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SYSTEMATIC REVIEW

Early left ventricular unloading during extracorporeal membrane oxygenation in cardiogenic shock: A systematic review and meta-analysis

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Abstract

Background: Left ventricular (LV) unloading is a crucial intervention to decrease the harmful consequences of extracorporeal membrane oxygenation (ECMO) on hemodynamic status in cardiogenic shock (CS) patients. However, a lingering question preoccupies experts: Should we intervene early or wait until clinical deterioration caused by increasing afterload is detected?

Methods: A systematic review and meta-analysis synthesizing studies, which were retrieved by systematically searching PubMed, Web of Science, SCOPUS, and Cochrane through December 2023. We used R V. 4.3 to pool dichotomous data using risk ratio (RR) and continuous data using mean difference (MD) with a 95% confidence interval (CI). PROSPERO ID: CRD42024501643.

Results: Eight studies with 2.117 patients were included. Early/prophylactic LV unloading was associated with a lower incidence of all-cause mortality [RR: 0.87 with 95% CI (0.79, 0.95), $p < 0.01$]. However, there was no significant difference between the two groups regarding cardiac mortality [RR: 1.01 with 95% CI (0.68, 1.48), $p = 0.98$], non-cardiac mortality [RR: 0.86 with 95% CI (0.46, 1.62), $p = 0.64$], and in-hospital mortality [RR: 0.95 with 95% CI (0.86, 1.05), $p = 0.30$]. There was no significant difference between the two groups regarding ECMO weaning, myocardial recovery, ECMO duration, and length of hospitalization.

Conclusion: Early/prophylactic LV unloading during ECMO for CS patients was associated with a decreased incidence of all-cause mortality and sepsis or infection, with no effect on ECMO weaning, myocardial recovery, ECMO duration, and hospital length of stay.

KEYWORDS

clinical trial, ECMO, LV unloading, meta-analysis, review, shock

1 | INTRODUCTION

Despite its advancement in treatment, cardiogenic shock (CS) remains a high mortality condition with a dismal prognosis regardless of its etiology and advancements in treatment.[1] Nonetheless, non-invasive treatments have exhibited shortcomings.[2] Hence, there has been a demand for more sophisticated, sometimes invasive approaches to support perfusion mechanically. Veno-arterial extracorporeal membrane oxygenation (V-AECMO) has been implemented in the medical field since 1977.[3] It possesses the ability to preserve hemodynamic stability and support organ perfusion, which makes it an excellent choice to bridge cardiogenic shock patients to more advanced treatment.[4,5]

The efficacy of V-AECMO in the management of CS caused by multiple etiologies has been described in multiple reports.[4–9] Despite the advantages of reducing preload, improving organ perfusion, and increasing in-hospital survival rate,[4] many shortcomings still limit its favorability, with an increase in afterload being one of the drawbacks. Poor clinical outcomes are linked to left ventricular (LV) overload, resulting in LV distension, blood stagnation, aortic valve closure, intracardiac thrombi, and pulmonary congestion. Each of these factors undermines the process of myocardial recovery.[10,11]

LV Unloading is a crucial part of decreasing the harmful consequences on hemodynamic status in CS. It has been reported to decrease mortality and improve outcomes in CS,[12,13] which can be achieved by various approaches that demonstrate efficacy. Despite the benefits of V-AECMO and LV unloading strategies, several complications associated with these strategies undermine the clinical outcomes, including severe bleeding, access-site-related ischemia, abdominal compartment syndrome, and the need for renal replacement therapy.[12] Also, the optimal approach remains a subject of debate.[14,15]

Increasing afterload in V-AECMO has been considered a main drawback that limits the benefits of this intervention, especially since it is used in already high-risk patients who may have multiple devastating comorbidities.[16] Subsequent overstretching can lead to programmed myocyte cell death, and mechanical loading can reduce cell shortening and alter the response of myocytes to the observed acidosis.[17,18] However, various modalities have been introduced to overcome this limitation.[15,19,20] Theoretically, LV unloading may enhance cardiac contractility and improve outcomes.[21–23] Nevertheless, a lingering question preoccupies experts: does timing matter? Should we intervene early or wait until clinical deterioration caused by increasing afterload is detected?[24]

Therefore, our primary goal is to explore and systematically review the timing aspect of the LV unloading strategy by comparing early/prophylactic versus delayed/reactive LV unloading on clinical outcomes in CS patients undergoing V-AECMO. We aim to contribute to the existing knowledge on this topic and provide valuable insights into the optimal timing.

2 | METHODOLOGY

2.1 | Protocol registration

When reporting this systematic review and meta-analysis, we followed the preferred reporting items of systematic reviews and meta-analysis (PRISMA) statement guidelines (Table S1).[25] Also, this work was conducted in adherence to the Cochrane Handbook of Systematic Reviews of Interventions.[26] The protocol for this meta-analysis has been registered and published in PROSPERO with the following ID: CRD42024501643.

2.2 | Data sources and search strategy

We searched PubMed, Cochrane, Scopus, and Web of Science for relevant studies from inception until December 21, 2023. For a sensitive strategy, we used MESH keywords, the search strategy used for PubMed: (ECMO OR "Extracorporeal Membrane Oxygenation" OR ECLS OR "Extracorporeal Life Support" OR "Extracorporeal Circulation") AND ("left atrial vent*" OR "left ventricular unload*" OR "LV unload*" OR "left heart decompress*"), then the search strategy was changed according to the specific requirements of each database, as shown in (Table S2). Furthermore, we searched manually by backward citation analysis to identify any relevant articles.

2.3 | Eligibility criteria

Studies satisfying the following inclusion PICO criteria were included in the systematic review:

1. Population: patients who underwent ECMO due to cardiogenic shock from any etiology.
2. Intervention: early/prophylactic LV unloading, regardless of the unloading methods; defined as either using LV unloading before ECMO or within 12 h from ECMO application, regardless of clinical indication.
3. Comparison: delayed/reactive LV unloading, regardless of the unloading methods; defined as either using

LV unloading after ECMO by 12 h or only when a clinical indication is evident.

4. Outcomes: our primary outcome was the mortality rates, including (all-cause mortality, cardiac mortality, non-cardiac mortality, and in-hospital mortality). Secondary outcomes included V-AECMO weaning, myocardial recovery, bridge to left ventricular assist device (LVAD) or heart transplantation, ECMO duration, length of hospital stay, and various complications.
5. Study Design: randomized controlled trials (RCTs) and observational comparative, retrospective, or prospective studies, including cohort and case–control studies.

