Outcomes of venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock: systematic review and meta-analysis

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Background: Despite advances in management techniques and medical therapy, refractory cardiogenic shock remains a life-threatening condition with high mortality rates. The present systematic review and meta-analysis aims to explore the outcomes associated with venoarterial extracorporeal membrane oxygenation (VA-ECMO) use in the setting of refractory cardiogenic shock, stratified per survivorship.

Methods: A literature search was performed using three electronic databases from the date of their inception up to June 2018. The literature search and subsequent data extraction were performed by two independent reviewers. Digitized survival data were extracted from Kaplan-Meier curves in order to re-create the original patient data using an iterative algorithm and were subsequently aggregated for analysis.

Results: Fifty-two studies were included, with 44 undergoing quantitative analysis. A total of 17,515 patients were identified, with a mean age of 58.4±9.4 years and a mean duration of ECMO support of 5.1±2.6 days; 68.7% of the patients were male. Aggregated survival rates at 1, 2, 3 and 5 years were 36.7%, 34.8%, 33.8% and 29.9%, respectively.

Conclusions: The present systematic review illustrates the expected survival results for VA-ECMO in the intermediate- to long-term. Extended follow-up and standardized reporting measures are urgently needed in order to carry out more definitive subgroup analyses.

Keywords: Extracorporeal membrane oxygenation (ECMO); ECLS; refractory cardiogenic shock

Introduction

Despite advances in management techniques and medical therapy, refractory cardiogenic shock remains a life-threatening condition with high mortality rates (1). Both low cardiac output and poor tissue perfusion characterize cardiogenic shock and hence a great deal of emphasis is placed on the use of inotropic and vasopressor agents, mechanical assistance and fluid maintenance to support cardiac function (2). Mechanical support for the management of cardiogenic shock was first assessed in animal trials as early as the 1930s, with extension to human trials in the late 1960s in the setting of infants with respiratory sepsis (3-5). The efficacy of extracorporeal membrane oxygenation (ECMO) as a tool for the management of shock syndromes was established in the 1970s, but it was introduced slowly to mainstream intensive care medicine after a series of setbacks (6-8). More recently, ECMO has been widely employed for a range of cardiovascular and respiratory conditions

resulting in cardiogenic shock that are refractory to medical management, namely, acute myocardial infarction (AMI), postcardiotomy-related shock (PCT), graft failure in heart transplant (GFIHT) and acute decompensated heart failure (ADHF), particularly in the wake of successful trials (9,10). The present systematic review and meta-analysis aims to explore the current outcomes associated with venoarterial-ECMO (VA-ECMO) use in the setting of refractory cardiogenic shock, stratified per survivorship, with a discussion on cannulation method and presenting pathology.

Methods

Literature search strategy

This review was performed in accordance with PRISMA recommendations and guidance (11). Electronic searches were performed on PubMed, Scopus and Medline from dates of database inception to June 2018, using ("venoarterial" OR "veno-arterial") AND ("extracorporeal membrane oxygenation" OR "ECMO" OR "extracorporeal life support" OR "ECLS" OR "VA ECMO" OR "VA-ECMO" OR "V-A-ECMO") AND ("cardiogenic shock"), as either keywords or MeSH headings. After removal of duplicate records, studies were reviewed according to the inclusion and exclusion criteria detailed below by two independent authors. A PRISMA diagram of the search strategy is presented in *Figure S1*. Additional references for discussion were included via a reference list search or via targeted database searches.

Inclusion and exclusion criteria

Studies were included if they had at least 10 patients in their cohorts and where VA-ECMO had been used in supporting patients with refractory cardiogenic shock. Non-English studies, review articles, conference and paper abstracts, editorials, letters and opinions were all excluded. Studies were also excluded if they did not present baseline patient characteristics, or the focus of the study was in a cohort composed of patients <18 years.

Quality assessment of included studies

An appraisal schema based on the Canadian National Institute of Health Economics' (IHE) Quality Assessment Tool (i.e., the modified Delphi technique) for Case Series Studies was employed to evaluate all included studies. The

evaluation was carried out by two independent reviewers. Studies were categorized based on the following domains: clarity of study objective, adequate description of the study population, description of the intervention, adequate reporting of outcome measures and appropriate reporting of results/conclusions. Quality findings are listed in *Table S1*.

