate was reported by studies from Asia/Pacific (11.5% [95% CI 5.2–19.5], seven studies, $I^2$ = 65.7%), followed by Africa (10.9% [95% CI 7.6–14.6], 15 studies, $I^2$ = 72.8%), Middle East (6.6% [95% CI 3.7–11.5], one study), North America (2.9% [95% CI 0.8–10.1], one study), and Europe (0.7% [95% CI 0–2.4], five studies, $I^2$ = 34.0%). All-cause mortality at 12 months was 9.8% [95% CI 6.2–14.0], $I^2$ = 80.5%) (*Figure 2B* and online supplementary *Figure S2B*). The highest mortality was reported from Africa (15.2% [95% 9.8–21.4], six studies, $I^2$ = 67.7%) followed by Asia/Pacific (13.6% [95% CI 2.7–29.8], three studies), Middle East (8.9% [95% CI 4.2–15], two studies), North America (5.1% [95% CI 1.4–10.6], three studies) and Europe (2.3% [95% CI 0–10.6], three studies).

There were significant regional differences in LV recovery (i.e. LVEF ≥50%) after 6 months. Overall, 44.1% ([95% CI 36.1–52.2],

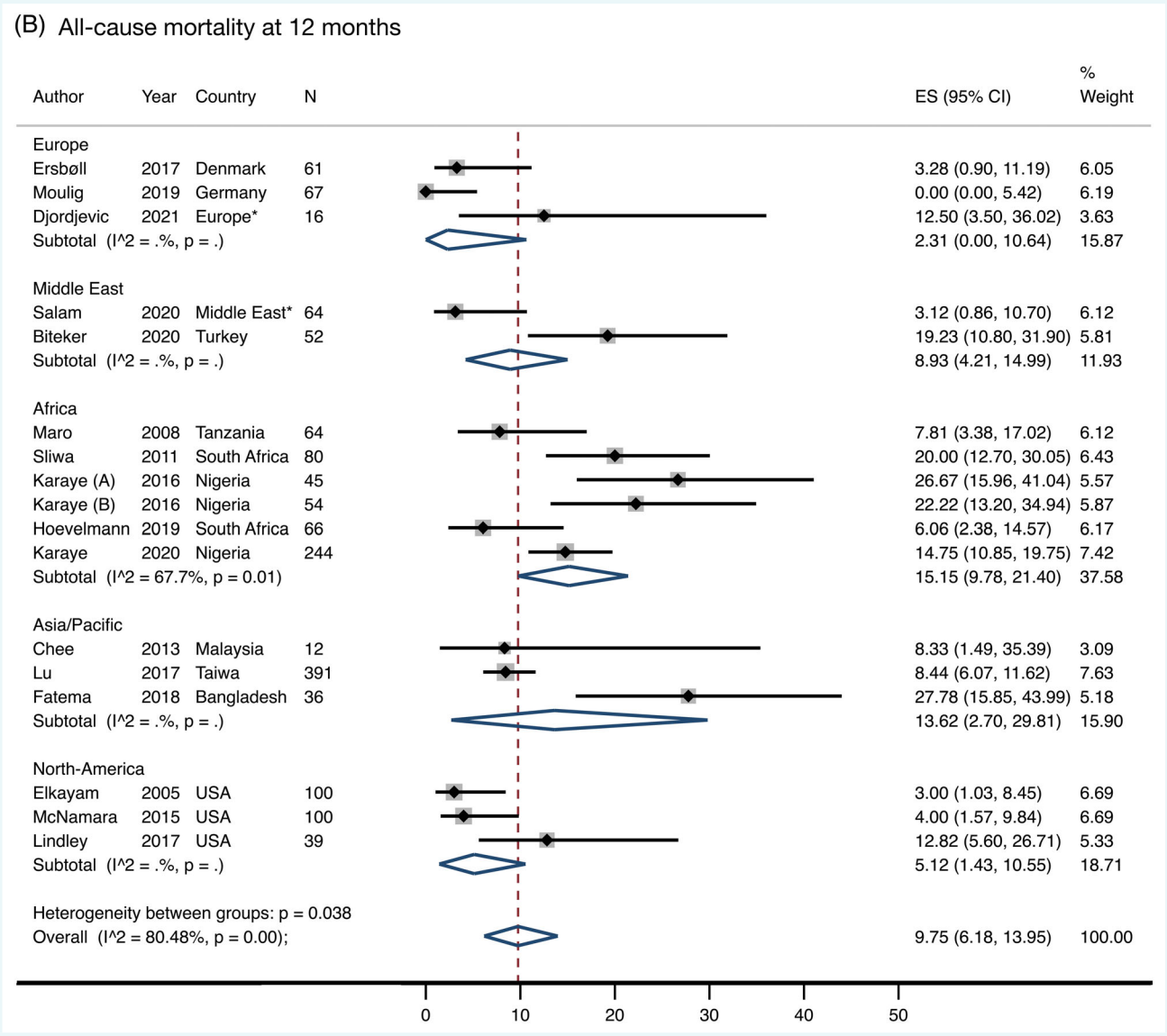



**Figure 2** Continued

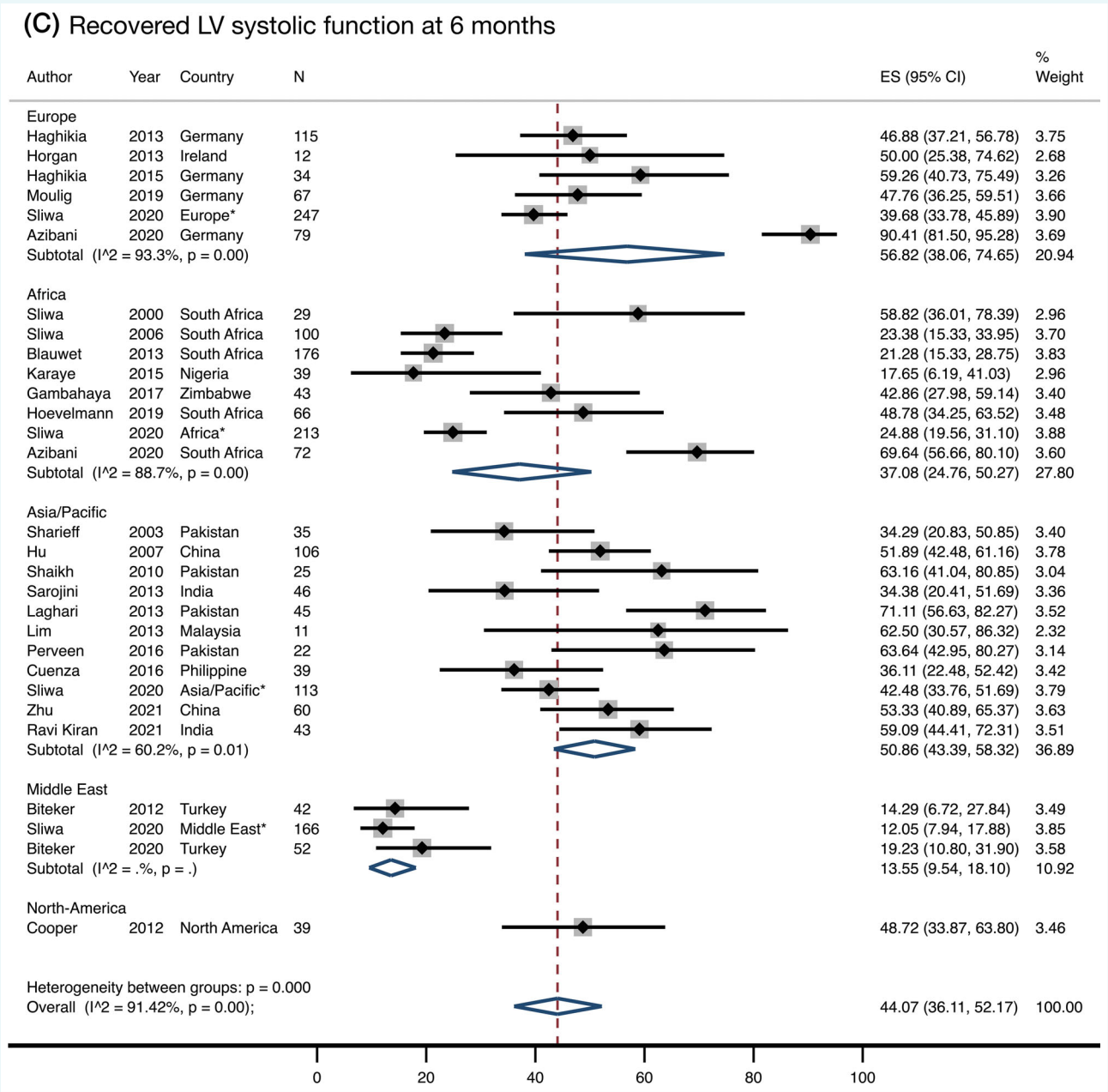
29 studies, $I^2$ = 91.4%) of patients recovered their LV function within 6 months. The lowest rate of LV recovery was reported in the Middle East (13.6% [95% CI 9.5–18.1], three studies), whereas the highest recovery was reported patients from Europe (56.8% [95% CI 38.1–74.7], six