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SYSTEMATIC REVIEW

Mechanical circulatory support for cardiogenic shock: a network meta-analysis of randomized controlled trials and propensity score-matched studies

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Abstract

Purpose: Cardiogenic shock is associated with high mortality. In refractory shock, it is unclear if mechanical circulatory support (MCS) devices improve survival. We conducted a network meta-analysis to determine which MCS devices confers greatest benefit.

Methods: We searched MEDLINE, Embase, and Scopus databases through 27 August 2023 for relevant randomized controlled trials (RCTs) and propensity score-matched studies (PSMs). We conducted frequentist network meta-analysis, investigating mortality (either 30 days or in-hospital) as the primary outcome. We assessed risk of bias (Cochrane risk of bias 2.0 tool/Newcastle–Ottawa Scale) and as sensitivity analysis reconstructed survival data from published survival curves for a one-stage unadjusted individual patient data (IPD) meta-analysis using a stratified Cox model.

Results: We included 38 studies (48,749 patients), mostly reporting on patients with Society for Cardiovascular Angiography and Intervention shock stages C–E cardiogenic shock. Compared with no MCS, extracorporeal membrane oxygenation with intra-aortic balloon pump (ECMO-IABP; network odds ratio [OR]: 0.54, 95% confidence interval (CI): 0.33–0.86, moderate certainty) was associated with lower mortality. There were no differences in mortality between ECMO, IABP, microaxial ventricular assist device (mVAD), ECMO-mVAD, centrifugal VAD, or mVAD-IABP and no MCS (all very low certainty). Our one-stage IPD survival meta-analysis based on the stratified Cox model found only ECMO-IABP was associated with lower mortality (hazard ratio, HR, 0.55, 95% CI 0.46–0.66).

Conclusion: In patients with cardiogenic shock, ECMO-IABP may reduce mortality, while other MCS devices did not reduce mortality. However, this must be interpreted within the context of inter-study heterogeneity and limited certainty of evidence.

Keywords: Mechanical circulatory support, Cardiogenic shock, Network meta-analysis, Mortality

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Introduction

Cardiogenic shock accounts for up to 5% of acute heart failure presentations and around 14–16% of patients reported in cardiac intensive care datasets [1, 2]. It complicates up to 15% of all myocardial infarctions, and is the leading cause of death post-infarction [3, 4]. Despite advances in research, mortality remains as high as 40–60% [5, 6]. While early revascularization in acute myocardial infarction-associated cardiogenic shock (AMICS) has reduced mortality, [5, 7] myocardial damage from revascularization may still precipitate cardiogenic shock, with uncertain long-term outcomes [8, 9]. Additionally, an increasing proportion of cardiogenic shock now arises from non-ischemic etiologies (non-myocardial infarction-associated cardiogenic shock, NMICS) [10–12]. Using pharmacological agents alone may increase left ventricular afterload and myocardial oxygen demand, resulting in complications [13–17]. Thus, mechanical circulatory support (MCS) devices have emerged as important therapeutic options [14, 18–20]

While guidelines governing indications and selection of MCS have been made, these recommendations are limited by little high-quality evidence [21–23]. As evidence remains uncertain [5, 24–30], MCS selection depends on clinician preference and local availability. Prior pairwise meta-analyses examining these devices remain equivocal: [31] reviews comparing extracorporeal membrane oxygenation (ECMO) and microaxial left ventricular devices (mVAD) [32], intra-aortic balloon-pumps (IABP) with ECMO, and mVAD with IABP report no important differences in mortality [33, 34]. Notable past trials of IABP against no MCS did not show significant benefits, with more recent randomized controlled trials (RCTs) comparing ECMO with no MCS also not showing significant benefits [35, 36]. While network meta-analyses have been conducted on this topic, these included uncontrolled observational studies that could introduce confounding [5], used fixed-effects statistical models associated with limitations [37] and did not include recently published studies [35, 38, 39]. We performed an updated systematic review and meta-analysis of high-quality RCTs and propensity score-matched studies (PSMs) to compare the outcomes of MCS devices with no MCS and each other, and investigate which MCS is the most effective in reducing mortality [40].

Methods

Search strategy and selection criteria

The review was registered with PROSPERO (CRD42022355759 on 27/09/2022) and conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement Extension for Network Meta-analyses (supplemental Table S1) [41]. We collaborated with an information specialist and searched MEDLINE, Embase, and Scopus databases from 1st January 1990 through 27th August 2023, using the following keywords and their variations: "cardiogenic shock", "mechanical circulatory support" and "randomized controlled trial" or "propensity" (supplemental Table S2). Reference lists of included studies and relevant review articles were also reviewed. Only RCTs and PSMs comparing an MCS device with another MCS device or with medical therapy (no MCS) in cardiogenic shock were included. Studies enrolling animals, patients primarily < 18 years old, and other observational designs were excluded. In the case of overlapping patient data, we included the largest study only.