Statistical analysis

Baseline patient characteristics, risk factors, operative details and outcomes of interest were extracted by two independent researchers. Kaplan-Meier curves were digitized where presented and an algorithmic computational tool was utilized, as outlined by Guyot and colleagues, to derive individual patient data (12). Censoring was assumed to be constant, unless the particular curve had a long follow-up of only minimal patients—in which case, censoring was manually entered. Death events and censoring data were compiled for the entire patient cohort and overall survival curves were produced as per the Kaplan-Meier method using IBM SPSS Statistics 25 (IBM Corp. Released 2017; IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY, USA: IBM Corp) after being digitized. Studies that included high-resolution Kaplan-Meier curves, alongside numbers at risk, where included in the aggregation. Where studies had broken their cohorts into subgroups, individual KM curves were generated for these first and then merged, prior to being included in the whole cohort analysis. Studies that failed to report numbers at risk, or had data points obscured by censoring brackets, were excluded. These measures were applied in order to reduce the heterogeneity of the population and increase the validity of the findings. Data collection and meta-analysis of study characteristics were carried out using IBM SPSS Statistics 25 and Review Manager 5 (version 5.3, Cochrane Collaboration, Oxford, United Kingdom).

Results

A total of 789 references were identified in the search. After applying the inclusion and exclusion criteria, 52 studies were included for qualitative analysis, of which 44 went on to quantitative analysis. Of these 44 quantitative studies, 25 were of medium quality and 19 were of high quality, as defined by the IHE assessment tool (see *Table S1*). Of the studies included for quantitative analysis, 20 of the studies were from European centers, 14 were Asian/Australasian and 10 were from the United States, with recruitment

Table 1 Summary of baseline study characteristics (total cohort)

Characteristics	Outcome
Total patients	17,515
Males (n, %)	12,036 (68.7%)
Age, mean ± SD (years)	58.4±9.4
BMI, mean ± SD (kg/m^2)	25.0±4.9
Body surface area, mean ± SD (m^2)	1.9±0.2
Etiology/cause of shock (where delineated) (n)	
Postcardiotomy	613
Acute myocardial infarction	993
Graft failure in transplant	466
Acute decompensated heart failure	213
Undefined/other refractory cardiogenic shock	15,230
Cannulation method (n)	
Central	646
Peripheral	2,088
Undefined	14,781
Preoperative LVEF, mean ± SD (%)	29.4±7.3
CPB duration, mean ± SD (min)	206.0±39.5
CPR (%)	75.5%
Time on ECMO, mean (days)	5.1±2.6
IABP (%)	53.4%
Lactate, mean ± SD (mmol/L)	12.0±5.0
Creatinine, mean ± SD (mg/dL)	1.5±0.7

The results presented are in weighted means, inter-quartile ranges, or n/%, ± standard deviation. Survival was considered to be at primary discharge. Characteristics were combined where presented. CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

periods between 1986 and 2016. A total of 17,515 patients were identified as having been placed on VA-ECMO for the management of refractory cardiogenic shock from 1996 to 2018. Only 2,734 patients (15.6%) were specified as having either undertaken central or peripheral ECMO, with the rest of the cohort remaining undefined. Full study characteristics are reported in *Table S2*.

The mean age of the population was 58.4±9.4 years and the mean time spent on ECMO support was 5.1±2.6 days. Within this population, 613 were treated for PCT,

993 for AMI, 466 for graft failure and 213 for ADHF. A total of 15,230 subjects were managed for other conditions resulting in refractory cardiogenic shock or were undefined. Body mass index (BMI) and body surface area (BSA) had mean values of 25.0±4.9 kg/m^2 and 1.9±0.2 m^2, respectively. Mean preoperative left ventricular ejection fraction (LVEF) was found to be 29.4%±7.3%. Cardiopulmonary resuscitation (CPR) and intra-aortic balloon pump (IABP) use were reported in 31.9% and 48.9% of studies, yielding totals of 1,081 and 3,989 patients, respectively. They were administered in 75.5% and in 53.4% of subjects, when weighted. Mean CPB time was found to be 206.0±39.5 minutes, where reported. Baseline serum lactate and creatinine were 12.0±5.0 mmol/L and 1.5±0.7 mg/dL and were reported in 47.7% (21/44) and 31.8% of studies (14/44), respectively (*Table 1*).