However, we excluded the following types of articles: (I) studies lacking a comparison group, (II) those containing unreliable, non-extractable, duplicated, or overlapped data sets, (III) articles with unavailable full texts, (IV) conference posters/abstracts, case reports/series, review articles, and protocols of clinical trials with unpublished results, and (VII) animal studies.

2.4 | Study selection

The authors (A.M.A., A.M., S.E., and Y.A.) used Covidence for duplicate detection and deletion. All records were screened blindly by at least two authors in two phases. The first phase was title/abstract screening for potential clinical studies on Covidence. In the second phase, we retrieved the full-text articles of the selected abstract for further eligibility screening using separate Google sheets. A third author resolved any conflict to avoid selection bias, and disagreements were resolved by discussion between the authors.

2.5 | Data extraction

Data were extracted by at least two authors of (A.M.A., A.M., S.E., and Y.A.), using separate Google sheets under three main domains: (I) study characteristics (study design, number of centers, country, database, and recruitment duration, total participants, intervention details, LV unloading method, main inclusion criteria, primary outcome, follow-up duration); (II) baseline characteristics of the included studies' population (number of patients in each group, age, gender, basal metabolic index (BMI), systolic blood pressure (SBP), LV ejection fraction (LVEF), extracorporeal cardiopulmonary resuscitation, comorbidities, and CS etiology); and (III) study outcomes as previously described.

2.6 | Risk of bias assessment

We comprehensively assessed bias in the included studies, utilizing the Cochrane Risk of Bias tool for Randomized Controlled Trials (RCTs) version 2 (ROB2).[27] The Cochrane ROB tool scrutinizes potential bias across seven study domains: (I) random sequence generation, (II) allocation concealment, (III) blinding of investigators and patients, (IV) blinding of outcome assessors, (V) incomplete outcome data, (VI) selective outcome reporting, and (VII) other sources of bias. Within each domain, we categorized each study as "low risk," "high risk," or "unclear" after a meticulous review of the data presented in the published articles by at least two independent authors for each study (A.M.A., A.M., S.E., and Y.A.).

For retrospective cohort studies, we employed the "Risk Of Bias In Non-randomized Studies of Interventions" (ROBINS-I) tool to assess bias risk.[28] The ROBINS-I tool evaluates bias risk across seven domains, yielding an overall classification corresponding to the highest risk level in any domain. At least two independent authors (A.M.A., A.M., S.E., and Y.A.) conducted this assessment for each study, adhering to the criteria outlined in the detailed guidance for ROBINS-I. This process was structured around three domains: pre-intervention bias (arising from confounding or participant selection), at-intervention bias (in the classification of the intervention), and post-intervention bias (due to deviations from intended interventions or missing data in outcome measurement and reporting). Any conflicts or disagreements were resolved through discussion with a third author.

2.7 | Statistical analysis

R version 4.3 was used to carry out statistical analysis using meta, metafor, and dmetar packages. To pool the results of dichotomous outcomes, we used the risk ratio (RR) while, for continuous outcomes, we used the mean difference (MD), both with a 95% confidence interval (CI) using the random-effects model when there was a significant heterogeneity (I^2 >50%) and the common-effect model when heterogeneity was not significant (I^2 <50%). To assess heterogeneity, we used the Chi-square and I-square tests, where the Chi-square test assesses the presence of heterogeneity, and the I-square test assesses its degree. We interpreted the I-square test as follows: not significant for 0–40 percent, moderate heterogeneity for 30–60 percent, and substantial heterogeneity for 50–90 percent, following the Cochrane Handbook (chapter nine).[26] We considered an alpha level below 0.1 for the Chi-square test to denote significant heterogeneity.

We used both influence analysis and the brute force approach to identify the outlier for the sensitivity analysis. Additionally, our study's heterogeneity patterns were assessed using the Baujat plot. The Baujat plot (y-axis) displays each effect size's influence on the pooled result, while the x-axis displays each effect size's total heterogeneity contribution. Studies or effect sizes that have high values on both the x- and y-axes could be regarded as influential cases; studies or effect sizes that have a high contribution to heterogeneity (x-axis) but little effect on the overall results could be regarded as outliers and could be eliminated to reduce the amount of heterogeneity between studies. Finally, we conducted a subgroup analysis based on the study design and the method of LV unloading.

3 | RESULTS

3.1 | Search results and study selection

We retrieved 1084 records from searching the previously mentioned data sources and excluded 598 identical records via the Covidence tool, with 486 records eligible for title and abstract screening. Seventy-six records were entered in full-text screening, and finally, eight studies were included[15,29–35]: (Figure 1).

3.2 | Characteristics of included studies

We included eight studies[15,29–35] with a total of 2117 patients; six studies were retrospective observational studies,[15,30–32,34,35] and two were RCTs.[29,33] Complete summary and baseline characteristics of the included RCTs are outlined in Tables 1 and 2.

3.3 | Risk of bias

ROB 2.0 assessment showed that Park et al.[29] had an overall low risk of bias; however, Kim et al.[33] had overall some concerns due to concerns in the randomization process (Figure 2A). ROBINS-I assessment showed that four studies had overall some concerns due to concerns in the confounding variables; two of them had additional concerns in the selection of the participants, classification of the interventions, and selection of the reported results.