Take-home message

This network meta-analysis of 48,749 patients found that extracorporeal membrane oxygenation with intra-aortic ballon-pump was significantly associated with reduced mortality (30 days or in-hospital) in cardiogenic shock compared to no mechanical circulatory support, while other devices did not record reduced mortality. This study is the first network meta-analysis including only high-quality randomized controlled trials and propensity score-matched studies, and therefore plays a key role to inform future randomized trials on the topic.

Data collection and risk of bias assessment

Data were collected using a prespecified data extraction form (supplemental Table S3). Where appropriate, we derived the means and standard deviations as per Wan et al. [42]. When studies presented a Kaplan–Meier curve without reporting study-level data, the individual participant data were reconstructed in a time-to-event fashion using the methods suggested by Guyot et al. [43]. Images of Kaplan–Meier curves were downloaded, preprocessed and digitized, before obtaining their step function values and timing of the steps and calibrating the time-to-event data using number-at-risk tables and total number of patients. The survival information was reconstructed by solving the inverted Kaplan–Meier product limit equations and computed the study level using a Cox regression model. In case of missing data, we contacted the corresponding authors of each study to clarify the missing data, and requested them to share unreported data.

Individual study risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool for RCTs and the Newcastle–Ottawa Scale (NOS) for cohort studies [44, 45]. Certainty of evidence was assessed using the Grading of Recommendations, Assessments, Developments and Evaluations (GRADE) approach for network

meta-analyses [46–51], ranking certainty of evidence from "high" (there is confidence that the true effect lies close to the estimate of the effect) to "very low" (there is very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect) [49]. Informative narrative statements were used to communicate confidence in pooled estimates [52]. Details on the certainty rating and informative narrative statements are detailed in supplemental Methods. CJWL, RRL, MPXHL, NSHL, MT and KR independently and in duplicate screened the studies, collected data, and assessed risk of bias assessment using Covidence (Melbourne, Australia); conflicts were resolved by consensus.

Data synthesis

The primary outcome was 30-days or in-hospital mortality, due to the close correlations between these metrics [53]. In-hospital mortality was used for analyses if both were present. Patients were analyzed based on treatment strategies including ECMO, ECMO-IABP, ECMO-mVAD, IABP alone, mVAD alone, mVAD-IABP, centrifugal VAD (TandemHeart, cVAD) and medical therapy without MCS. When not reported, we derived 30-day mortality from published Kaplan–Meier curves. Secondary outcomes were collected as available, including stroke, bleeding, limb ischemia, and hemolysis. Binary outcomes are presented as pooled odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). Random-effects meta-analyses (Mantel and Haenszel) were conducted for binary outcomes [54, 55]. The feasibility for network meta-analysis was assessed by evaluating the availability of evidence, homogeneity of study designs, patients, and characteristics of interventions across the included studies (transitivity), the structural properties of the network (connectivity) and network coherence.

Frequentist random-effects network meta-analysis was conducted [56, 57], and comparisons between the MCS devices were visualized using a network graph, with the thickness of each edge representing the number of studies comparing two MCS devices. The total network inconsistency was calculated based on the full design-by-treatment interaction random-effects model [58, 59]. The node-splitting method was used to assess for coherence between direct and indirect estimates. The ranking probabilities were estimated using the frequentist analog of the Surface Under the Cumulative Ranking (SUCRA) curve based on 10,000 repetitions, with a higher P score indicating a higher probability of being more effective [60, 61]. We did not impute missing data in view of the study-level nature of the data used in the analysis.

Post hoc analyses

We conducted several post hoc analyses. First, studies deemed as high risk of bias ("high risk" by the Cochrane ROB2.0 tool, or scoring < 7 points on the Newcastle–Ottawa Scale) were excluded. Second, we attempted to create more precision by grouping MCS devices that were similar in function. cVAD and mVAD were combined as one group of "percutaneous VAD" (PVAD) due to both being left-sided VADs, and ECMO-IABP and ECMO-mVAD combined as "ECMO with unloading" due to both being ECMO paired with a left ventricular unloading mechanism. Third, the analysis was stratified by study type (RCTs and PSMs), and explored for interaction effects using the ratio of ORs [62]. We also estimated the effects based on the etiology of cardiogenic shock (AMICS, NMICS, and mixed). Fourth, risk difference (RD) as well as the number needed to treat (NNT) were calculated for each intervention [63]. Risk differences are presented alongside ORs. Fifth, as IPD meta-analysis is able to better account for heterogeneity and inconsistencies that may be present in a network meta-analysis [64], our reconstructed IPD was used to conduct a one-stage meta-analysis, using a stratified Cox model as the primary model [65] and a random-effects Cox proportional hazards model to assess the robustness of the results. For this analysis survival times were administratively censored at 30 days. Finally, for the primary outcome (mortality), we assessed the power of each pairwise meta-analysis by conducting a trial sequential analysis (TSA) (refer to supplemental Methods for more details).