Survivors *vs.* non-survivors (*Table 2*)

Survival-to-discharge was found to be 43.0% in a total cohort of 5,292 patients. Of these 5,292, 3,575 patients were male. The mean age of survivors versus non-survivors was 55.1±13.2 and 56.1±12.8 years and the mean duration of ECMO support was 4.0±2.1 and 3.8±3.5 days, respectively. Mean CPB time was found to be 192.6±110.2 and 216.6±99.8 min. CPR was carried out in 31.2% of survivors versus 58.3% in non-survivors. Lactate and creatinine levels were found to be slightly higher in non-survivors than in survivors. The rates of acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), liver dysfunction, bleeding and CVA/neurological dysfunction were all higher in non-survivors. Infection was found to be higher in survivors. Forest plot analysis for in-hospital complications are reported in *Figure S2*.

Whole cohort: long-term survival

Aggregated survival rates at 1, 2, 3, 4 and 5 years were 36.7%, 34.8%, 33.8%, 31.7% and 29.9%, respectively. The overall cohort data is presented in *Figure 1*. The follow-up period was between 2000 and 2015.

Discussion

Contemporary outcomes of VA-ECMO administration

Since their inception, extracorporeal life support systems have seen tremendous modifications throughout several,

Table 2 Baseline characteristics of survivor *vs.* non-survivor studies

Characteristics of cohort (n=5,292)	Survivors (n=2,278)	Non-survivors (n=3,014)	P value (MD/OR)
Males (n, %)	1,545 (67.8%)	2,030 (67.4%)	0.72 (1.01; 95% CI, 0.97 to 1.05)
Age, mean ± SD (years)	55.1±13.2	56.1±12.8	0.006 (−1.00; 95% CI, −1.71 to −0.29)
Time on ECMO, mean ± SD (days)	4.0±2.1	3.8±3.5	0.010 (0.20; 95% CI, 0.05 to 0.35)
CPB time, mean ± SD (min)	192.6±110.2	216.6±99.8	<0.001 (−24; 95% CI, −29.76 to −18.24)
CPR (%)	31.2	58.3	<0.001 (0.33; 95% CI, 0.18 to 0.58)
Lactate, mean ± SD (mmol/L)*	14.0±13.3	19.2±15.2	<0.001 (−5.20 95% CI, −5.97 to −4.43)
Creatinine, median (range) (mg/dL)*	1.3 (1.1–1.7)	1.6 (1.2–2.3)	
In-hospital complications (%)			
ARDS	15.0	34.1	0.002 (0.34; 95% CI, 0.17 to 0.68)
AKI	13.6	22.7	0.10 (0.54; 95% CI, 0.26 to 1.13)
Liver dysfunction*	13.9	29.8	0.007 (0.38; 95% CI, 0.19 to 0.77)
Bleeding*	9.1	13.5	0.27 (0.61; 95% CI, 0.25 to 1.48)
CVA/neurological dysfunction	12.5	22.5	0.07 (0.50; 95% CI, 0.24 to 1.05)
Infection	24.6	11.5	0.02 (2.44; 95% CI, 1.15 to 5.20)