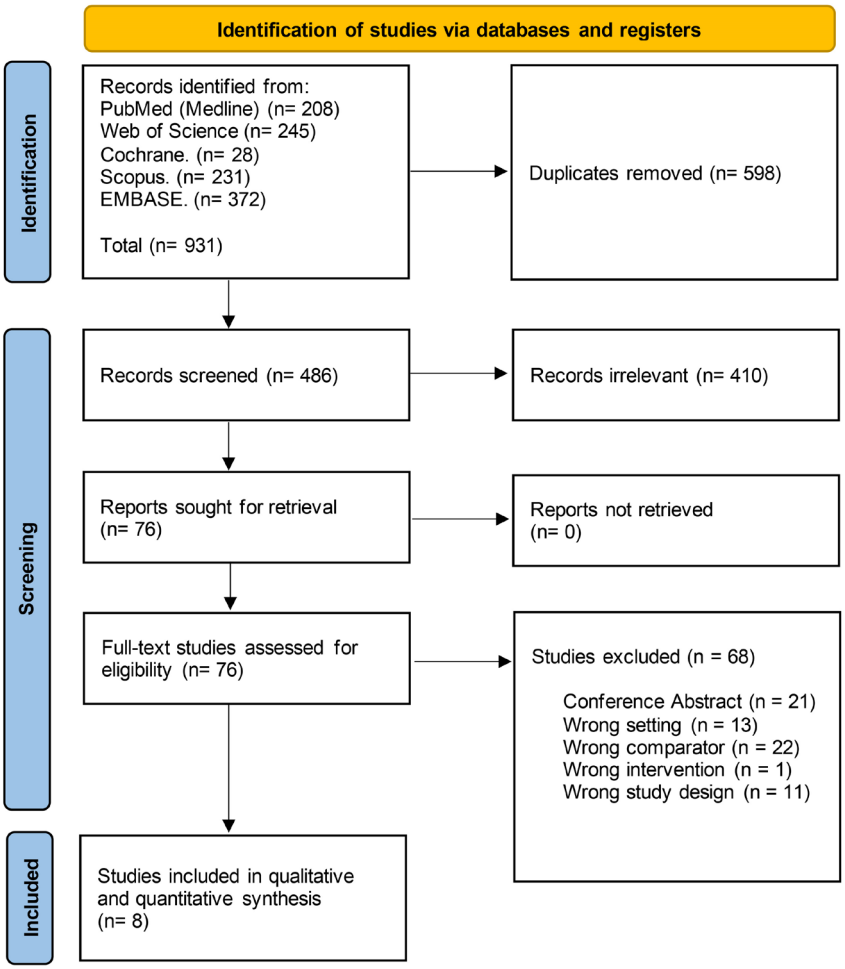

FIGURE 1 PRISMA flow chart of the screening process. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Summary characteristics of the included studies.

Study ID	Study design	Country	Database & recruitment duration	Total participants	Interventions details		LV unloading method	Primary outcome	Follow-up duration
					Early/prophylactic	Late/reactive			
Char et al.[32]	Single-center retrospective study	USA	January 2015 to June 2020	140	LV unloading device added at the time of ECMO insertion or those patients with an LV support device in place before initiation of ECMO	Patients who received a device in response to clinical criteria after ECMO, irrespective of initiation time	IABP or Impella	Survival to discharge.	180-day
Kim et al. (EARLY-UNLOAD)[33]	Single-center, open-label, randomized controlled trial	South Korea	From March 4, 2021, to September 15, 2022.	116	Left ventricular unloading within 12 h after V-AECMO implantation	LV unloading in case of increased left ventricular afterload	Transseptal left atrial cannulation	All-cause mortality	30 days
Grandin et al.[34]	Multi-center retrospective study	463 centers, with the majority located in North America (59.8%) and Europe (17.3%).	The ELSO registry until 2019	999	Prophylactic (LV unloading before or at the time of ECMO cannulation)	LV unloading at any time after ECMO initiation	IABP or pVAD	In-hospital mortality	NA
Jin et al.[30]	Single-center retrospective study	Korea	From January 2013 to December 2016	50	LV unloading performed at ECMO initiation	Reactive (LV unloading performed to treat complications of impaired left ventricle LV unloading, irrespective of the time of initiation)	Transseptal left atrial cannulation	All-cause 30-day mortality	202 [33–737] days.
Park et al. (EVOLVE-ECMO)[29]	Prospective, multicenter, open-label, randomized controlled trial	Republic of Korea	NA	60	LV unloading before or within 12 h of initiating ECMO	LV unloading was performed to treat medically refractory pulmonary edema	Transseptal left atrial cannulation	V-AECMO weaning	NA
Piechura et al.[15]	Single-center retrospective study	USA	Brigham and Women's Hospital records (from September 2015 to January 2019)	63	LV unloading before or at the time of ECMO cannulation	Patients who received a device in response to clinical criteria after ECMO, irrespective of initiation time	IABP or Impella	Survival rate.	30 days
Radakovic et al.[31]	Single-center retrospective study	Germany	A prospective clinical database (from January 2014 to June 2021)	268	LV unloading therapy in selected patients thought to be at a higher risk of developing LV distension	LV unloading is implemented post hoc to treat the consequences of clinically or hemodynamically apparent LV distension	Impella	All-cause 30-day mortality	30 days
Schrage et al.[35]	Multi-center retrospective cohort study	NA	STOP-SHOCK retrospective study (from 2005 to 2019)	421	LV unloading implantation 24 h before until 2 h after V-AECMO implantation	LV unloading implantation >2 h after V-AECMO implantation.	Impella	All-cause 30-day mortality	30 days

Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular; NA, not available; pVAD, percutaneous ventricular assist devices; V-AECMO, veno-arterial extracorporeal membrane oxygenation.

Additionally, two studies had an overall serious risk of bias (Figure 2B).

3.4 | Primary outcomes (mortality)

Early/prophylactic LV unloading was associated with a lower incidence of all-cause mortality [RR: 0.87 with 95% CI (0.79, 0.95), $p < 0.01$]. However, there was no significant difference between the two groups regarding cardiac mortality [RR: 1.01 with 95% CI (0.68, 1.48), $p = 0.98$], non-cardiac mortality [RR: 0.86 with 95% CI (0.46, 1.62), $p = 0.64$], and in-hospital mortality [RR: 0.95 with 95% CI (0.86, 1.05), $p = 0.30$] (Figure 3).

Pooled studies were homogeneous in all-cause mortality ($p = 0.08$, $I^2 = 47\%$), cardiac mortality ($p = 0.69$, $I^2 = 0\%$), non-cardiac mortality ($p = 0.48$, $I^2 = 0\%$), and in-hospital mortality ($p = 0.96$, $I^2 = 0\%$). However, regarding all-cause mortality ($I^2 = 47\%$), sensitivity analysis revealed that this moderate heterogeneity was best resolved after omitting studies by Radakovic et al.,[31] with ($I^2 = 0\%$), (no outliers detected [random-effects model]) (Figures S1 and S2).

Finally, the test of subgroup analysis was insignificant in all-cause mortality either based on study design ($p = 0.36$) or the LV unloading method ($p = 0.79$) (Figures S3 and S4). Also, in-hospital mortality was insignificant, either based on the study design or the LV unloading method ($p = 0.62$) (Figures S5 and S6).

3.5 | Secondary outcomes

3.5.1 | Secondary efficacy outcomes

There was no significant difference between the two groups regarding the incidence of ECMO weaning [RR: 1.06 with 95% CI (0.87, 1.28), $p = 0.59$] (Figure 4A), myocardial recovery [RR: 1.29 with 95% CI (0.00, 405.84), $p = 0.68$] (Figure 4B), bridge to LVAD heart transplantation [RR: 1.20 with 95% CI (0.89, 1.61), $p = 0.24$] (Figure 4C), ECMO duration [MD: 0.68 with 95% CI (−0.39, 1.75), $p = 0.21$] (Figure 4D), and length of hospitalization [MD: −86 with 95% CI (5.49, 3.77), $p = 0.72$] (Figure 4E).