Statistical heterogeneity (inconsistency) was assessed as part of the GRADE approach, using I-squared but also the Chi-squared test and visual inspection of the forest plots [50]. Publication bias was assessed qualitatively using visual inspection of funnel plots. Statistical analysis was conducted using R 4.1.2.

Role of the funding source

There was no funding source for this study.

Results

Characteristics of included studies

Of 4135 references, we reviewed 155 full-texts, including 38 studies with 40 pairwise comparisons comparing eight treatment strategies (48,749 patients. Figure 1, full references in electronic supplementary material, ESM). There were no favorable responses when contacting authors in cases of missing data. 13 studies (1529 patients) were RCTs, and 25 (47,220 patients) were PSMs. Twenty-four studies included patients with AMICS, 13 studies included patients with mixed etiologies of cardiogenic shock, and 1 study included patients with NMICS. All

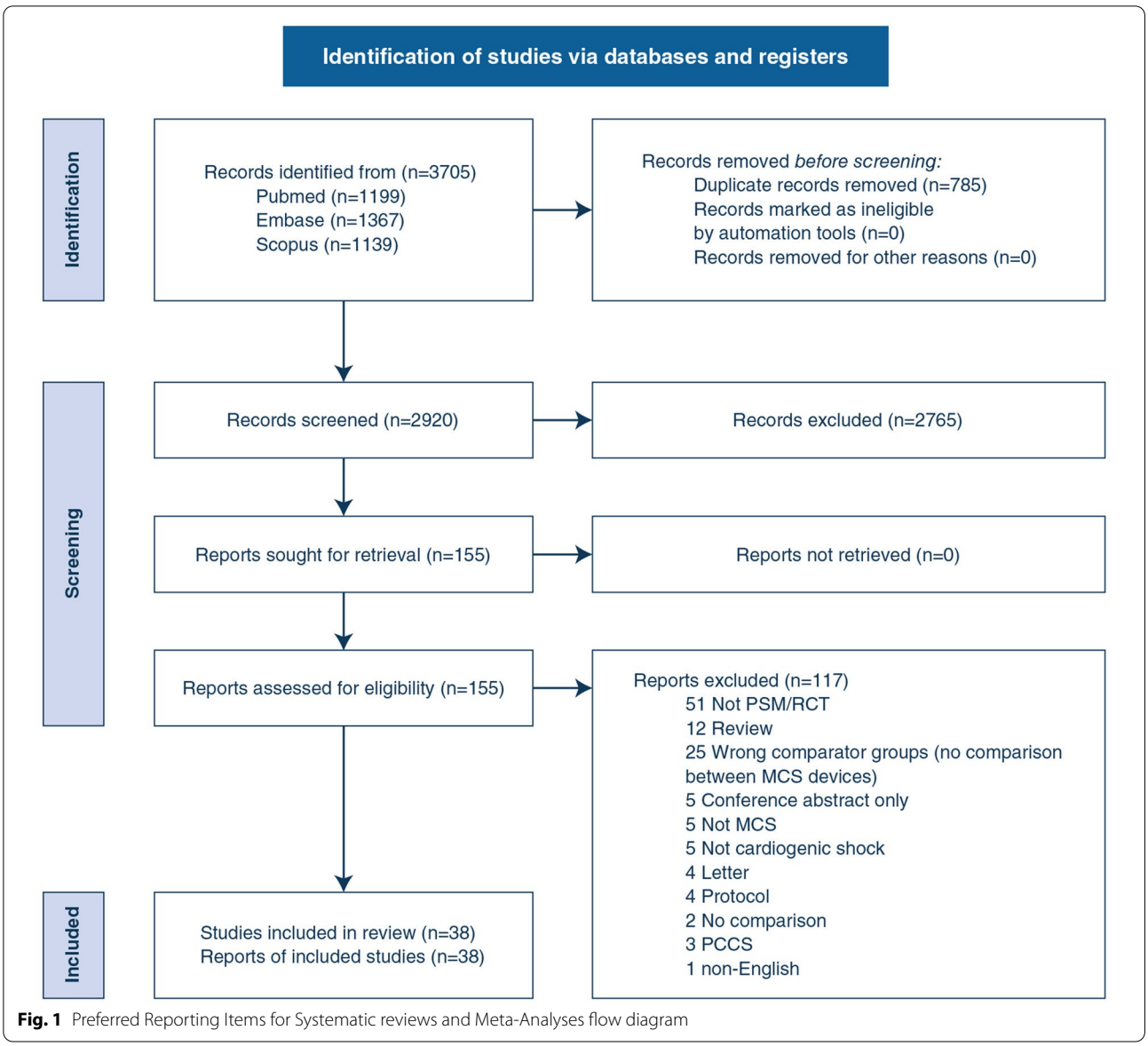

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram

studies were published between 2005 and 2023; only three studies were published before 2010. Five studies were from Asia, 23 from Europe, nine from America, and one study was multiregional (North America, Australia, Europe). 18 studies reported on in-hospital mortality, 15 reported on 30-day mortality. Three reported on both (of which in-hospital mortality was taken), and two reported neither 30-days nor in-hospital mortality (thus, 30-day mortality was extrapolated from Kaplan–Meier curves). The interventions studied included ECMO (16 studies, 3847 patients), ECMO-IABP (4 studies, 1466 patients), ECMO-mVAD (3 studies, 300 patients), IABP (21 studies, 20,031 patients), mVAD (12 studies, 9047 patients), mVAD-IABP (1 study, 7 patients), cVAD (2 studies, 40 patients), and medical therapy without MCS (21 studies, 14,011 patients). All included ECMO patients underwent peripheral ECMO. The pooled age of all patients was 63.1 years (95% CI 62.1–64.2) and 74.1% (95% CI 70.9–77%) were male. The pooled body mass index (BMI) was 27.5 (95% CI 26.8–28.2), and the pooled left ventricular ejection fraction (LVEF) was 28.4% (95% CI 24.5–32.3%). Table 1 and supplemental Table S4 summarize the characteristics of the studies, supplemental Table S5a presents basic study demographics, while supplemental Table S5b presents pooled demographics of each intervention. Of included studies, 27 reported a prespecified definition for cardiogenic shock, all corresponding to a SCAI classification of C to E. Supplemental Table S6 presents details of

cardiogenic shock. Supplemental Table S7 reports risk of bias including propensity score-matched studies (7a) and randomized trials (7b), and supplemental Table S8 collates the GRADE assessments for all interventions.