The results presented are in means, inter-quartile ranges, or n/%. Survival was considered to be those alive of the total cohort at primary discharge. *, lactate and creatinine levels were taken as soon as ECMO started (i.e., at baseline), or when first convenient. Bleeding was defined as any incident where unexpected blood loss occurred. Liver dysfunction was defined as any change from normal functioning, including shock liver and generalized inflammation. Significance is set at a P value of 0.05. BMI, body mass index; LVEF, left ventricular ejection fraction; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury requiring renal replacement therapy; CVA, cerebrovascular accident; MD, mean difference; OR, odds ratio; CI, confidence interval.
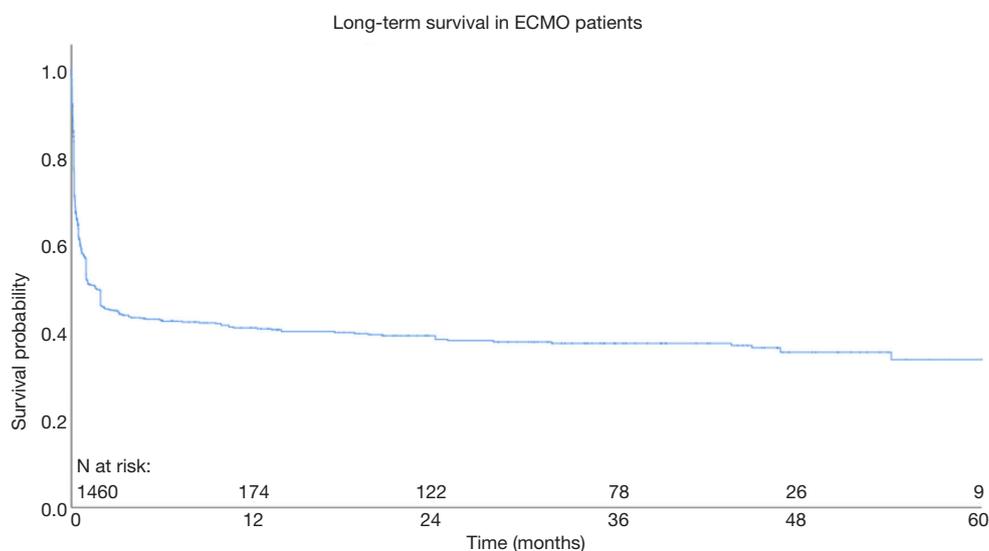
Figure 1 Aggregated survival for the entire cohort using Kaplan-Meier estimation.

rapid eras of development. With applications in pediatric heart and lung disease and in adults suffering from shock syndromes, ECLS has always been associated with high-risk cohorts. The high-risk nature of the patient population undergoing VA-ECMO is reflected by the findings of this analysis, with an overall survival-to-discharge rate of 43.0%. This is in line with the data presented in the literature (13-16). Intermediate-term survival appears to be consistent, with aggregated survival rates at 1, 2, 3 and 4 years at 36.7%, 34.8%, 33.8%, 31.7% and 29.9%, respectively.

Significant prognostic factors: survivors *vs.* non-survivors

In an effort to increase the validity and reliability of this analysis, whilst minimizing the heterogeneity of an already diverse population, only the studies that had delineated outcomes of their survivor *vs.* non-survivor cohorts were included for subgroup analysis. In the contemporary setting, a number of factors have been found to be predictive of increased mortality on VA-ECMO. Time elapsed prior to VA-ECMO administration has been found to be shorter in survivors than in non-survivors (13,17). Out-of-hospital cardiac arrests are associated with poorer outcomes, likely due to the pre-existence of comorbidities and poor return of spontaneous circulation after life support administration (14). Non-survivors typically have increased uptake of renal replacement therapies, which is reflected by the present analysis with higher rates of AKI noted in this cohort (18). CEF scores, SOFA scores, APACHE II scores, SAPS II scores and troponin levels on day 1 of ECMO administration have been correlated with in-hospital mortality, with a high Youden index and prediction of correctness illustrated, particularly by ACEF (19,20). Non-survivors have also been found to have higher levels of CK-MB than survivors, reflecting a greater degree of myocardial injury and irreversibility (18). ECMO duration is not typically different between survivor and non-survivor cohorts (21,22). It is of note that survivors were more than twice as likely to have infections whilst in hospital. It is possible that this is as a result of the heterogeneity of the infection reporting within ECMO studies and from variance in the amount of time patients were in hospital; survivors would be more likely to survive the immediate postoperative period to discharge and hence be exposed to infection risks for an increased amount of time, whereas non-survivors would die prior. Forest plot analysis of a small subset of studies with clearly defined outcome data

between survivors and non-survivors failed to clarify this finding, with survivors being less likely to have infections, but the result not being significant (see *Figure S2*). Specific delineations between infection types (e.g., surgical site infection, line infection, etc.) in future studies would be helpful in elucidating this further.