Pooled studies were homogeneous in ECMO weaning ($p = 0.26$, $I^2 = 26\%$), bridge to LVAD or heart transplantation ($p = 0.31$, $I^2 = 16\%$), ECMO duration ($p = 0.67$, $I^2 = 0\%$), length of hospitalization ($p = 0.25$, $I^2 = 26\%$). However, Pooled studies were heterogeneous regarding myocardial recovery ($p < 0.01$, $I^2 = 87\%$); however, the sensitivity analysis was not applicable.

Finally, the test of subgroup analysis was insignificant in bridge to LVAD or heart transplantation either based on study design ($p = 0.89$) or the LV unloading method ($p = 0.36$) (Figures S7 and S8). Also, the test of subgroup analysis was insignificant in ECMO duration either based on study design ($p = 0.57$) or the LV unloading method ($p = 0.76$) (Figures S9 and S10).

3.5.2 | Complications

The early or prophylactic approach was associated with a lower incidence of sepsis or infection [RR: 0.76 with 95% CI (0.63, 0.92), $p < 0.01$]. However, there was no significant difference between the two groups regarding the incidence of ischemic or hemorrhagic stroke [RR: 0.79 with 95% CI (0.42, 1.49), $p = 0.40$], limb ischemia [RR: 0.83 with 95% CI (0.61, 1.12), $p = 0.15$], any bleeding [RR: 0.89 with 95% CI (0.52, 1.50), $p = 0.56$], cannula site bleeding [RR: 0.92 with 95% CI (0.72, 1.18), $p = 0.51$], hemolysis [RR: 0.87 with 95% CI (0.70, 1.08), $p = 0.20$], renal injury or renal replacement therapy [RR: 0.82 with 95% CI (0.46, 1.46), $p = 0.36$], and cardiac tamponade [RR: 3.0 with 95% CI (0.32, 28.30), $p = 0.34$] (Figures 5 and 6).

Pooled studies were homogeneous in limb ischemia ($p = 0.79$, $I^2 = 0\%$), cannula site bleeding ($p = 0.27$, $I^2 = 24\%$), hemolysis ($p = 0.11$, $I^2 = 50\%$), sepsis or infection ($p = 0.27$, $I^2 = 22\%$), and cardiac tamponade ($p = 0.44$, $I^2 = 0\%$). However, pooled studies were heterogeneous regarding ischemic or hemorrhagic stroke ($p = 0.02$, $I^2 = 57\%$), any bleeding ($p = 0.01$, $I^2 = 68\%$), and renal injury or renal replacement therapy ($p = 0.06$, $I^2 = 59\%$). Sensitivity analysis did not justify the heterogeneity in ischemic or hemorrhagic stroke (no outliers detected [random-effect model]) (Figures S11 and S12). However, sensitivity analysis best resolved the heterogeneity in any bleeding by omitting Char et al.[32] ($I^2 = 43\%$) (no outliers detected [random-effect model]) (Figures S13 and S14), and in renal injury or renal replacement therapy after omitting Schrage et al.[35] ($I^2 = 33\%$) (no outliers detected [random-effect model]) (Figures S15 and S16).

Finally, the test of subgroup analysis was insignificant in sepsis or infection based on the LV unloading method ($p = 0.26$) (Figures S17). However, the test of subgroup analysis was significant in ischemic or hemorrhagic stroke either based on study design ($p = 0.03$) or the LV unloading method ($p = 0.04$), with no difference between both groups in either RCTs or observational studies (Figures S18 and S19). Furthermore, the test of subgroup analysis was insignificant in the rest of the subgroups ($p > 0.1$) (Figures S20–S27).

TABLE 2 Baseline characteristics of the included participants.

Study ID	Number of patients in each group		Age (years), mean (SD)		Gender (male), *N* (%)		BMI, mean (SD)		SBP, mean (SD)		LVEF, mean (SD)		Extracorporeal cardiopulmonary resuscitation, *N* (%)	
	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive
Char et al.[32]	92	48	61 (2.5)	62.5 (4.8)	67 (72.9)	31 (64.6)	NA	NA	NA	N/A	NA	NA	9 (9.8)	10 (20.8)
Kim et al. (EARLY-UNLOAD)[33]	58	58	7.8 ± 14.4	67.3 ± 12.8	39 (67.2)	43 (74.1)	23.7 (3.42)	24.1 (1.3)	90 (15)	88.3 (16)	17 (8.36)	16.3 (9.1)	25 (43.1)	28 (48.3)
Grandin et al.[34]	666	333	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Na et al.[30]	18	32	51.3 (17.8)	48.3 (19.3)	13 (72.2)	17 (53.1)	23.3 (4.7)	24.9 (4.3)	NA	NA	19.8 (4.4)	21.7 (10)	NA	NA
Park et al. (EVOLVE-ECMO)[29]	30	30	63.9 (12.8)	60.5 (12.2)	19 (63.3)	20 (66.7)	23.9 (4.4)	23.4 (4.6)	95.8 (25.2)	86.3 (17.2)	25.8 (13.2)	28.3 (13.3)	9 (30.0)	9 (30.0)
Piechura et al.[15]	33	30	60 (11.0)	52 (16.5)	22 (67)	23 (77)	NA	NA	NA	NA	NA	NA	NA	NA
Radakovic et al.[31]	131	137	NA	NA	96 (73.3)	99 (72.8)	NA	NA	NA	NA	NA	NA	70 (56.9)	78 (53.4)
Schrage et al.[35]	310	111	56 (13)	53 (14)	244 (78.8)	80 (72)	NA	NA	NA	NA	NA	NA	123 (40.6)	27 (24.5)

Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction; NA, not available; SBP, systolic blood pressure; SD, standard deviation.

4 | DISCUSSION

Our systematic review and meta-analysis demonstrated that early/prophylactic LV unloading was associated with a lower rate of all-cause mortality and a reduced risk of infection and sepsis compared to delayed/reactive LV unloading. However, no significant difference was observed in in-hospital mortality, ECMO weaning, myocardial recovery, bridge to LVAD or heart transplantation, ECMO duration, hospital length of stay, and other complications.