Primary outcome

15,845 of 48,749 patients (32.5%) died (supplemental Table S9). Figure 2 highlights the network geometry—most studies compared an MCS device with no MCS, and the most reported MCS was an IABP. Compared to no MCS, ECMO-IABP was probably associated with reduced mortality (OR 0.54, 95% CI 0.33–0.86; RD −12.4%, 95% CI −2.1 to −22.6%, moderate certainty). Compared to no MCS, there was an uncertain effect of cVAD (OR 0.90, 95% CI 0.34–2.39; RD −1.1%, 95% CI −25.8 to 23.5%), ECMO (OR 0.99, 95% CI 0.75–1.30; RD −0.3%, 95% CI −6.2 to 5.5%), ECMO-mVAD (OR 0.61, 95% CI 0.34–1.10; RD −10.4%, 95% CI −23.9 to +3.1%), IABP (OR 1.01, 95% CI 0.80–1.29; RD 0.2%, 95% CI −4.8 to 5.3%), mVAD (OR 0.97, 95% CI 0.70–1.34, RD −0.1%, 95% CI −7.1 to 7%), and mVAD-IABP (OR 4.52, 95% CI 0.17–120.26; RD 18.8%, 95% CI −20.8 to 58.5%, all very low certainty for predominantly PSM data and imprecision, Table 2). Figure 3 demonstrates a survival benefit when using ECMO-IABP against no MCS, and while IABP and mVAD demonstrated survival benefits based on network estimates, these were abandoned in favor of direct and indirect estimates respectively (see supplemental Methods). Compared to ECMO-IABP, ECMO was associated with higher mortality (OR 1.78, 95% CI 1.19–2.68, moderate certainty). Supplemental Figure S1 highlights the total network inconsistency in the meta-analysis. Supplemental Figure S2 presents the ranking of each intervention based on the P-scores. Table 2 presents the summary of findings table for the meta-analysis, including the odds ratios, risk differences and number needed to treat, and supplemental Fig. S3 presents the forest plot for direct and indirect estimates based on the node-splitting method.

Post hoc sensitivity analyses

The pooled estimates compared to no MCS did not change when analyzing interventions using "PVAD" combining mVAD and cVAD (OR 0.99, 95% CI 0.72–1.36, RD −1.1%, 95% CI −33.1 to 30.7%, very low certainty), and "ECMO-unloading", combining ECMO-IABP and ECMO-mVAD (OR 0.56, 95% CI 0.37–0.86; RD −11.6%, 95% CI −2.4 to −20.9%, moderate certainty). When one study rated as high risk of bias was excluded, pooled estimates remained relatively unchanged [66]. Estimates for ECMO, IABP, and mVAD were reported by both PSM studies and RCTs. There were no significant interaction effects between PSM studies and RCTs for IABP ($p_{interaction}=0.75$) and mVAD ($p_{interaction}=0.71$), or ECMO ($p_{interaction}=0.57$). From reconstructed individual participant data from 25 studies (11,088 patients), IPD meta-analysis comparing the different MCS devices in cardiogenic shock was conducted. ECMO-IABP was associated with reduced mortality (stratified hazard ratio (HR) 0.55, 95% CI 0.46–0.66, random effects HR 0.57, 95% CI 0.48–0.69) compared to no MCS, with no reductions in mortality for other interventions. The