studies, $I^2$ = 93.3%) (*Figure 2C* and online supplementary *Figure S3A*). After 12 months, 58.7% ([95% CI 48.1–68.9], 10 studies, $I^2$ = 75.8%) of patients had recovered their LV function (*Figure 2D* and online supplementary *Figure S3B*).

## Predictors of outcome

Twenty-five studies included in this systematic review described predictors of outcomes. *Table 1* summaries the risk factors reported to be associated with favourable and adverse outcomes.

Studies that included patients with a median baseline LVESD >50 mm (as compared with those with a median baseline LVESD ≤50 mm) reported higher all-cause mortality (12.7% [95% CI 7.7–18.7] vs. 3.5% [95% CI 1.9–5.5], $I^2$ = 89.7%) at 6 months, as well as significantly lower rates of LV recovery (17.7% [95% CI 13.0–22.8] vs. 34.2% [95% CI 25.6–43.3], $I^2$ = 90.2%) (*Figure 3A,C*). Studies that included patients with a median LVEDD >60 mm at baseline showed a lower rate of LV recovery at 6 months (22.1% [95% CI 14.0–31.3], $I^2$ = 81.6%) compared with those with a median LVEDD ≤60 mm (36.0% [95% CI 28.7–43.7], $I^2$ = 83.6%). Studies that included women with an initial median LVEF ≤30% were not associated with a significantly different LV recovery at 6 or 12 months compared to those with a median LVEF >30% at time of diagnosis.