A previous study by Kowalewski et al.[36] demonstrated the general benefits of LV unloading during V-AECMO, with techniques like Impella, IABP, and pVADs improving survival and ECMO weaning outcomes. While this broad review provides insights into the effectiveness of these unloading strategies, it lacks a focused analysis of the timing of intervention, presenting mixed findings on complications across LV unloading techniques.[36] IABP indirectly reduces afterload, improving systolic ejection, and coronary perfusion. In contrast, the Impella device provides continuous, direct flow venting, more effectively reducing LV volume and pressure, albeit with a higher risk of bleeding and hemolysis. Both techniques in their study demonstrated improved survival rates and higher ECMO weaning success, with Impella potentially offering more effective unloading in select patients.[36]

Our study showed that all-cause mortality was significantly decreased among patients who received early/prophylactic LV unloading. The advantages of mechanical unloading (MU) can be elucidated through various physiological effects, including the enhancement of coronary blood flow, the mitigation of LV pressures, volumes, and wall stress, as well as the enhancement of right ventricular performance.[37–39] This finding is in line with previous meta-analyses.[22,38] However, both cohorts in our pooled studies showed no significant differences in cardiac, non-cardiac, and in-hospital mortality, with limited data, which may encourage more research to address the causes. It is also important to highlight that there were no significant differences observed in our analysis in terms of cardiac, non-cardiac, or in-hospital mortality. This outcome could potentially be explained by the risk of fluid overload and the associated mortality that may arise from it.[40] Additionally, it is worth noting that patients undergoing V-AECMO for CS as the primary etiology could be profoundly ill and more susceptible to complications such as brain death, which might also influence mortality rates.[41]

In patients diagnosed with CS, V-AECMO is commonly employed as a hemodynamic stabilization technique,

Comorbidities *N* (%)																	
AF		HTN		CAD		Dyslipidemia		DM		COPD		CKD		Smoking		Stroke/TIA	
Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive	Early/prophylactic	Late/reactive
NA	NA	64 (69.6)	26 (54.2)	55 (59.8)	20 (41.7)	49 (53.3)	23 (47.9)	36 (39.1)	17 (35.4)	7 (7.6)	5 (10.4)	28 (30.4)	5 (10.4)	NA	NA	10 (10.9)	6 (12.5)
7 (12.1)	8 (13.8)	33 (56.9)	32 (55.2)	NA	NA	NA	NA	24 (41.4)	26 (44.8)	NA	NA	13 (22.4)	8 (13.8)	18 (31.0)	22 (37.9)	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		4 (22.2)	7 (21.9)	3 (16.7)	5 (15.6)	1 (5.6)	3 (9.4)	5 (27.8)	5 (15.6)	NA	NA	0 (0.0)	1 (3.1)	8 (44.4)	9 (28.1)	NA	NA
11 (36.7)	7 (23.3)	8 (26.7)	7 (23.3)	13 (43.3)	13 (43.3)	NA	NA	13 (43.3)	8 (26.7)	NA	NA	7 (23.3)	4 (13.3)	NA	NA	2 (6.7)	8 (26.7)
NA	NA	17 (52)	17 (57)	17 (52)	12 (40)	13 (39)	13 (43)	8 (24)	7 (23)	NA	NA	4 (12)	6 (20)	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	35 (26.7)	34 (24.8)	NA	NA	17 (13.0)	18 (13.1)	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

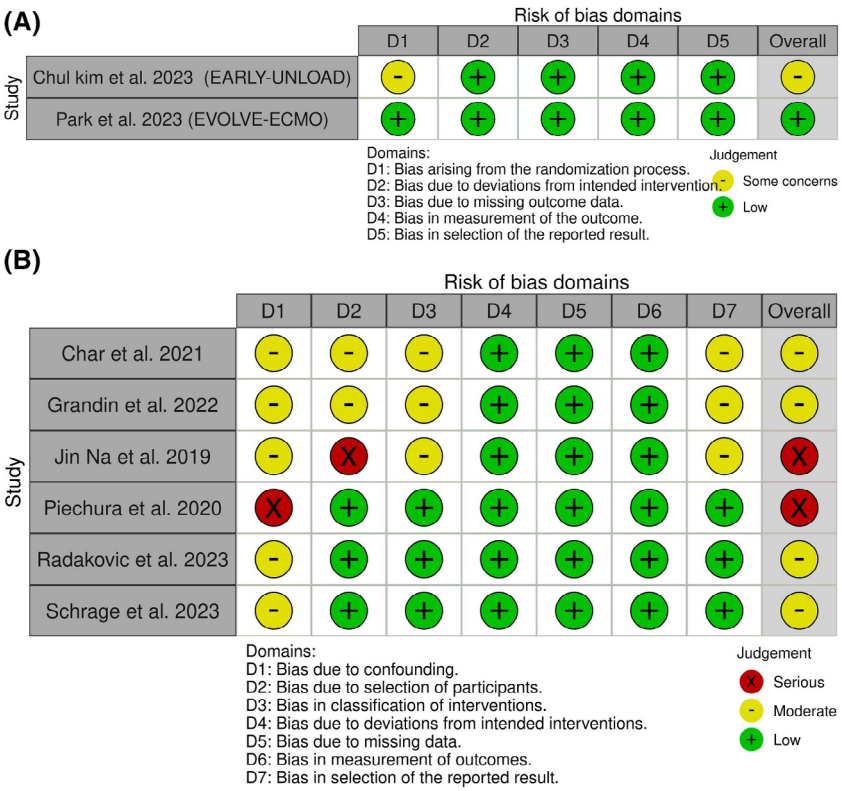

FIGURE 2 Quality assessment of risk of bias in the included studies. (A) ROB-2 assessment of randomized controlled trials. (B) ROBINS-I assessment of observational studies. [Color figure can be viewed at wileyonlinelibrary.com]

serving as a bridge to advanced treatment such as heart transplantation.[15,29,32] Recent RCTs failed to identify significant differences between the two approaches in terms of hospitalization duration, ECMO duration, ECMO weaning, and bridge to LVAD heart transplant,[29,33] which is in line with our findings. However, a retrospective study conducted

