

Venoarterial Extracorporeal Membrane Oxygenation as Mechanical Circulatory Support in Adult Septic Shock: A Systematic Review and Meta-Analysis with Individual Participant Data Meta-Regression Analysis.

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Abstract

Background: While recommended by international societal guidelines in the paediatric population, the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as mechanical circulatory support for refractory septic shock in adults is controversial. We aimed to characterise the outcomes of adults with septic shock requiring VA-ECMO, and identify factors associated with survival.

Methods: We searched Pubmed, Embase, Scopus and Cochrane databases from inception until 1st April 2021, and included all relevant publications reporting on >5 adult patients requiring VA-ECMO for septic shock. Study quality and certainty in evidence were assessed using the appropriate Joanna Briggs Institute checklist, and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach respectively. The primary outcome was survival to hospital discharge, and secondary outcomes included intensive care unit length of stay, duration of ECMO support, complications while on ECMO, and sources of sepsis. Random-effects meta-analysis (DerSimonian and Laird) were conducted.

Data synthesis: We included 14 observational studies with 468 patients in the meta-analysis. Pooled survival was 36.4% (95% confidence interval [CI] :23.6%-50.1%). Survival among patients with left ventricular ejection fraction (LVEF) <20% (62.0%, 95%CI: 51.6%-72.0%) was significantly higher than those with LVEF>35% (32.1%, 95%CI: 8.69%-60.7%, p=0.05). Survival reported in studies from Asia (19.5%, 95%CI: 13.0%-26.8%) was notably lower than those from Europe (61.0%, 95%CI: 48.4%-73.0%) and North America (45.5%, 95%CI: 16.7%-75.8%). Extracorporeal cardiopulmonary resuscitation was associated with reduced chances of survival (Risk ratio: 0.403, 95%CI: 0.197-0.826, p=0.01). GRADE assessment indicated high certainty of evidence for pooled survival.

Conclusions: When treated with VA-ECMO, the majority of patients with septic shock and severe sepsis-induced myocardial depression survive. However, VA ECMO has poor outcomes in adults with septic shock but without severe left ventricular depression. VA-ECMO may be a viable treatment option in carefully selected adult patients with refractory septic shock.

Background

Sepsis is a leading cause of death among critically ill patients and a global public health burden, leading to high healthcare costs.[1, 2] In 2017 alone, there were 48.9 million cases of sepsis and 11.0 million deaths (19.7% of all global deaths) related to sepsis.[3] The burden of sepsis is highest in early childhood, followed by a second peak in incidence in late adulthood.[4] Recognising sepsis as a global health priority, the World Health Assembly adopted a resolution to reduce its burden through better awareness, early diagnosis, and aggressive management.[2]

Approximately 15% of patients with sepsis develop septic shock, defined as persistent hypotension requiring vasopressors and elevated lactate levels despite adequate fluid resuscitation, where hospital mortality is in excess of 40%.[3] A subset of adult patients with septic shock develop concomitant left ventricular dysfunction, often described as septic cardiomyopathy.[5] However, septic cardiomyopathy is poorly defined in the literature and may be an underdiagnosed entity due to a lack of formal diagnostic criteria.[5–9] Adult patients with septic cardiomyopathy have 2–3 times increased mortality compared with those with septic

shock alone.[6] Single-centre studies have shown dismal survival rates (10–30%) when severe left ventricular (LV) dysfunction coexisted in patients with septic shock.[10]

Unlike many aetiologies of cardiomyopathy, septic cardiomyopathy is reversible, and early detection and intervention of septic cardiomyopathy in patients with septic shock may reduce mortality [10]. The encouraging outcomes of extracorporeal membrane oxygenation (ECMO) in paediatric septic shock have led to it being recommended as a potential therapy in some societal guidelines.[11–17] However, the haemodynamic pattern of septic shock is markedly different across age groups: new-born infants typically present with pulmonary hypertension and right heart failure, young children with left heart failure, and adolescents and adults with distributive shock.[15] Given the contrast in haemodynamic status between adult and paediatric shock, the use of ECMO, and in particular venoarterial ECMO (VA-ECMO), in adult septic shock remains controversial.