Studies that reported beta-blocker prescription of ≥80% were associated with a significantly lower all-cause mortality at

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6 months (3.0% [95% CI 0.4–6.2]) than those where beta-blocker prescription was <80% (11.4% [95% CI 9.4–13.6], $p = 0.003$) (*Figures 3A*, *4A*, and online supplementary *Figure S4*). At 12 months, studies that reported ≥80% prescription of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) were associated with significantly lower all-cause mortality (4.2% [95% CI 0.9–9.2] as compared with studies that reported <80% (12.6 [7.8–18.2], $p = 0.017$) and significantly higher LV recovery (52.3% [95% CI 39.2–65.2] vs. 16.9 [10.6–24.2], $p < 0.001$) (*Figures 3B,D*, *4B,D*, and online supplementary *Figure S5*). Similarly, studies in which ≥80% of patients were prescribed either bromocriptine or cabergoline reported a significantly higher proportion of LV recovery at 6 months (65.0% [95% CI 40.7–85.8] vs. 35.6% [95% CI 22.8–49.5], $p = 0.039$) and 12 months (44.8% [95% CI 33.0–56.9] vs. 24.2% [95% CI 14.6–35.4], $p = 0.013$) (*Figures 3C,D*, *4C,D*), as well as significantly less all-cause mortality at 12 months (0% [95% CI 0–2.6] vs. 11.1% [95% CI 5.9–17.6], $p < 0.001$) (*Figures 3B*, *4B*).

## Certainty of the evidence

According to GRADE, we classified the risk of bias (online supplementary *Table S4*),[8] indirectness, and imprecision domains for

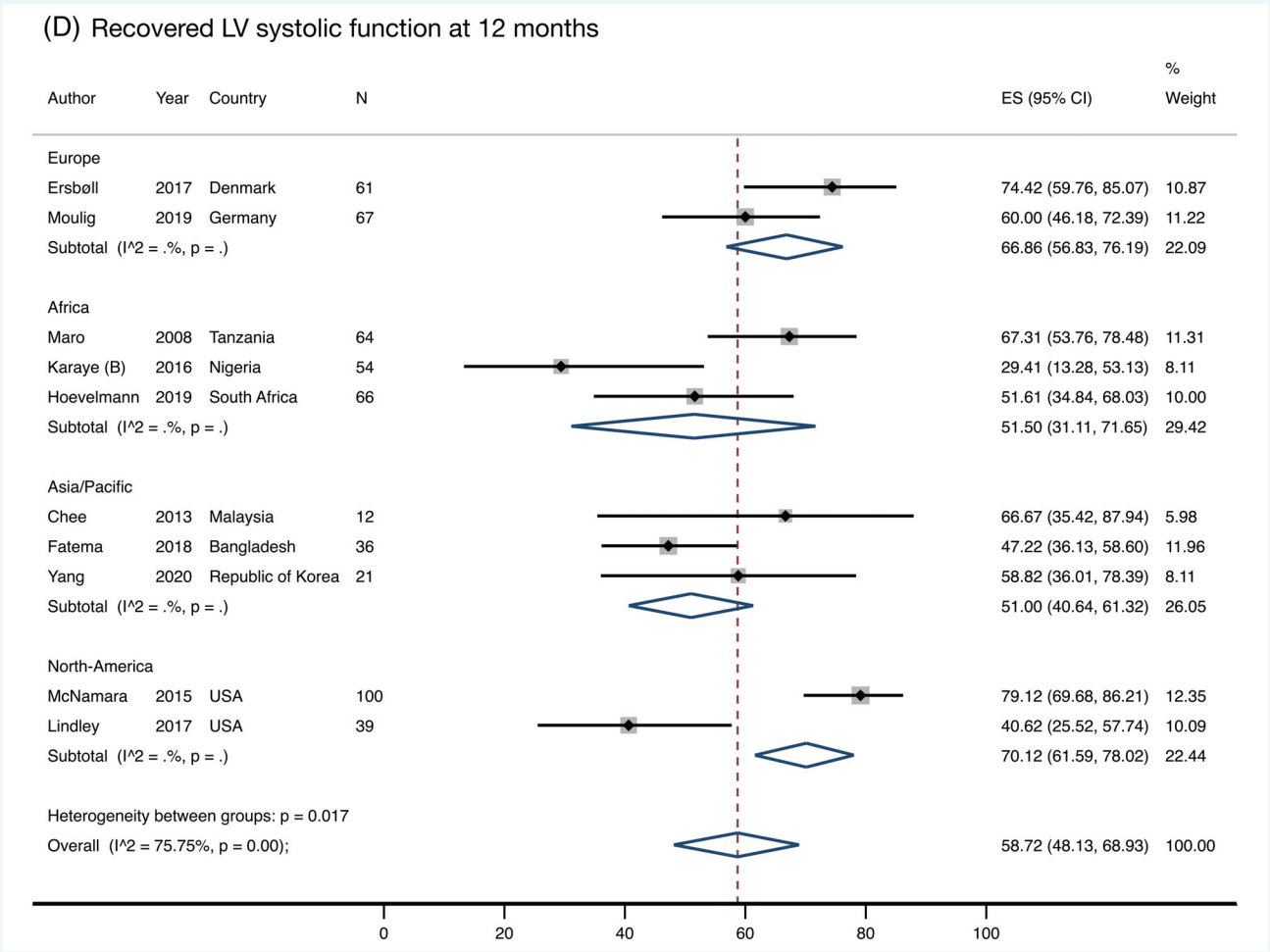


**Figure 2** Continued

mortality and/or LV recovery at 6 and/or 12 months respectively, as not serious (online supplementary *Table S5*). We recognized significant heterogeneity between the studies for global all-cause mortality ($I^2$ = 79.1%; 80.5%) and LV recovery ($I^2$ = 91.4%; 75.8%) at 6 and 12 months, respectively. However, on further inspection, this inconsistency appeared diminished within regional study groupings.