Cardiac arrest prior to VA-ECMO administration, lack of IABP use, older age, low or high BMI, high serum lactate levels and clinician unfamiliarity with ECMO systems/ poor interdisciplinary cohesion have been highlighted as predictors of in-hospital mortality (17,23,24). High serum lactate, in particular, has been a consistently reported variable in the literature, with ranges of 5–20 mmol/L being shown to be predictive of mortality. Indeed, the present analysis affirms this relationship. It has been suggested that providing early support prior to reaching precarious levels could improve outcomes (17,18). Hospital volume has not been found to be predictive of poorer outcomes (23). Favourable outcomes with the use of a left ventricular assist device have also been illustrated, as temporary mechanical support allows for more efficacious stabilization of the patient in emergency settings. Most often, the reported causes of death whilst on ECMO are multi-system organ failure (MOF), likely stemming from infection and/or poor perfusion, and lack of neurological recovery (25).

Postcardiotomy, AMI, graft failure, ADHF

The initiation of VA-ECMO in postcardiotomy subjects has been found to improve survival and is associated more often with central cannulation, as the chest is already open and easy conversion from CPR to ECMO can take place (26,27). As the vast majority of ECMO cohorts are composed of subjects presenting with cardiac arrest, AMI-related outcomes are closely tied to the aforementioned predictors of survival and hence will be improved as treatment strategies are refined. Graft failure and ADHF are two etiologies that require far more attention, with little data being presented on their specific outcomes outside of select institutions; Loforte and colleagues present an ideal framework for the presentation of outcomes in this area (9).

Central *vs.* peripheral cannulation

Whether to cannulate centrally versus peripherally remains an ongoing point of contention. As mentioned previously, central cannulation is ideal in the setting of postcardiotomy shock. Higher flows can also be tolerated, with better

whole-body perfusion as a result. Central cannulation and right axillary cannulation are more physiologically sound than retrograde cannulation, providing more natural and effective perfusion to the whole body (18). Central cannulation does run the risk of mediastinal bleeding, often requiring exploration to be resolved (28). In contrast, peripheral cannulation has been shown to cause retrograde perfusion and conflicting flow, limiting tissue recovery (26).

Whilst peripheral cannulation confers better lower body perfusion, poor upper body, coronary and cerebral perfusion calls into question its efficacy in severely hemodynamically unstable subjects; there is a need for data on temporary and permanent neurological deficits secondary to peripheral VA-ECMO administration, as at present, very minimal data exist. Limb ischemia and nerve injury—in the setting of axillary cannulation—are also concerns. Infection risk is notably lowered in peripheral administration and is often preferred to central cannulation given the necessity of anticoagulation therapy (29). Weaning from mechanical ventilation is typically also easier and safer in the peripheral setting, with recommendations being made in recent studies that peripheral cannulation should be considered first, except in the instance where the patient has small femoral vessels, or where they are suffering from PCT (30).

Long-term survival

Limited data exist on the long-term survival outcomes of subjects who underwent VA-ECMO for the management of refractory cardiogenic shock. This study presents an aggregation of the existing survival data, drawn from studies that carried out their own survival analysis (see *Figure 1*). From the analyses, it appears that survival is relatively consistent in the first five years following VA-ECMO (36.7% to 29.9%). Additional subgroup analysis on long-term survival was not able to be carried out, as too few studies presented KM curves stratified based on etiology.

Limitations

There are a number of limitations which constrain the present analysis. First and foremost, the reporting style for the studies examining whole-cohort outcomes are disparate, with clinical characteristics varying substantially and with a number of critical characteristics not being reported at all (e.g., CPB/CPR administration and duration,

complications, etc.). This is despite the overwhelming majority of the included studies being published within the last decade. This restricts meaningful, detailed subgroup analysis for a number of clinically relevant covariates. This was largely circumvented by focusing on the most commonly reported variables (e.g., serum lactate, creatinine, etc.). The baseline characteristics of the cohort presented is therefore not exhaustive, with room for additional analysis as more studies are published; without standardization of reporting methods for core clinical characteristics, increased study volume is the only pathway to increased validity. With a few notable exceptions, a substantial proportion of the studies included in the quantitative analysis did not report survival outcomes stratified by etiology/indication for ECMO. Tsai and colleagues present an ideal framework for the presentation of survival data in the contemporary setting (19). Additionally, long-term survival analysis could also be benefited by extended follow-up times, although the reporting rate of survival analysis was acceptable, with 56.8% of studies (25/44) presenting Kaplan-Meier curves.