VA-ECMO has been found to be a risk factor for mortality when compared to venovenous ECMO (VV-ECMO) in patients with sepsis.[18–20] This might be due to the differing indications for ECMO in sepsis (concomitant hypoxemia and right ventricular dysfunction in VV-ECMO vs. cardiomyopathy and vasoplegia in VA-ECMO), potentially reflecting less severe disease for patients supported with VV-ECMO. Nonetheless, single-centre observational studies have shown that a subset of septic adults (specifically those with septic cardiomyopathy) may benefit from VA-ECMO for mechanical circulatory support.[21–23] We conducted a systematic review of literature on the use of VA-ECMO as mechanical circulatory support in adult patients with septic shock.

Methods

Search strategy and selection criteria

This study was registered with PROSPERO (CRD42020161827), and was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement.[24] We searched Medline, Embase, Cochrane, and Scopus databases from inception to 1st April, 2021, using the following keywords and their variations: “extracorporeal membrane oxygenation”, “extracorporeal life support”, “adult” and “septic shock” (Additional File 1). We assessed all relevant studies and their citation lists to identify articles for inclusion.

All studies written in English or with English translation, reporting on 5 or more adult patients (≥ 18 years) with septic shock supported with VA-ECMO were included. We excluded any non-human or paediatric studies, and any case reports to avoid publication bias. To avoid duplication of patient data, we excluded studies utilizing the Extracorporeal Life Support Organisation registry data. In the case of overlapping patient data across two or more studies in our primary meta-analysis, we included the larger study. Two reviewers (RRL and WHP) independently screened the articles for eligibility; any conflicts were resolved by consensus or by a third reviewer (KR).

Data collection

Data were collected independently by two reviewers (RRL and WHP) using a prespecified data extraction form; any conflicts were resolved by consensus or by a third reviewer (KR). Data collection covered study characteristics (study design, study duration, year of publication, country of ECMO centre), patient demographics (number of patients, proportion of male/female patients, mean age, pre-ECMO cardiac arrest, primary diagnosis), pre-ECMO characteristics (shock-to-ECMO interval, pH, serum lactate, left ventricular ejection fraction [LVEF], Sequential Organ Failure Assessment [SOFA] score), survival to hospital discharge, and other relevant clinical outcomes (intensive care unit [ICU] and hospital length of stay [LOS], ECMO duration, and complications during ECMO).[25] Individual participant data (IPD) were also collected for 4 studies that presented data individually for each patient.

Risk of bias assessment

Using the Joanna Briggs Institute (JBI) checklists for case series and cohort studies (Additional File 2), two reviewers (RRL and WHP) independently assessed the eligibility of studies; any conflicts were resolved by consensus or by a third reviewer (KR). The possibility of publication bias was assessed using Egger's test.

Statistical analysis

Statistical analyses were performed on R3.6.1, using the *meta* (v4.12-0), *dmeter* (v0.0.9000), and *lme4* (v1.1-23) packages.[26–28] For continuous variables, we pooled the means from the aggregate data presented in each study as per Wan et al.[29] The primary outcome was survival to discharge. Secondary outcomes included ICU LOS, ECMO duration, complications during ECMO, and source of infection.

We anticipated significant interstudy heterogeneity given the varied presentation of sepsis and septic shock and general lack of guidelines for patient selection and management for ECMO. As such, random-effects meta-analyses (DerSimonian and Laird) were conducted, and 95% confidence intervals (CIs) were computed using the Clopper-Pearson method.[30–32] Survival outcomes are presented as pooled proportions and 95% CIs, while dichotomous outcomes are presented as pooled risk ratios (RR) and 95% CIs. Planned subgroup analyses were conducted with continuity correction to include studies with zero events, and include: geographical location (Asia, Europe, and North America), pre-ECMO serum lactate (above and below 5 mmol/l), LVEF (< 20%, 20–35%, > 35%), and pre-ECMO cardiopulmonary resuscitation (CPR). As inter-study heterogeneity can be misleadingly large when assessed using I^2 statistics for observational studies, we used the Grading of Recommendations, Assessments, Developments and Evaluations (GRADE) approach to assess the inter-study heterogeneity.[33, 34] A sensitivity analysis was performed for all analyses by omitting 1 study at a time to identify outliers or influential studies.

Summary-level meta-regression was conducted when at least 6 data points[35, 36] were collected to explore potential sources of heterogeneity or prognostically-relevant study-level covariates. One-stage IPD meta-regression was conducted using the binomial distribution and logit link to compute adjusted and unadjusted ORs.[37] Intrastudy nesting of patients was accounted for by including a random slope term that allows the treatment effect to vary between studies. Fixed effects logistic regression was conducted when intrastudy patient correlation was found to be negligible. P value less than or equal to 0.05 was considered as statistically significant.