# Discussion

This systematic review summarizes the available global data on the clinical presentation, management, in-hospital complications, as well as 6- and/or 12-month outcome of women with PPCM. We show that the clinical presentation of women with PPCM is similar worldwide. However, there are significant global differences in the prescription of treatment, prevalence of in-hospital complications, as well as differences in all-cause mortality and LV recovery after 6 and 12 months.

Our meta-analysis identified a high prevalence of in-hospital complications at the time of PPCM diagnosis. Overall, about 10% of patients received invasive ventilation, 21.5% inotropic support and 3.1% mechanical support (which included LV assist devices, extracorporeal membrane oxygenation, impella pumps, intra-aortic balloon pumps). The highest use of mechanical support was reported by studies from Europe, whereas the highest use of inotropic support was reported from the Asia/Pacific region. The prevalence of LV thrombus at PPCM diagnosis was higher in Africa, Asia/Pacific and Middle East compared to Europe. This may reflect the delayed access to health care facilities in these regions compared to the Western World. Thromboembolic events occurred in 6.1% of patients at presentation, with no significant geographical differences between continents.

Overall, 44.1% of patients recovered their LV function (≥50%) within 6 months and 58.7% within 12 months. Although the initial clinical presentation was similar across all continents, there were significant regional differences in LV recovery at follow-up between geographical regions. The highest rates of LV recovery at 6 months were reported for Europe followed by Asia/Pacific, North America, Africa and Middle East. These rates of LV recovery seem to be higher than in other forms of dilated cardiomyopathy

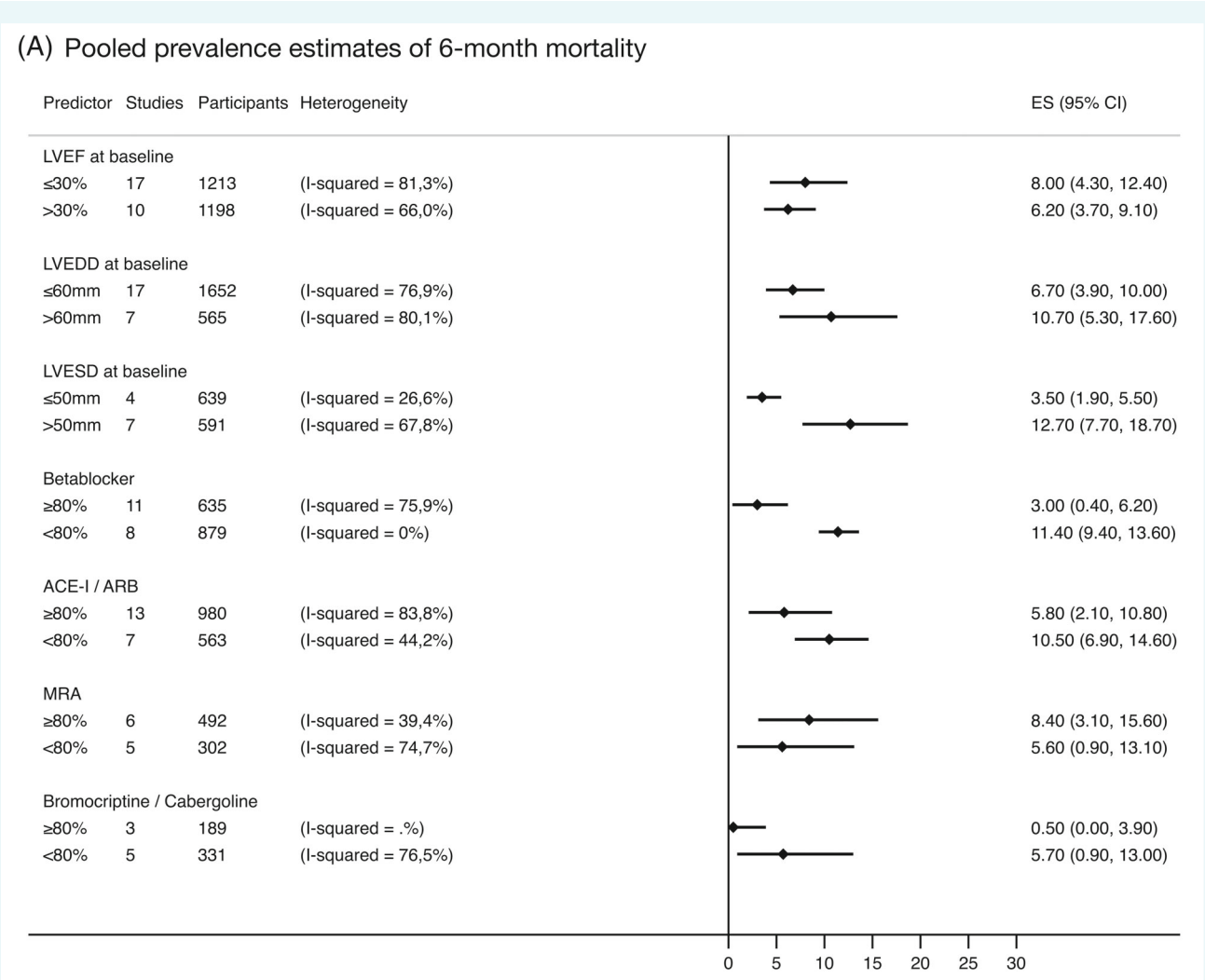


**Figure 3** Pooled prevalence estimates of mortality (*A*, *B*) and left ventricular recovery (*C*, *D*) at 6 and 12 months, respectively, as compared by echocardiographic parameters and prescribed treatment. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; ES, effect size; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist.