Table 1 Characteristics of studies included in the meta-analysis

Characteristic	Reported data
Number of included studies	Total: 38 studies
	Propensity score matched: 25 studies
	Randomized trials: 13 studies
Etiologies of cardiogenic shock	Acute myocardial infarction: 24 study
	Non-myocardial infarction: 1 study
	Mixed etiologies: 13 studies
Interventions	
• ECMO	16 studies, 3847 patients
• ECMO-IABP	4 studies, 1466 patients
• ECMO-mVAD	3 studies, 300 patients
• IABP	21 studies, 20,031 patients
• mVAD	12 studies, 9047 patients
• mVAD-IABP	1 study, 7 patients
• cVAD	2 studies, 40 patients
• Medical therapy only	21 studies, 14,011 patients
Number of deaths/total patients	15,845/48,749 patients
SCAI classification	
• A–B	0 studies
• C–E	38 studies
Pooled age/years	63.1, 95% CI 62.1–64.2
Pooled male proportions/%	74.1, 95% CI 70.9–77.0
Pooled BMI	27.5, 95% CI 26.8–28.2
Pooled LVEF/%	28.4, 95% CI 24.5–32.3
Outcomes	Studies/patients included in analysis
• Mortality	• 38 studies, 48,749 patients
• Bleeding	• 20 studies, 8646 patients
• Limb ischemia	• 18 studies, 3705 patients
• Acute kidney injury	• 17 studies, 22,424 patients
• Hemolysis	• 7 studies, 1632 patients
• Stroke	• 18 studies, 16,073 patients
• Infections	• 7 studies, 12,815 patients
Individual patient data/Kaplan–Meier curves reported	25 studies

Basic characteristics of included studies, full study characteristics are available in supplemental Table S4

Abbreviations: *BMI* body mass index, *cVAD* centrifugal ventricular assist device, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *mVAD* microaxial ventricular assist device, *SCAI* society of cardiac angiography and interventions

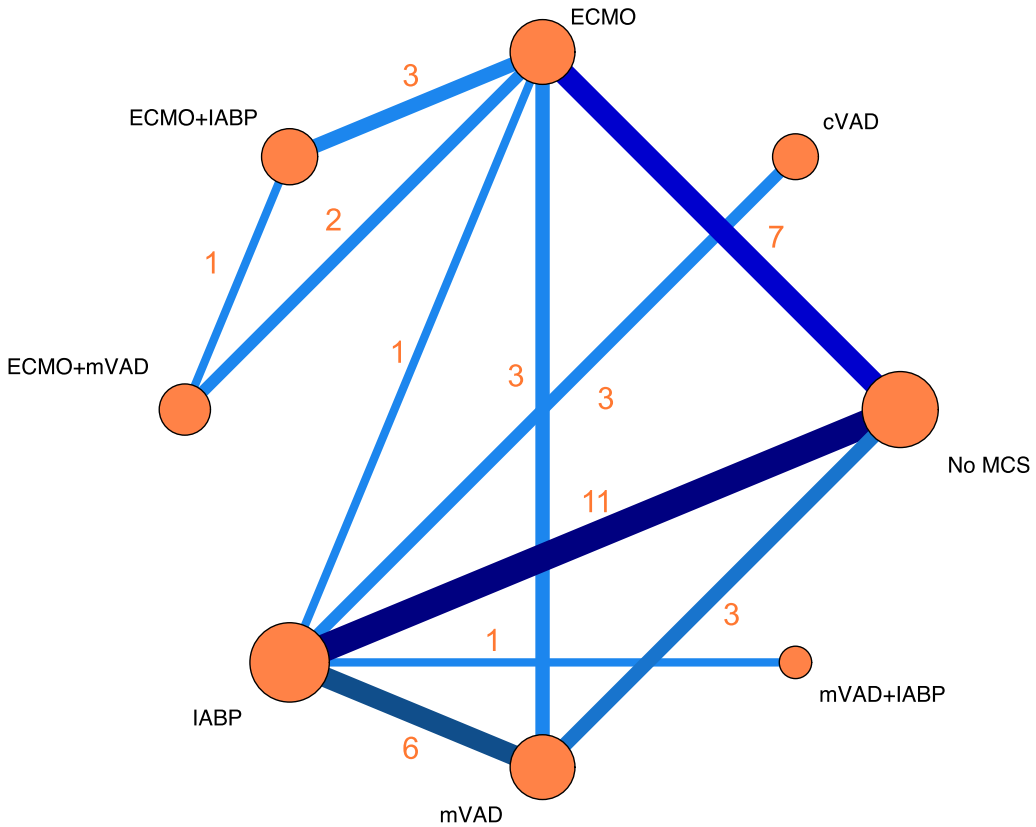

Fig. 2 Network geometry plot for the primary analysis. The size of each node (circle) represents the number of studies reporting on the intervention. The thickness and depth of color of each edge (line) represent the number of studies in each pairwise comparison

random-effects Cox proportional hazards model found that mVAD was associated with increased mortality (HR 1.23, 95% CI 1.05–1.45). Supplemental Tables S10 summarizes the results of the sensitivity analyses, and the estimates from PSMs and RCTs and stratified based on etiology of shock. Supplemental Table S11 presents reconstructed survival curves alongside original Kapla–Meier curves. Finally, trial sequential analysis found that the required information size was not reached for all pairwise meta-analyses between two modalities, aside from ECMO-IABP vs ECMO, and IABP vs mVAD (see supplemental Table S12 for details).