Results

Study details and demographics

Of 2448 references screened, our search yielded 87 potentially relevant studies across the 4 databases. 16 studies reporting on 534 adult patients with septic shock undergoing VA-ECMO were included in our systematic review.[19, 21, 38–51] All studies were retrospective and observational in nature: there was one multi-centre propensity score matched study, 11 single-centre retrospective cohort studies, and four single-centre retrospective case series. There were nine studies from Asia, five studies from Europe, and one study from North America. One study reported on patients from both Europe and North America. There were four studies with overlapping data; two of them were excluded from the primary meta-analysis. In total, 14 studies (468 patients) were included in our primary meta-analysis (Additional File 3). The pooled mean age (13 studies, 396 patients) was 53.2 years (95%CI: 50.6–55.9), while the pooled prevalence of male patients (13 studies, 396 patients) was 63.0% (95%CI: 55.5%-70.3%). Pneumonia was reported in 56.7% (95%CI: 44.0%-69.0%) of patients as the primary diagnosis. The pooled pre-ECMO serum pH (11 studies, 337 patients) and lactate (14 studies, 407 patients) were 7.15 (95%CI: 7.13–7.17) and 7.58 mmol/l (95%CI: 6.05–9.12 mmol/l) respectively. 21.7% (95%CI: 11.2%-34.4%) of patients underwent extracorporeal cardiopulmonary resuscitation (ECPR; 12 studies, 358 patients). The pooled time to ECMO cannulation from onset of septic shock was 23.4 hours (95%CI: 20.1–26.8). Baseline demographics and patient outcomes of the included studies are summarised in Additional Files 4 and 5.

Primary meta-analysis

The pooled survival to hospital discharge (14 studies, 468 patients) was 36.4% (95%CI: 23.6%-50.1%, Fig. 1). Leave-one-out (LOO) analysis did not yield any potential outliers.

Subgroup analysis

Subgroup analysis yielded significant differences when considering the geographical region and the presence of ECPR. Survival reported by studies from Asia (9 studies, 19.5%, 95%CI: 13.0%-26.8%) was notably lower than in those from Europe (6 studies, 61.0%, 95%CI: 48.4%-73.0%) and America (1 study, 45.5%, 95%CI: 16.7%-75.8%). Among 5 studies (190 patients), ECPR was associated with lower survival (RR 0.403, 95%CI: 0.197–0.826, $p = 0.01$). Finally, survival reported by studies in which LVEF < 20% (3 studies, 62.0%, 95%CI: 51.6%-72.0%) was significantly higher than those where LVEF > 35% (3 studies, 32.1%, 95%CI: 8.7%-60.7%, $p = 0.05$). Survival reported by studies where LVEF was between 20% and 35% was 42.3% (95%CI: 6.7%-82.8%, Fig. 2) Pre-ECMO serum lactate (14 studies, 407 patients) was not significantly associated with survival ($p = 0.21$). The results of the subgroup analysis are summarised in Table 1.

Table 1
Results of subgroup analysis

Subgroup		Pooled survival (%)	95% CI (%)
Geographical region (p < 0.001)	Asia	19.5	13.0 to 26.8
	Europe	61.0	48.4 to 73.0
	America	45.5	16.7 to 75.8
Presence of E-CPR (p = 0.01)	E-CPR	Survival = 20.5% (25 of 122)	
	No E-CPR	Survival = 32.1% (85 of 265)	
LVEF (p = 0.09)	< 20%	62.0	51.6 to 72.1
	20 to 35%	42.3	6.70 to 82.8
	> 35%	32.1	8.70 to 60.7
Serum lactate (p = 0.20)	< 5 mmol/l	50.5	29.8 to 71.2
	> 5 mmol/l	32.2	16.2 to 50.7
<i>Abbreviations:</i> CI: confidence interval; ECMO: extracorporeal membrane oxygenation; VA: Venoarterial; VV: venovenous; E-CPR: extracorporeal cardiopulmonary resuscitation			

Univariable and IPD meta-regression analyses

Univariable meta-regression analyses revealed that factors like sex, age, SOFA score, lactate levels and ECPR were not associated with better survival (Table 2). 4 studies (134 patients) provided IPD on age, gender, pre-ECMO SOFA score, CPR, serum lactate, LVEF and duration of ECMO. Multivariable one-stage IPD meta-regression (Table 3) analyses revealed that age was an independent risk factor for mortality (unadjusted OR for survival: 0.974, 95% CI: 0.949–0.999, p = 0.04), but this association was not observed when accounting for the other covariates (adjusted OR: 0.972, 95% CI: 0.941–1.002, p = 0.07). Other factors were not associated with survival benefits on IPD analysis.