(DCM). The Intervention in Myocarditis and Acute Cardiomyopathy (IMAC-2) study, which included 373 patients with idiopathic DCM or myocarditis from North America, reported LV recovery (LVEF ≥50%) in 25% of patients at 6 months.[66]

Our analyses revealed that all-cause mortality was significantly higher in Asia/Pacific, Africa and Middle East compared to Europe and North America. This is in keeping with a previous meta-analysis,[67] which compared the mortality in women with PPCM between advanced and developing countries. They found that the death rate in developing countries was significantly higher than those reported in advanced countries (14% [95% CI 10–18%]) vs. 4% [95% CI 2–7%]).[67] DCM comprises different cardiac pathologies of various aetiologies. Therefore, reported mortality rates differ. In the IMAC-2 study, all-cause mortality was 2% with a transplant-free survival of 94% at 12 months.[66]

Heterogeneity of LV recovery and all-cause mortality was high and could be explained by regional differences in access to health care and intensive care treatment, and availability of contemporary HF therapy. Our findings suggest, expectedly, that studies that included patients with more severe LV dilatation were associated with higher all-cause mortality (baseline LVESD) and lower rates of LV recovery (baseline LVEDD and LVESD). In previous reports, baseline LVEDD and LVESD were frequently described as predictors of adverse outcomes in PPCM.[17–19,40,44,45,58] In the IMAC-2 study, baseline LVEDD was the strongest predictor of LV recovery at 6 months.[66] A smaller LV size at baseline is thought to be associated with a more reversible cardiac pathology.[66]

It is well established that inhibition of the renin–angiotensin–aldosterone system and sympathetic nervous system reduce mortality in patients with HF with reduced ejection fraction.[68–71]