Secondary outcomes

Twenty included studies (8646 patients) reported on bleeding. Compared to no MCS, ECMO, mVAD, ECMO-mVAD, and mVAD-IABP were associated with bleeding (low certainty), while it is uncertain if IABP or cVAD are associated with bleeding (very low certainty). It is also uncertain if ECMO-IABP is associated with less bleeding (very low certainty). From 18 studies (3705 patients), ECMO and ECMO-mVAD may be associated with limb ischemia (low certainty), while it is uncertain if mVAD, cVAD, ECMO-IABP, and mVAD-IABP were associated with limb ischemia (very low certainty) compared to no MCS. It is also uncertain if IABP is associated with less ischemia (very low certainty). Seventeen studies (22,424 patients) reported on acute kidney injury (AKI). Compared to no MCS, there is an unclear association between cVAD, IABP, mVAD, ECMO-IABP, ECMO-mVAD, and ECMO with AKI (very low certainty). Seven studies (1632 patients) reported on hemolysis. It is unclear if any MCS device is associated with hemolysis compared to no MCS. Supplemental Table S12 summarizes the network geometry and forest plots for secondary outcomes, and other secondary outcomes of stroke and hospital-acquired infections.

Discussion

This network meta-analysis found ECMO-IABP was associated with reduced mortality compared with no MCS in patients with SCAI cardiogenic shock stage C to E with moderate certainty. It was superior to ECMO alone, suggesting the need for a ventricular unloading

Table 2 Summary of findings table

Intervention*	Odds ratio		Risk difference		Number needed to treat***	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
cVAD	0.9	0.34–2.39	− 1.2%	− 25.8 to 23.5%	NNTB 87	NNTH 4.3 to ∞ to NNTB 3.9
ECMO	0.99	0.75–1.3	− 0.3%	− 6.2% to 5.5%	NNTB 294.1	NNTH 18.1 to ∞ to NNTB 16.1
ECMO-IABP**	0.54	0.33–0.86	− 12.4%	− 2.1 to − 22.6%	NNTB 8.1	NNTB 4.4 to NNTB 47.2
ECMO-mVAD	0.61	0.34–1.1	− 10.4%	− 23.9 to 3.1%	NNTB 9.6	NNTH 32.1 to ∞ to NNTB 4.2
IABP	1.01	0.8–1.29	0.2%	− 4.8 to 5.3%	NNTH 416.7	NNTH 20.7 to ∞ to NNTB 18.8
mVAD	0.97	0.7–1.34	− 0.1%	− 7.1 to 7%	NNTH 1026.1	NNTH 14.1 to ∞ to NNTB 14
mVAD + IABP	4.52	0.17–120.26	18.8%	− 20.8 to 58.5%	NNTH 5.3	NNTH 1.7 to ∞ to NNTB 4.8

Pooled estimates in odds ratio, risk difference, and numbers needed to treat for included interventions

cVAD centrifugal ventricular assist device, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *mVAD* microaxial ventricular assist device

* Comparisons made with no MCS

** Significant findings have been highlighted in bold

*** We adopted Altman's NNT scale where the number needed to treat is expressed as a number needed to treat (Benefit, or NNTB) or NNT (harm, or NNTH). As there are risk differences which cross the null effect, the number needed to treat approaches infinity. As such, the 95% CI is expressed in three parts: first, the reciprocal of the lower confidence interval, infinity if the absolute risk difference crosses the effect, and the reciprocal of the upper confidence interval. More details can be found in [63]

device when using ECMO. Other devices and combinations of devices did not demonstrate important effects on mortality compared with no MCS. MCS devices were associated with increased bleeding, limb ischemia and AKI when compared with no MCS, though based on low or very low certainty.

While important in refractory cardiogenic shock, it is unclear which MCS device provides survival benefits due to fairly consistent survival rates [10, 67, 68]. Landmark RCTs and subsequent pairwise meta-analyses suggest no differences in survival between several MCS devices with no MCS [32, 69–73]. Prior network meta-analyses including unadjusted observational data report equivocal results: one found no differences across all interventions [37], while another found benefits using ECMO, ECMO-mVAD and ECMO-IABP [5]. Our study of only RCTs or PSMs found significant benefits in ECMO-IABP, and ECMO-unloading compared to no MCS. By restricting the analysis to RCTs and PSMs, our study reduced the effect of some potential confounders from unadjusted observational studies in prior network meta-analyses, giving more confidence to our estimates. The inclusion of newer studies allowed more updated and comprehensive analyses. Though no important differences with other interventions were found, this is limited by severe imprecision that does not necessarily rule out important effects. This may be attributed to several factors, including study design, shock etiology and severity, patient phenotype, institutional practices, and center volume. We accordingly lowered the certainty regarding these estimates.