Table 2
Results of univariable metaregression analysis

Covariate	Number of studies	Odds ratio	Lower 95% CI	Upper 95% CI	P-value
Age	13	0.990	0.979	1.006	0.06
LVEF	8	0.991	0.978	1.002	0.13
Male sex	12	0.512	0.148	1.770	0.29
Publication year	16	1.025	0.970	1.083	0.38
Lactate	14	0.978	0.926	1.034	0.43
SOFA	14	0.982	0.935	1.031	0.46
E-CPR	11	0.853	0.350	2.079	0.73
Patients with pneumonia	12	1.078	0.435	2.673	0.87

Abbreviations: CI: confidence interval, ECMO: extracorporeal membrane oxygenation, SOFA: sequential organ failure assessment, LVEF: left ventricular ejection fraction, E-CPR: extracorporeal cardiopulmonary resuscitation

Table 3
Results of one-stage individual patient data (IPD) meta-regression analysis

Factor	Unadjusted			Adjusted		
	OR	95% CI	P	OR	95% CI	P
ECMO Duration	0.997	0.940–1.059	0.91	1.024	0.951–1.115	0.55
Lactate	0.980	0.905–1.060	0.61	0.934	0.845–1.029	0.17
E-CPR	0.919	0.292–3.261	0.89	0.526	0.086–3.006	0.32
SOFA score	1.030	0.929–1.136	0.55	1.028	0.878–1.211	0.74
Age	0.974	0.949–0.999	0.04	0.972	0.941–1.002	0.07
Male gender	0.609	0.293–1.248	0.18	0.742	0.309–1.769	0.46
LVEF	1.026	0.982–1.065	0.14	1.022	0.978–1.072	0.34

Abbreviations: OR: odds ratio; CI: confidence interval; ECMO extracorporeal membrane oxygenation; SOFA: Sequential organ failure assessment; E-CPR: extracorporeal cardiopulmonary resuscitation

Secondary outcomes

The pooled ICU LOS (8 studies, 209 patients) was 19.38 days (95%CI: 11.56–27.19). The pooled ECMO duration (10 studies, 337 patients) was 5.78 days (95%CI: 4.11–7.45). Among 8 studies (396 patients), survivors also had significantly longer ECMO durations (2.18 days, 95%CI: 0.27–4.10, $p = 0.03$) than non-survivors. After LOO analysis, the pooled mean difference was 2.84 days (95%CI: 1.09–4.58, $p = 0.002$). A total of 124 complications were reported across 6 studies (198 patients). Haemorrhagic (49, 39.5%), infectious (36,

29.0%), and mechanical (23, 18.5%) were the most commonly reported complications while receiving ECMO. 9 studies (262) reported on the pathogens cultured from the patients, but did not identify whether these pathogens were the primary causative organism of septic shock, or were nosocomial and acquired after the initial septic shock episode. Of the 330 pathogens cultured among 262 patients (9 studies), gram negative and positive bacteria were the most commonly cultured pathogen (142 each, 43.0%), followed by fungi (25, 7.58%), viruses (10, 3.03%) and others (11, 3.33%).

Assessment of study quality

Appraisal using the JBI checklists for cohort studies and case series suggested a high level of quality across the included studies for this review, with the majority of the studies receiving at least 9/10 in the appropriate checklist (Additional File 2). Egger's test yielded non-significant results for publication bias. A summary of the GRADE assessment for certainty of evidence is provided in Additional File 6. As the outcome was survival, the starting level of evidence for observational studies was high. Certainty for pooled survival was high, the certainty for ECMO duration was downgraded to moderate for serious imprecision, and the certainty for ICU LOS was downgraded to low for serious inconsistency and imprecision.

Discussion

This systematic review and meta-analysis quantitatively summarised the evidence for survival of adult patients with septic shock requiring VA-ECMO. Pooled survival across 14 studies and 438 patients was 36.4%. Subgroup analyses revealed that pre-ECMO LVEF and ECPR significantly influenced survival rates of patients with septic shock initiated on ECMO in addition to variations in survival by geographic region of study origin.