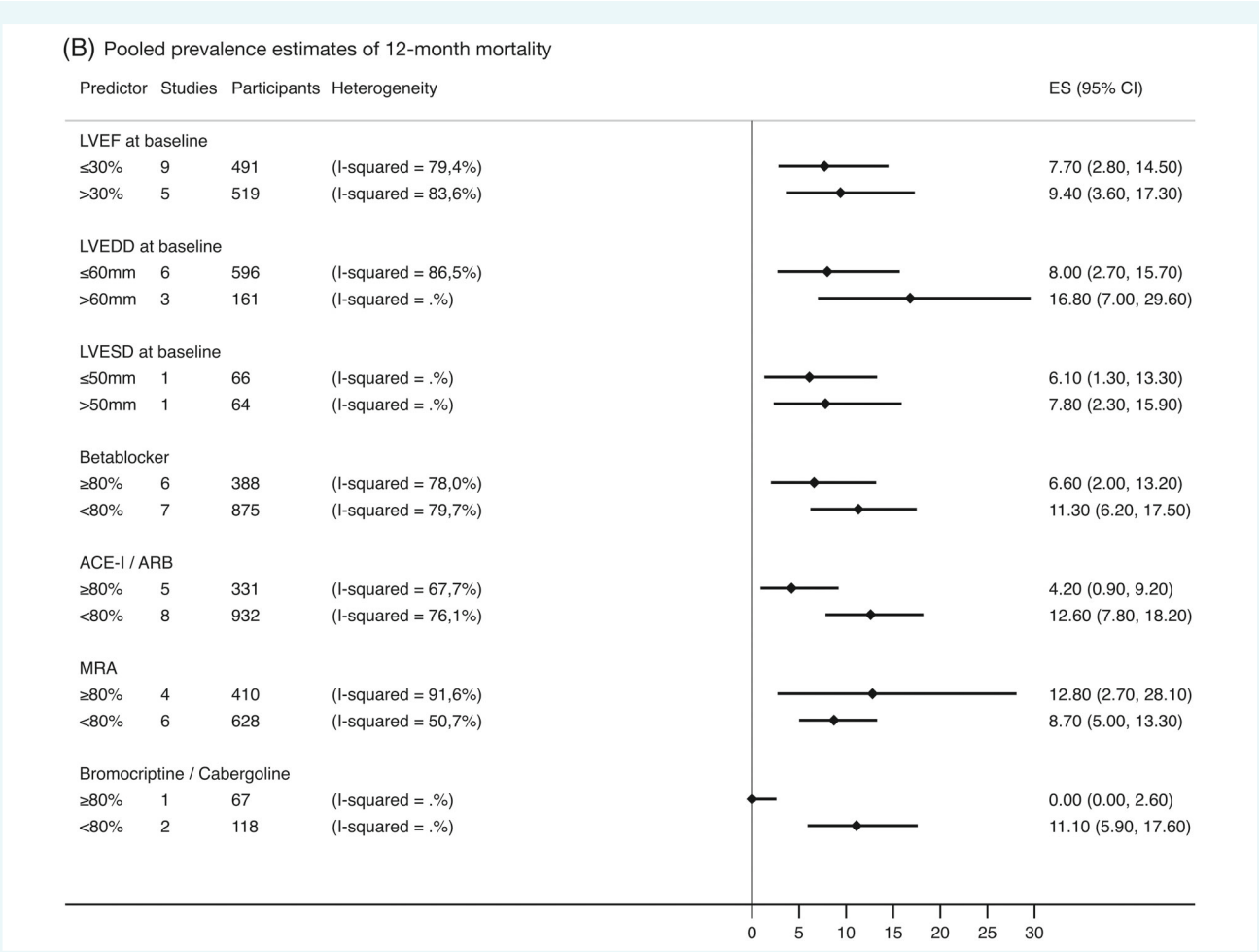


**Figure 3** Continued

These therapies have been the cornerstone of HF therapy since the early 2000s, which also corresponds with time period in which most of the included studies were performed. It is therefore encouraging that our meta-analysis showed that studies in which patients with PPCM were optimally treated according to contemporary guideline-directed HF therapy showed better outcomes. We found that frequent prescription of beta-blockers (≥80%) was associated with significantly reduced all-cause mortality at 6 months. In fact, studies that reported the lowest prescription of beta-blocker use had the highest reported all-cause mortality.[16,19,28,40,35,36,38] A possible explanation for the observed disparities in all-cause mortality may be the preferential use of digoxin instead of beta-blockers in many African countries.[72] Furthermore, studies that reported ≥80% prescription of ACE-I/ARB were associated with significantly lower all-cause mortality at 12 months and better LV recovery. Underuse of these established HF therapies may be important in the observed discrepancies in outcome. It is also important to note, that none of the included studies reported on the use of angiotensin receptor–neprilysin inhibitors or sodium–glucose cotransporter 2 inhibitors.

Furthermore, we demonstrated that a high prescription of bromocriptine or cabergoline was associated with lower all-cause mortality and higher rates of LV recovery, respectively. In 2010, the bromocriptine proof-of-concept pilot study was published, followed by a multicentre clinical trial in 2017, which encouraged the use of bromocriptine.[61,73] Our results also support the findings of a recent systematic review and meta-analysis on the effects of bromocriptine in PPCM.[74] This analysis included eight studies (two randomized controlled trials, six observational studies) involving 593 patients and they found that the addition of bromocriptine to guideline-directed HF therapy was associated with significantly higher survival and higher LVEF improvement.[74]

It cannot be assumed that prescription rate of HF therapy corresponded with adherence to treatment. Despite effective treatment options, prior studies have found that merely about half of patients with HF are adherent to at least 80% of their prescribed medication.[75]

Recognizing PPCM as a leading cause of cardiovascular mortality and morbidity in women, efforts should be made to improve the access to health care including the availability of

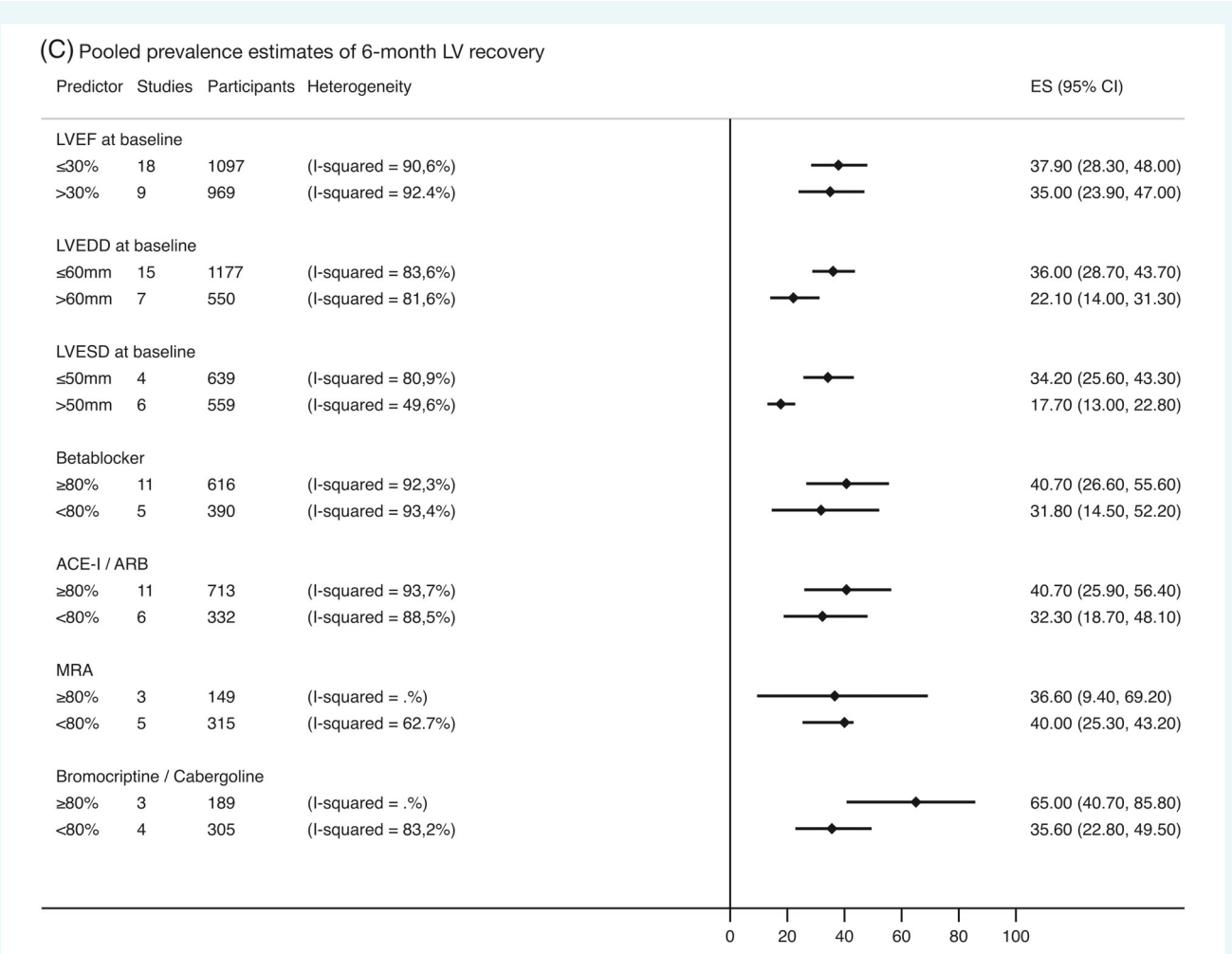


**Figure 3** Continued

guideline-directed treatment options for PPCM. This would help to improve the outcome and prognosis of women with PPCM globally.