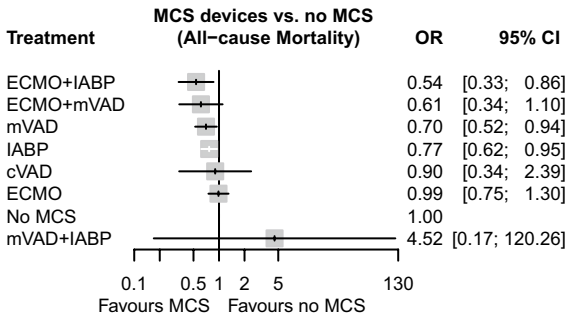

Fig. 3 Network forest plot demonstrating network estimates for all outcomes. While the IABP and mVAD estimates demonstrate significance here, we derived the final estimates from direct and indirect estimates, respectively, for those outcomes, based on our supplemental Methods

Important findings of this study were the survival benefit from ECMO-IABP compared to no MCS, and that ECMO-IABP was superior to ECMO alone; ECMO-mVAD was not significantly beneficial compared to ECMO or no MCS. Concordant with four consecutive RCTs that sequentially revealed no statistically significant benefits in ECMO alone, we also found no benefit of ECMO alone in cardiogenic shock compared with no

MCS [35, 36, 74, 75]. This may be related to numerous factors influencing ECMO success [76, 77] including possible consequences of increased afterload (particularly in peripheral VA-ECMO in these studies) [78], which could be inherent to ECMO in such settings. Such findings were further reflected in a recent individual participant data meta-analysis of RCTs on ECMO in cardiogenic shock [79]. Therefore, until clinicians can better optimize the use of ECMO in cardiogenic shock, our results suggest and that it may be preferable to use concurrent unloading devices to improve mortality [80]. Only 7% of patients receiving ECMO from the 4 RCTs had concurrent unloading devices, which might have contextually impacted its benefit [81]. Our study has built upon these points using the highest-quality available evidence for ECMO with unloading strategies, and was able to not only determine that ECMO-IABP could significantly improve outcomes compared to ECMO alone with a moderate GRADE certainty, but also provide an overall perspective on the potential relative efficacies of each MCS device based on the available evidence. The non-significant findings of ECMO-mVAD against ECMO may be due to smaller sample sizes and imprecision, and stronger associations with complications for ECMO-mVAD usage against ECMO-IABP usage, or even when using mVAD alone against IABP alone [82–85]. Additionally, although our TSA analysis determined a sufficient effect and information size was achieved to determine a clearer clinical benefit in ECMO-IABP usage against ECMO alone, information from these two analyses were also largely derived from PSMs, thus certainty in these conclusions (while more certain than before), remains low. Such results are hypothesis generating and further data from RCTs are necessary. Currently, two RCTs investigating ECMO-unloading (NCT04184635 ANCHOR investigating ECMO-IABP, and NCT05577195 UNLOADECMO investigating ECMO-mVAD) are underway. Results of these trials will inform future clinical management of patients receiving ECMO for cardiogenic shock. In the IPD meta-analysis, we found that mVAD was associated with mortality. This was inconsistent with our direct, indirect, and network estimates, since not all studies reported a survival curve for individual participant data reconstruction. This result should be cautiously interpreted in the context of the overall meta-analysis.

Consistent with prior literature [86], we found that MCS devices (particularly when combined, especially ECMO-mVAD) were associated with complications compared to no MCS, which can be associated with higher mortality rates and nullified survival benefits [87–89]. Thus, combining MCS devices may potentially improve mortality only in centers with sufficient experience and case volumes based on robust inclusion criteria [90]. Yet, this is only in the context of studies included in our meta-analysis. Hence, it is not simply that certain MCS devices failed to produce benefits, but rather that MCS devices—as used in those studies—failed to provide benefits. Therefore, we cannot exclude the possibility that these devices may confer survival benefits outside the context of these studies. Beyond instituting MCS devices alone, computational fluid dynamics studies have shown that ECMO flows that counter native cardiac output may result in vortices and consequentially, complications [91]. Newer pulsatile ECMO devices which synchronize with the cardiac cycle are currently under development [92, 93]. Paradigm shifts in MCS device designs, including miniaturization and other engineering strategies may reduce complications and encourage administration of combination therapy [92, 94–96].

This study has several strengths. The meta-analysis is based on a pre-registered protocol, robust librarian-verified search strategy, and strict eligibility criteria. We used the GRADE approach, a robust and holistic tool to assess the certainty in our effect estimates. The large number of included studies increased precision and including only RCTs and PSM studies aided in consistency and better fulfilling the transitivity assumption compared to prior studies. Second, by combining direct and indirect evidence, we estimated the effect between two interventions which was not otherwise directly observed. Finally, we did a sensitivity analysis reconstructing individual participant data from published survival curves, which has not been done in previous meta-analyses on this topic. This also allowed us to pool HRs and help confirm the survival benefit that each MCS strategy provides.