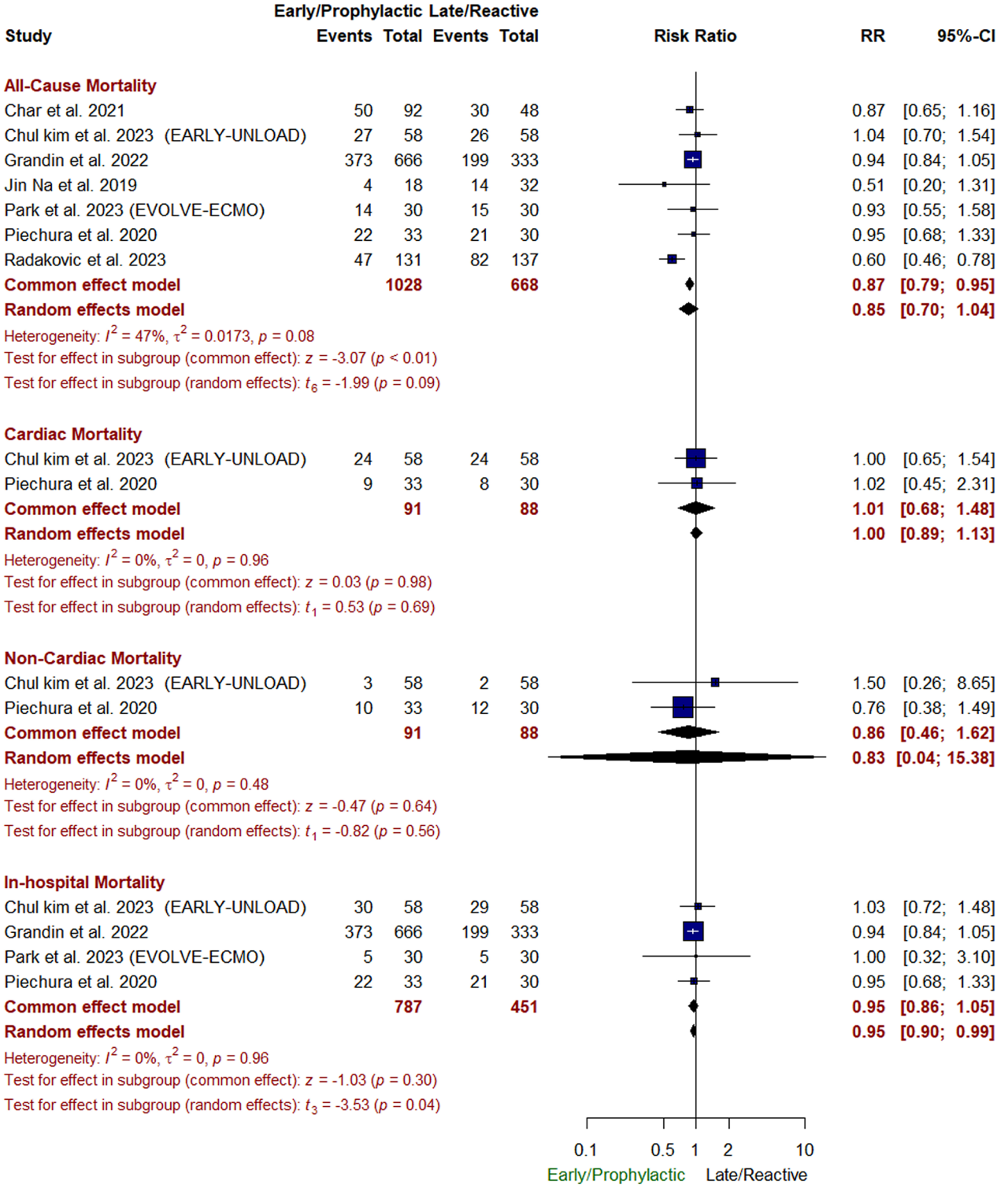

FIGURE 3 Forest plot of the primary efficacy outcome (mortality). CI, confidence interval; RR, risk ratio. [Color figure can be viewed at wileyonlinelibrary.com]

by Jin et al. showed a higher rate of successful bridging to heart transplantation in the prophylactic group.[30] It is crucial to interpret this finding cautiously, considering the limitation of a retrospective study, which may be susceptible to selection bias and reported result bias. However, our analysis showed that ECMO weaning, bridge to heart transplantation, ECMO duration, and length of hospitalization were comparable between these two approaches. Further research is warranted to validate these findings and provide a more comprehensive understanding.

Despite its life-saving potential, V-AECMO is linked to several complications: neurological issues, such as