## Limitations

Our systematic review employed robust methods in synthesizing the evidence, which included a rating of the quality of the evidence according to GRADE guidelines.[14] As expected, there was significant heterogeneity amongst the global prevalence of all-cause mortality and LV recovery. This could be explained by regional differences in the prescription of established guideline-directed HF therapy and access to intensive medical care, as we could demonstrate in this review. Indeed, the differences in management and outcomes of PPCM in different parts of the world are a central message of this systematic review.

While we acknowledge possible selection bias (as we only included publications that had a specified outcome reported for 6 and/or 12 months after diagnosis), this is, to the best of our knowledge, the largest review summarizing in-hospital complications and 6- and/or 12-month outcomes of women with PPCM.

Although we attempted to exclude all duplicate publications, i.e. where it was known that the same cohort was used in subsequent publications, we could not control for the possibility that some of the included studies contained data on patients that were included in more than one publication. Our meta-analysis could also not explore individual patient-level data, as meta-analyses pool data from included studies. These are general limitations of systematic reviews and meta-analyses, and not only within our study.

We endeavoured to conduct a global evaluation; however, we found that the literature reporting on outcomes of PPCM is derived predominantly from patients in the United States, South Africa, Nigeria and Germany. Thus, our analyses are limited by the lack of reported outcomes from South America, Central America, Australasia as well as large parts of Africa, Europe, the Middle East and Asia (online supplementary *Figure S1*). Furthermore, none

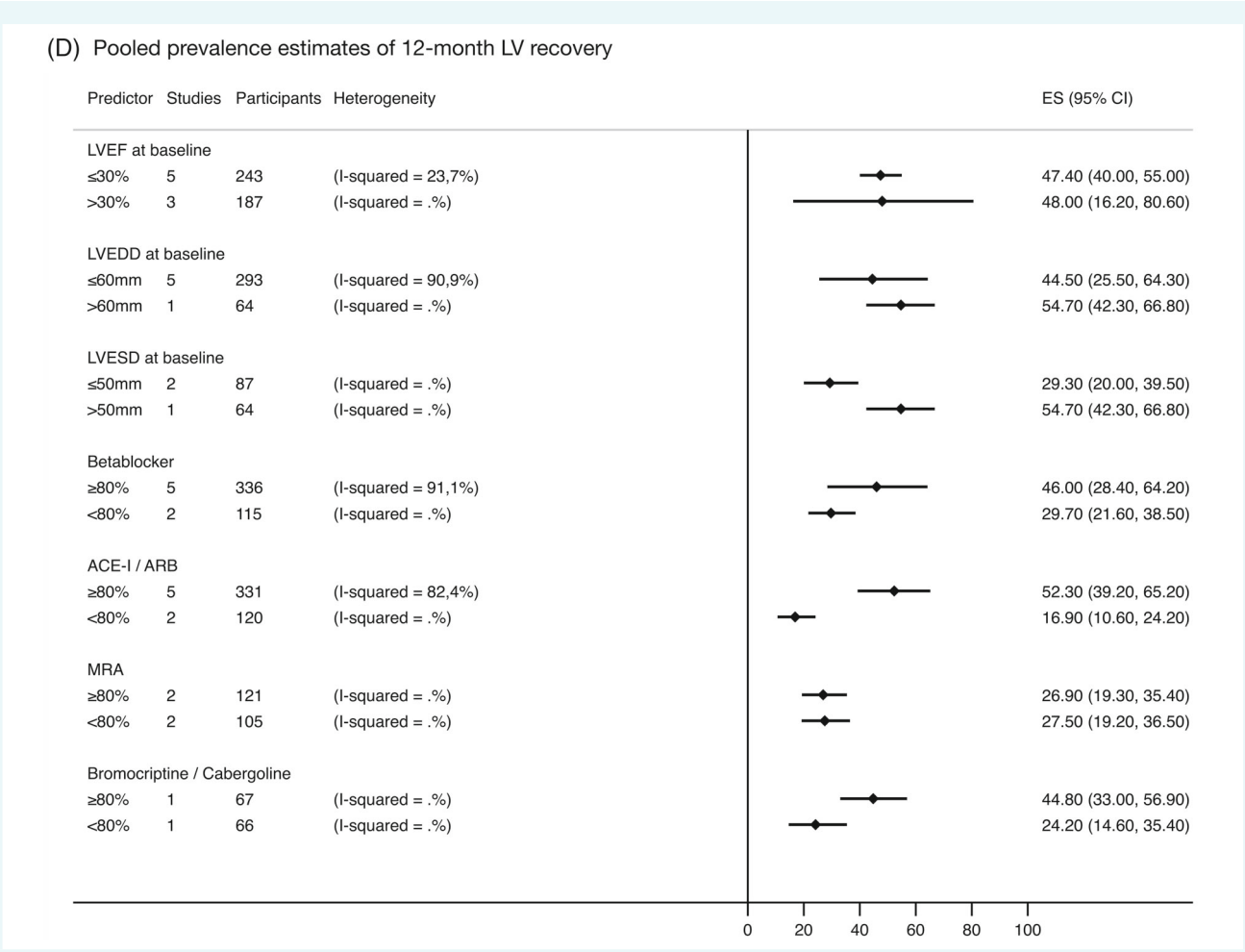


**Figure 3** Continued

of the studies included in this systematic review reported on adherence rates. Future studies should report on adherence to established HF therapy in PPCM and investigate possible reasons for non-adherence. No causal inferences should be made from the associations between treatment prescription and outcomes that we describe in this manuscript, as there may be numerous confounding factors.