While data are scarce, studies investigating VA-ECMO adult patients with preserved LVEF have reported dismal outcomes.[40, 46, 49] It has been proposed that septic patients who have hyperdynamic left ventricular function on echocardiography have poorer outcomes than those with normo- or hypo-kinetic profiles, and this stratification may permit better patient selection for VA-ECMO in septic shock.[5] A propensity-score weighted analysis found that select patients with severe myocardial dysfunction (very low LVEF) receiving VA-ECMO during the first four days of septic shock had significantly lower mortality than those without ECMO,[50] with similar findings among observational case series reporting on VA-ECMO for adult and paediatric septic cardiomyopathy.[11, 12, 47] Concordant with these observations, our analysis found that survival among patients with LVEF > 35% was significantly lower than those with LVEF < 20% (62.0 % Vs 32.1%). Patients with LVEF between 20% and 35% had intermediate survival (42.3%), suggesting a possible graded effect of LVEF on outcomes. While plausible, further research investigating pre-ECMO LVEF and its relation with mortality on VA-ECMO for adult septic shock is needed to conclusively substantiate our findings.

Currently, the diagnostic criteria for adult septic cardiomyopathy are not fully established, due to the complexity and variations in the cardiovascular response to infection.[52, 53] It is also difficult to determine how well myocardial dysfunction correlates with organ dysfunction in general, and how much it independently contributes to poorer outcomes.[53] This is compounded by the lack of longitudinal echocardiography data to ascertain cardiac function at premorbid, disease, and recovery states.[8] Nonetheless, it is understood that transient and reversible myocardial depression is common in septic patients, and is associated with low or normal LV filling pressures despite depressed systolic function.[54, 55] Three broad criteria were proposed to

characterise septic cardiomyopathy: LV dilatation with normal- or low-filling pressure, reduced ventricular contractility, and ventricular dysfunction with reduced response to volume infusion.[7] While increasing perfusion and cardiac output can improve survival among these patients,[56, 57] the use of very high-dose vasopressors might contribute to a vicious circle of vasoconstriction and refractory cardiovascular failure.[21] By providing mechanical circulatory support, VA-ECMO can potentially restore systemic perfusion pressure and increase oxygen delivery. This corrects the cellular hypoxia and metabolic acidosis during septic cardiomyopathy, ameliorating vasopressor dependence and potentially improving the chances of survival.

In septic patients with preserved cardiac function, VA-ECMO may be contraindicated as it reduces preload, increases afterload, and increases capillary leakage, eventually decreasing cardiac output.[58] Of note were 6 patients from the study by Falk and colleagues, who underwent VV-ECMO and then converted to VA-ECMO. All 6 patients had LVEF >35% and none of them survived to discharge. This might also explain why survival reported by studies from Europe was higher than those from Asia. While patients in European studies presented with severe myocardial depression, Asian studies described patient profiles of distributive shock and relatively preserved LV function. Apart from this, the proportion of patients undergoing ECPR, which is associated with greater mortality (RR survival = 0.403, p = 0.01), was higher in studies from Asia. While ECPR may be construed as a version of VA-ECMO, factors contributing to poor survival on ECPR are manifold and may not be similar to VA-ECMO.[59]

Strengths of this study include the broad inclusion criteria and relevant exclusion criteria. Our review included 14 studies, pooling data from 8 different countries across 3 regions. We elucidated factors correlating with survival via subgroup analysis and meta-regression, reducing confounding. Coupled with non-significant results from Egger's test, we sourced for unpublished data for IPD meta-analysis, limiting publication bias. Nonetheless, we recognise several limitations of this study. The absence of randomised studies increases the risks of confounding and bias, in particular, confounding by indication. Furthermore, there are different initiation thresholds and varying protocols and practices between individual institutions, which can introduce confounding factors given the lack of risk adjustment or propensity-scoring techniques. Finally, the need for VA-ECMO in adult septic cardiomyopathy is uncommon, which makes these results applicable to a narrow spectrum of patients in clinical practice. While it would be most appropriate to perform a prospective randomized clinical trial in this patient population, there would be considerable challenges in doing so, including the low incidence of patients with septic shock and septic cardiomyopathy, and the ethical challenges surrounding randomization in ECMO studies.[60–62]

Conclusions

Our systematic review and meta-analysis of the current literature suggests that VA-ECMO may be a viable salvage therapy among select patients with septic shock and concomitant myocardial depression. By contrast, ECMO is associated with especially poor outcomes among patients with septic shock but without severe ventricular dysfunction. Overall pooled survival in our meta-analysis was 36.4%. Patients with septic cardiomyopathy had considerably better survival than those with normal LV function. While the results of this review might only be translatable to a small population of patients with septic shock and concomitant cardiomyopathy, judicious selection of these patients for VA-ECMO could improve mortality.