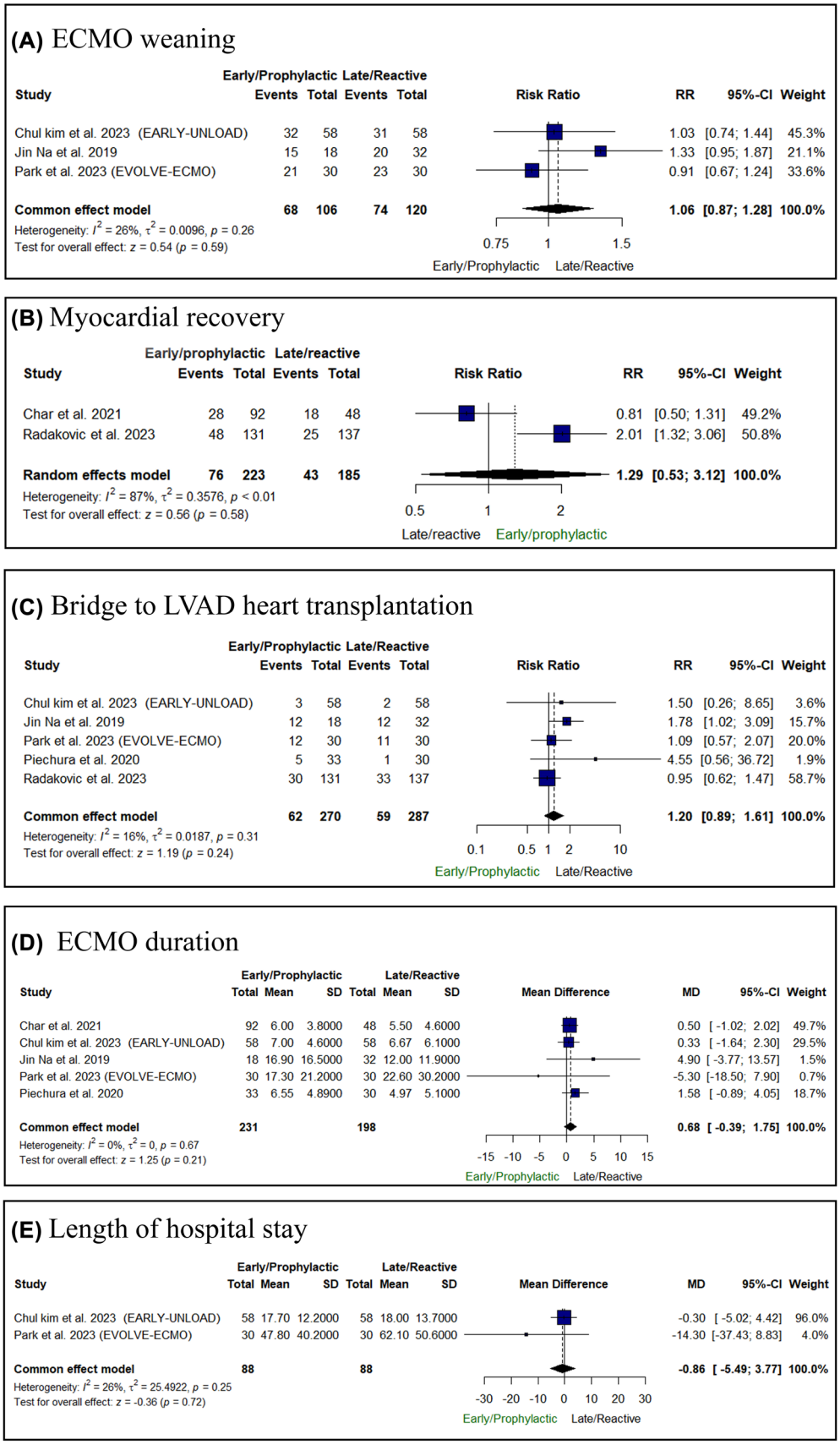

FIGURE 4 Forest plot of the secondary efficacy outcomes, RR: risk ratio; MD: mean difference; CI: Confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

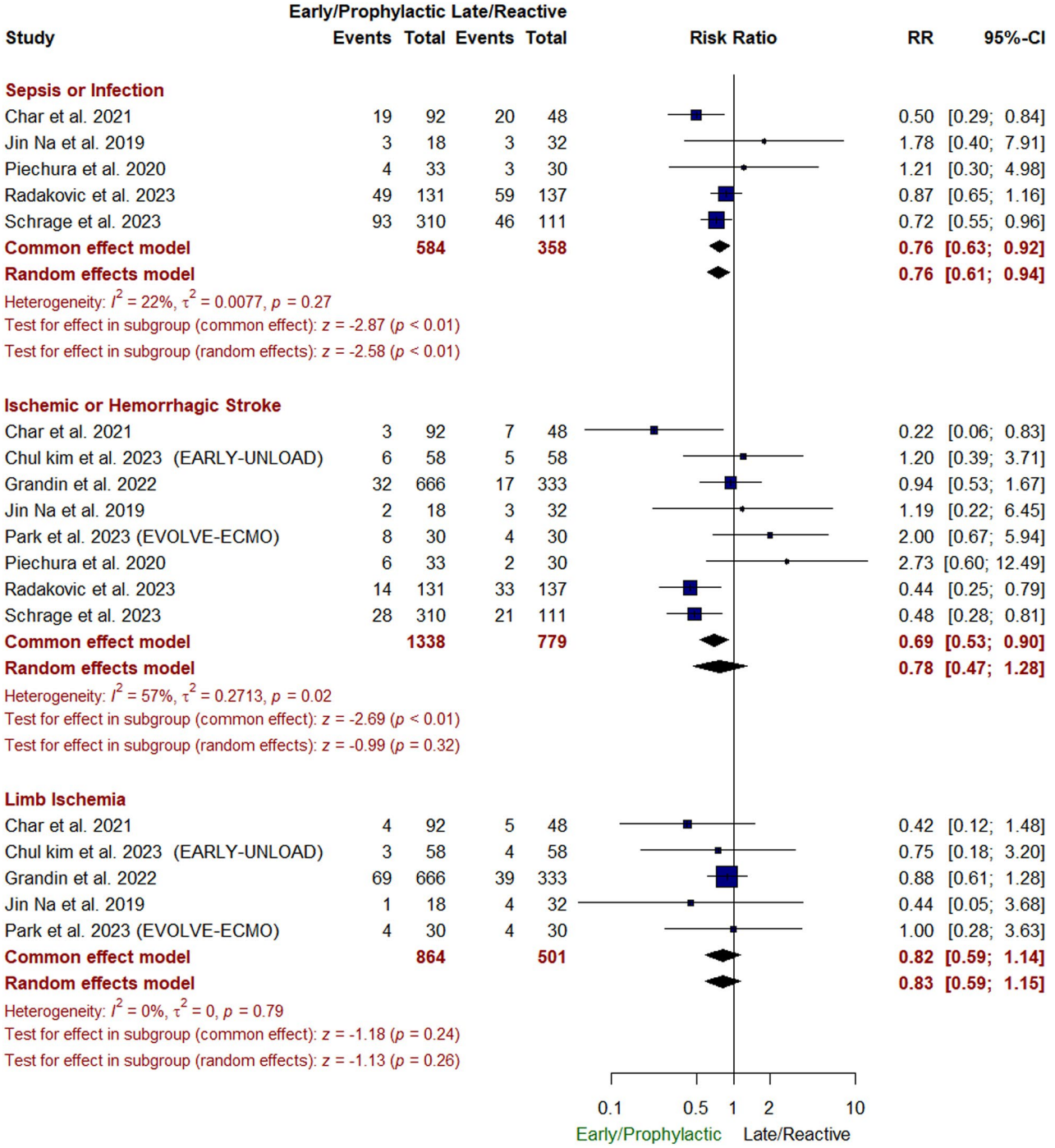

FIGURE 5 Forest plot of the complications (A). CI, confidence interval; RR, risk ratio. [Color figure can be viewed at wileyonlinelibrary.com]

intracranial bleeding, brain death, and ischemic strokes, are frequent and often result in high mortality rates,[42] and vascular complications, including acute limb ischemia and major hemorrhage, are also common, especially in patients with peripheral arterial disease and ischemic cardiopathy. Therefore, the decision to implement an LV unloading device might sound like an escalation for the already critically ill patients. Russo et al. demonstrated that LV unloading was not associated with an increased rate of complications except for the hemolysis rate, which can be explained by the higher number of patients who received intra-aortic balloon pump (IABP) as an unloading strategy in their study.[43] However, they did not investigate the timing factor and whether the complication rate could differ if unloading was employed early compared to the bail-out strategy. This aligns with our analysis; in fact, sepsis and infection rates decreased among early cohorts, which may be explained by the reactive venting of the left heart, likely performed after clinical deterioration, increasing the susceptibility to infection.[32]