While our study shows that PPCM is associated with significant all-cause mortality, there is, however, limited information about the causes of death. The European Observational Research Programme (EORP), which included 739 women with PPCM from 49 countries, reported that 42% of deaths were related to HF and 30% were thought to be related to sudden cardiac death.[1] Future studies should aim to better delineate the mode of death in women with PPCM.

## Conclusion

To the best of our knowledge, this is the largest study to date reporting on the outcomes of patients with PPCM. Although more than half of patients with PPCM worldwide had LV recovery (LVEF ≥50%) after 1 year, global mortality rates were high. However, we identified important regional differences in both all-cause mortality and LV recovery in PPCM. These differences may be explained by variable prescription of guideline-directed medical therapy and access to health care services in different parts of the world. Studies that reported high prescription rates of beta-blockers, ACE-I/ARBs and bromocriptine were associated with better rates of LV recovery and lower all-cause mortality. Timely initiation and up-titration of HF therapy should therefore be strongly encouraged to improve outcome in PPCM.

## Supplementary Information

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

### Acknowledgements

We would like to acknowledge the contribution of the expert librarian Patricia Makwambeni, University of Cape Town, for her assistance in developing the search strategies. J.H. was supported

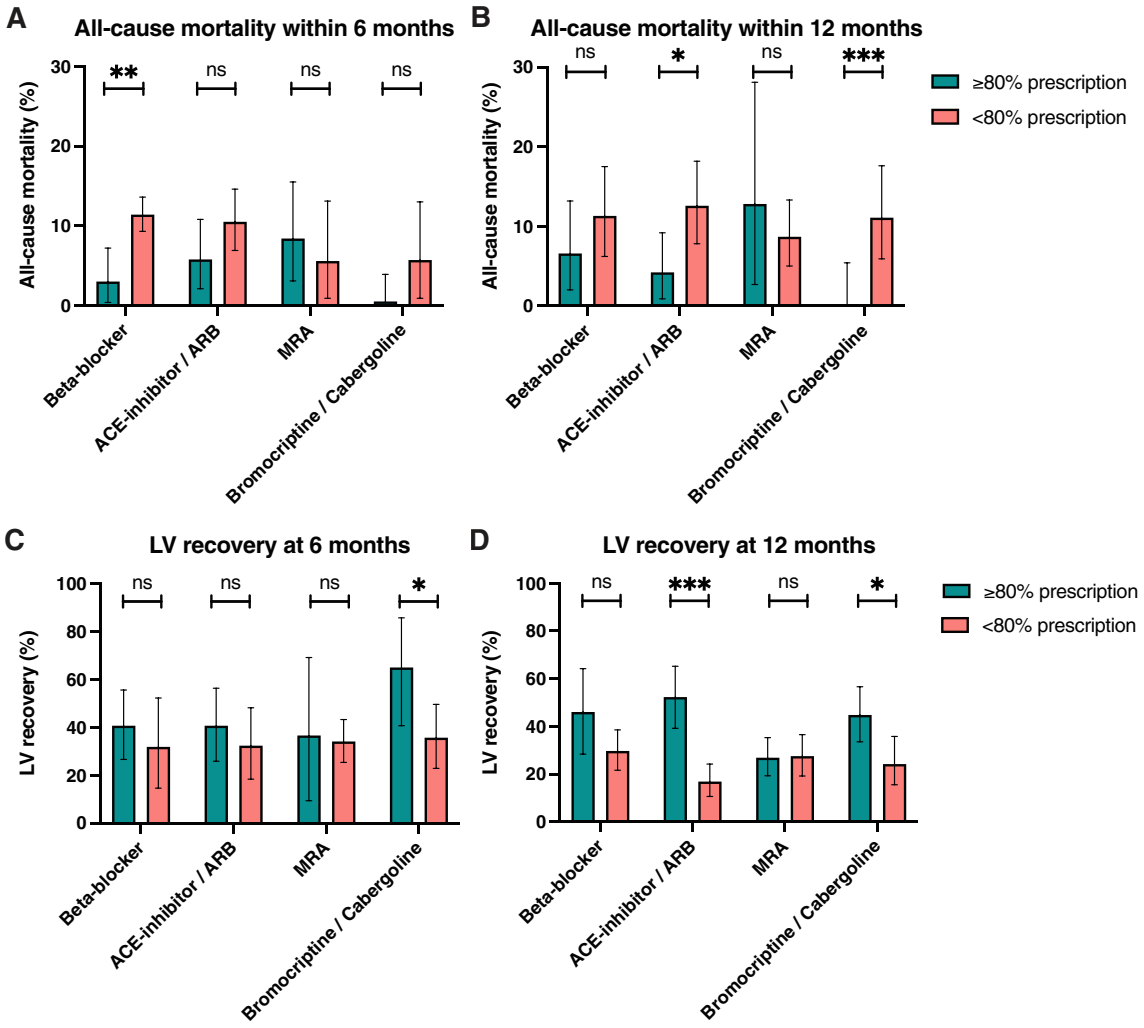


**Figure 4** All-cause mortality (*A*, *B*) and left ventricular (LV) recovery (*C*, *D*) at 6 and 12 months, respectively, as categorized by studies that reported ≥80% or <80% prescription of guideline-directed heart failure treatment (***$p$ <0.001; **$p$ = 0.001–0.009, *$p$ = 0.010–0.050). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

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**Conflict of interest**: none declared.

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