There are limitations to the analysis. First, though effect estimates derived from PSM studies have been shown to be approximately similar to RCTs, residual confounding, such as a possible volume-outcome relationship, cannot be excluded [97–99], particularly in the context of important statistical heterogeneity. Second, there was also clinical heterogeneity (including possible volume–outcome relationship) including variable inclusion criteria and possibly severities of disease. It is possible smaller centers report more complications and deaths with MCS devices, negating potential benefits reported by more experienced centers. This is particularly in studies using administrative data, where data on disease severity, center volume, and demographics may not be as granular. Nevertheless, we only included studies with patients with SCAI shock stage C to E. Given that we were limited by study-level data, we could not conduct sensitivity analyses investigating the efficacy of MCS devices based on individual SCAI stages. In addition, we could not assess a time effect or the optimal timing of MCS device initiation. With a larger number of PSM studies and the significant heterogeneity,

we accordingly lowered the certainty of estimates to 'low' or 'very low' certainty. While we were able to place higher certainty on our key findings comparing ECMO-IABP with ECMO and no MCS, this was nonetheless a significant limitation for most of our findings. As such, until further information from RCTs are available, these results should be interpreted with caution. Third, current software does not allow subgroup network meta-analysis. While we explored for interaction effects between PSM studies and RCTs, we could not quantitatively assess or adjust for confounders, such as institutional practices, disease phenotypes, and center volume. Furthermore, there are comparatively fewer studies in certain treatment arms. As such, the lack of important effects may reflect imprecision, rather than actual lack of differences. Fourth, we were unable to differentiate between mVAD devices (Impella 2.5, 3.5, 5.0, 5.5) in our analysis, which would more clearly delineate the benefits or risks of each device. Fifth, while we were able to demonstrate an improvement in ECMO-IABP against ECMO, there is a paucity of studies reporting on the hemodynamics of ECMO in conjunction with unloading therapies to highlight the physiological mechanisms which may underlie this benefit. Finally, it was also unclear in most studies whether combination therapy (such as ECMO-IABP or ECMO-mVAD) was administered simultaneously on initiation, or sequentially after initial failure of one device, which can be associated with outcomes [100].

In conclusion, we conducted a network meta-analysis of 48,749 cardiogenic shock patients that assessed various modalities of MCS, compared against each other and against no MCS. Based on moderate certainty, we found that ECMO-IABP and ECMO-unloading may be associated with lower mortality rates when compared to ECMO as a standalone therapy.

Supplementary Information
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Author contributions
Study design: RRL, CJWL, KR. Search strategy and screening of articles: CJWL, RRL, MPXLL, NSHL, MT, KR. Risk of bias assessment: CJWL, RRL, MPXLL, NSHL, MT, KR. Data collection: CJWL, RRL, MPXLL, NSHL, MT, KR. Data analysis and interpretation: CJWL, RRL, CST, BR, KR. Tables and figures: CJWL, RRL, MPXLL, NSHL, MT. Drafting of manuscript: CJWL, RRL. Critical revision of manuscript for important intellectual content: CJWL, RRL, MPXLL, NSHL, MT, SLL, BR, AC, KS, GM, KR. All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft. CJWL, RRL, MPXLL, NSHL, MT, KR have accessed and verified the data. CJWL, RRL, and KR were responsible for the decision to submit the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in the published studies and their supplementary information files.

Declarations

Conflicts of interest
RRL receives research support from the Clinician Scientist Development Unit, Yong Loo Lin School of Medicine, National University of Singapore. SLL receives support from the National Medical Research Council Transitional Award (MOH-001146) and National University Health System Clinician Scientist Program; she has received research grants from Zoll Foundation, National University Health System, National Kidney Foundation of Singapore and Singapore Heart Foundation. AC receives personal fees from Getinge, Xenios, and Baxter International Inc. He serves on the Executive Committee and Scientific Committee of ECMONet, and is Past-President of the European Extracorporeal Life Support Organization (EuroELSO). DB receives research support from and consults for LivaNova. He has been on the medical advisory boards for Abiomed, Xenios, Medtronic, Inspira and Cellenkos. He is the President-elect of ELSO and the Chair of the Executive Committee of the International ECMO Network (ECMONet), and he writes for UpToDate. KS serves on the Scientific Committee and Network Committee of ECMONet. He reports receiving lecture honoraria outside of the submitted work from Getinge and Abiomed. GM is the President of ELSO. KR is part of the steering committee of ELSO, and serves as the chair of its Publication Committee. He is the past co-chair of the Scientific Oversight Committee. . He has received honoraria from Xenios for educational lectures on ECMO. All other authors declare no competing interests.

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