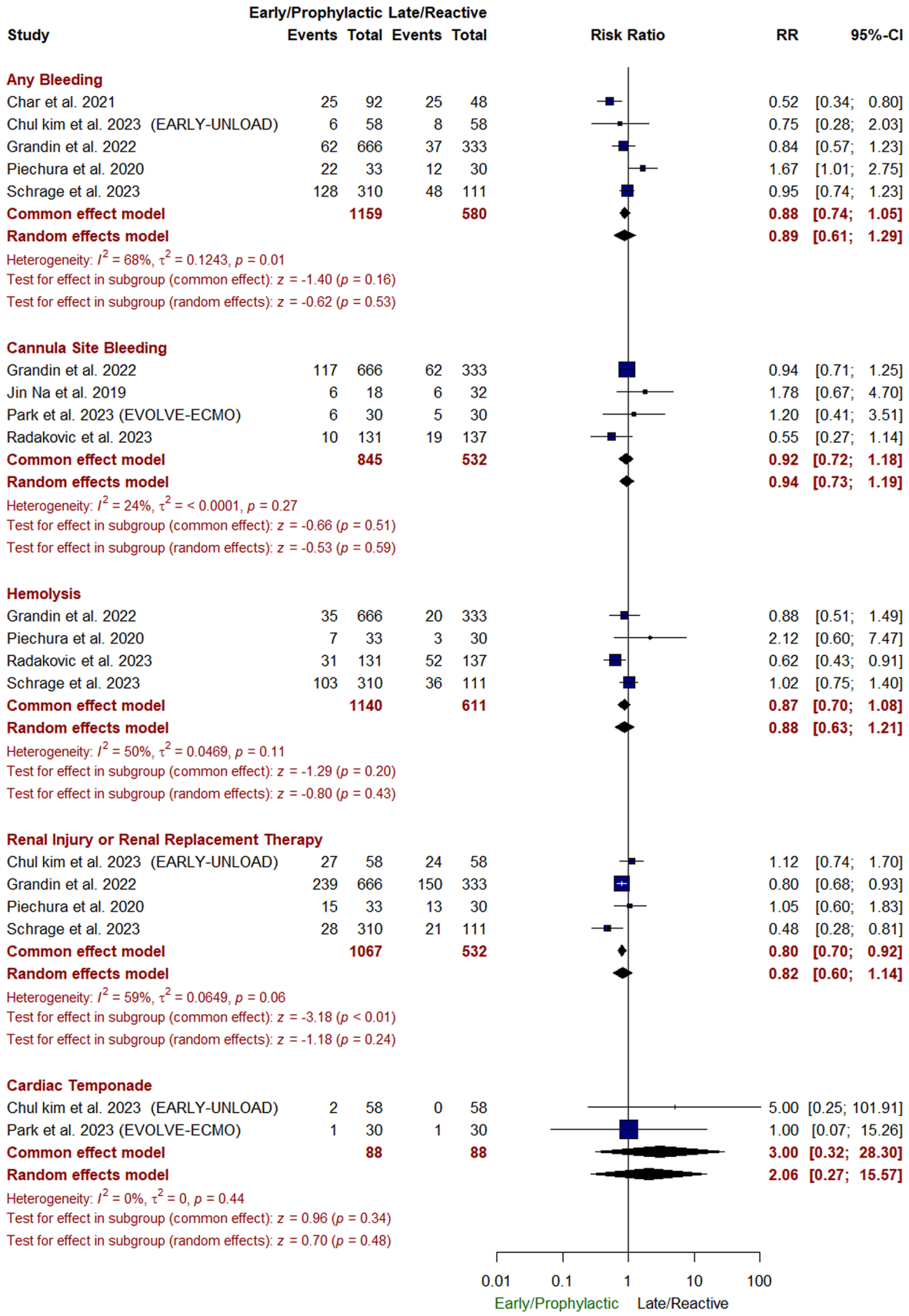

FIGURE 6 Forest plot of the complications (B). CI, confidence interval; RR, risk ratio. [Color figure can be viewed at wileyonlinelibrary.com]

5 | STRENGTHS AND LIMITATIONS

To the extent of our knowledge, this is the first systematic review and meta-analysis to synthesize the available evidence on early/prophylactic versus delayed/reactive LV unloading in patients with CS undergoing V-AECMO, constituting the gold-standard evidence in this regard. However, our analysis is limited by a few limitations: first, due to the clinical and delicate feature of the studied objective, six of eight included studies were retrospective studies,[15,30–32,34,35] which increases the risk of selection and reported data biases. Second, cutoff points for the timing were not the same between the studies, so we considered studies applying LV unloading either before V-AECMO or within 12 h from initiation as early/prophylactic group and studies applying LV unloading either only when a clinical indication is warranted or after 12 h as delayed/reactive group. Therefore, some patients may be overlapping between the studied interventions. Third, some outcomes have a moderate rate of heterogeneity. Fourth, we did not investigate the effect of various LV unloading methods, which may have an impact on the outcomes and the complication rate due to the lack of data for each LV unloading method. Finally, most of the included studies had a short-term follow-up of only 30 days, so we could not assess longer term outcomes.

6 | IMPLICATIONS FOR CLINICAL PRACTICE

The implementation of the LV unloading strategy should be case-based, as no current guidelines are available. Several key factors should be considered before making the decision. For instance, evaluating the arterial waveform and pulmonary artery and considering the diastolic pressures can be helpful in determining which patients can benefit from the early approach. Nevertheless, further assessment of the impact of an active LV unloading strategy is necessary, as different devices may yield varying outcomes.[32,44]

7 | IMPLICATIONS FOR FUTURE RESEARCH

Most of the published studies are retrospective observational studies; thus, more RCTs are needed to establish guidelines for the cutoff points of timing and the best technique used for unloading. Two current RCTs are now ongoing that may help shed light on this subject: REMAP ECMO (NCT05913622) and UNLOAD-ECMO (NCT05577195). The REMAP ECMO trial investigates the efficacy of early unloading on weaning success, while the UNLOAD-ECMO trial examines the impact of early unloading on mortality. However, additional RCTs are essential to explore the optimal timing, establish cutoff points, and demonstrate the relationship between mortality and early unloading.

8 | CONCLUSION

Early/prophylactic LV unloading during V-AECMO for CS patients was associated with a decreased incidence of all-cause mortality and sepsis or infection, with no effect on ECMO weaning, myocardial recovery, ECMO duration, and hospital length of stay. However, our pooled analysis heavily depends on retrospective observational data with a high risk of bias.

AUTHOR CONTRIBUTIONS

M.A. conceived the idea. B.A. and M.A. designed the research workflow. B.A. and M.A. searched the databases. A.M.A., A.M., S.E., and Y.A. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and M.A. resolved the conflicts. A.A.I. performed the analysis. A.N., M.A., Y.A., A.M.A., S.E., and A.M. wrote the final manuscript. M.T. and B.A. supervised the project. All authors have read and agreed to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request from the corresponding author.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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SUPPORTING INFORMATION

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

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