Abbreviations

LV
left ventricular

ECMO
extracorporeal membrane oxygenation

VA
venoarterial

VV
venovenous

LVEF
left ventricular ejection fraction

SOFA
sequential organ failure assessment

ICU
intensive care unit

LOS
length of stay

IPD
individual participant data

JBI
Joanna Briggs Institute

RR
risk ratio

(E)CPR
(extracorporeal) cardiopulmonary resuscitation

GRADE
Grading of recommendations, assessment, development, and evaluations

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The dataset generated and analysed during the current study can be found in the included studies and their supplementary information files.

Competing interests

DB receives research support from ALung Technologies. He has been on the medical advisory boards for Baxter, Abiomed, Xenios and Hemovent. All other authors declare no competing interests.

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Author contributions

The study was designed by KR and GM. RRL and WHP screened the articles, assessed the risk of bias and extracted the data under the supervision of KR. RRL analysed and interpreted the data under the supervision of CST and KR. Tables and figures were produced by RRL. RRL and KR shared the primary responsibility of writing the manuscript, to which all authors contributed to and revised. GM, NB, DB, AC and KR critically revised the manuscript for important intellectual content. All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft.

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Figures

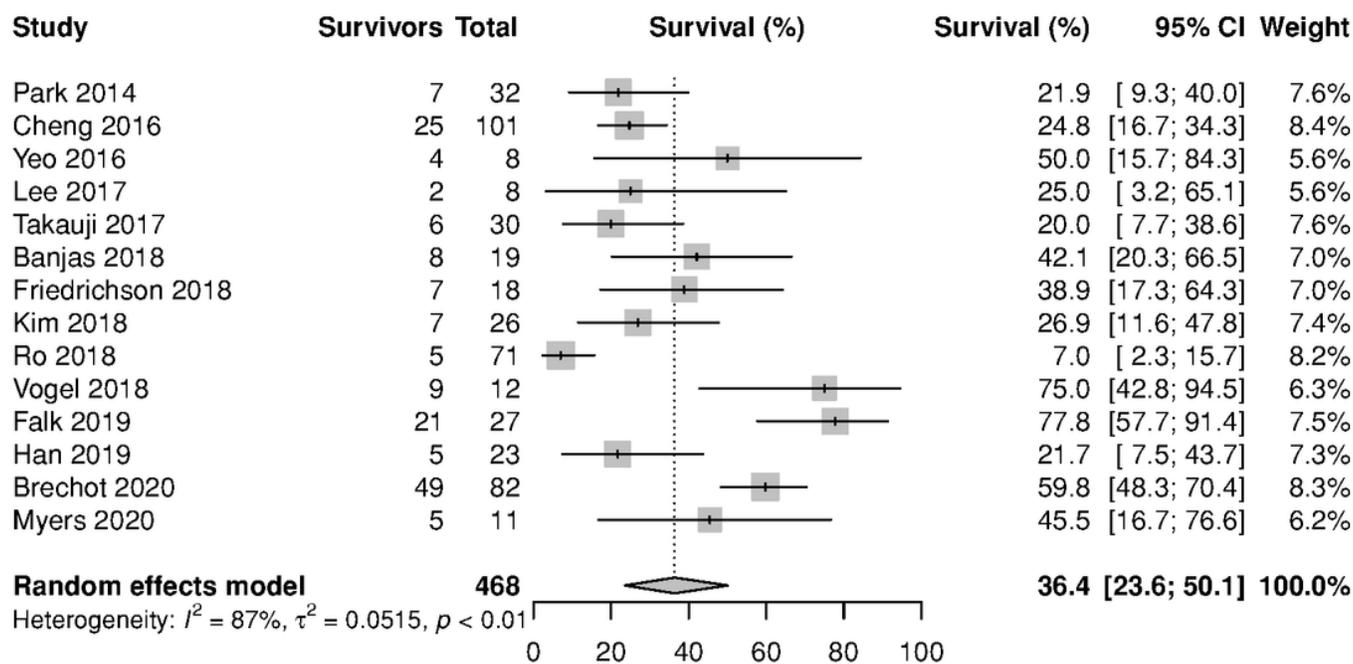


Figure 1

The pooled survival to hospital discharge (14 studies, 468 patients) was 36.4% (95%CI: 23.6%-50.1%),

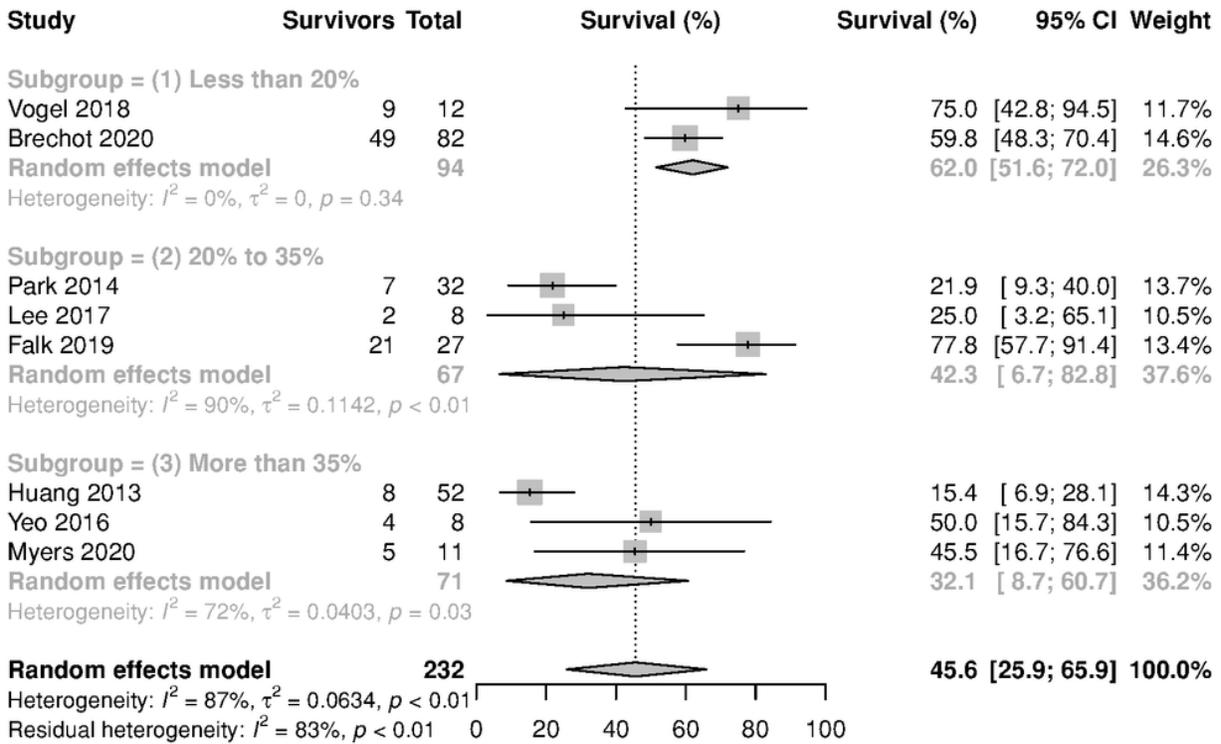


Figure 2

Subgroup analysis yielded significant differences when considering the geographical region and the presence of ECPR. Survival reported by studies from Asia (9 studies, 19.5%, 95%CI: 13.0%-26.8%) was notably lower than in those from Europe (6 studies, 61.0%, 95%CI: 48.4%-73.0%) and America (1 study, 45.5%, 95%CI: 16.7%-75.8%). Among 5 studies (190 patients), ECPR was associated with lower survival (RR 0.403, 95%CI: 0.197-0.826, $p=0.01$). Finally, survival reported by studies in which $LVEF < 20\%$ (3 studies, 62.0%, 95%CI: 51.6%-72.0%) was significantly higher than those where $LVEF > 35\%$ (3 studies, 32.1%, 95%CI: 8.7%-60.7%, $p=0.05$) Survival reported by studies where LVEF was between 20% and 35% was 42.3% (95%CI: 6.7%-82.8%

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