A number of the highly weighted studies included in the analysis were unable to report cannulation method as their retrospective data were drawn from large, low-resolution registries (i.e., those with limited operative data), which limits the reliability of the subgroup analysis. Retrospective study also introduces the risk of publication bias, which can be reduced by having clear survivor *vs.* non-survivor analyses. Of the total cohort of 17,515 patients, only 2,734 (15.6%) detailed the cannulation method. The indication for ECMO was also reported with a fair degree of variability and instead, a broader definition of refractory cardiogenic shock, including pathologies other than those of interest, was often used. Few studies broke their patient cohorts down into age groups, although all of patients within the overall cohort were adults and non-elderly.

Conclusions

The findings of this analysis are consistent with common clinical experiences regarding ECMO administration. Overall, ECMO studies tend to suffer from great heterogeneity, with a large number of patients presenting for a variety of conditions that place them at high risk of mortality. This high-risk nature is reflected by the aggregated survival analyses. More thorough and consistent reporting is urgently required in order to overcome this issue.

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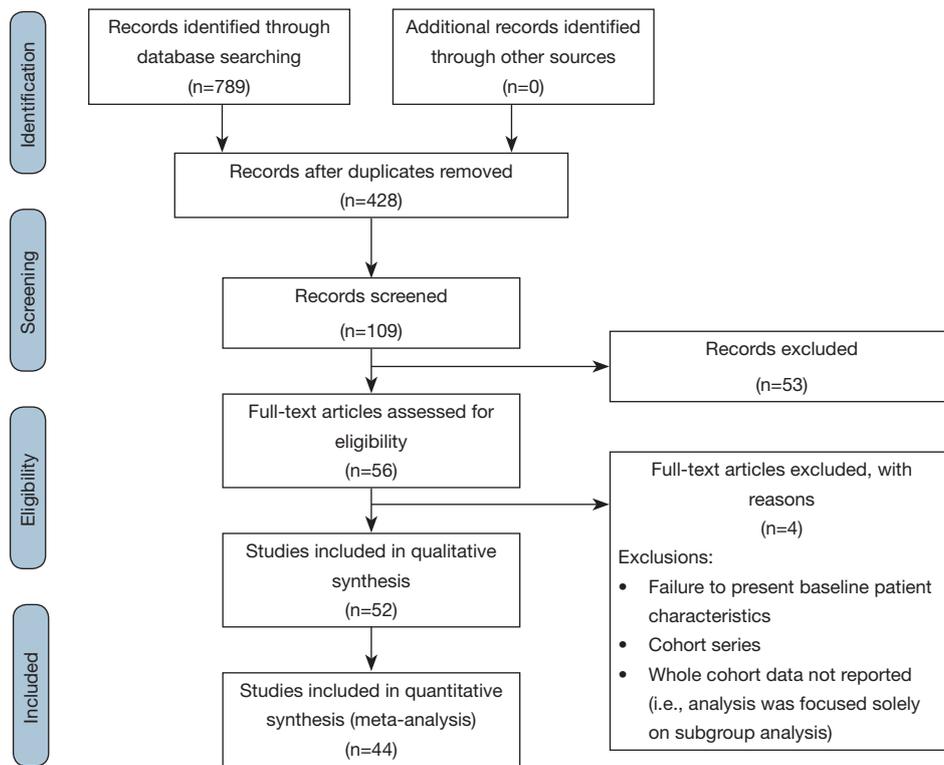
Figure S1 PRISMA flow chart detailing the literature search process for contemporary VA-ECMO outcomes in the setting of cardiogenic shock. ECMO, extracorporeal membrane oxygenation.

Table S1 Study details and quality assessment findings for quantitative analysis

Study	Year of publication	Region	Recruitment years	Patients (n)	Study design	IHE quality scoring
Aso	2016	Japan	2010–2013	4,658	Retrospective, database	H
Aubin	2017	Germany	2011–2015	160	Retrospective, database	H
Bakhtiary	2008	Germany	2003–2006	45	Retrospective	M
Bougouin	2017	France	2011–2015	52	Retrospective	H
Boulate	2013	France	2004–2012	55	Retrospective	M
Burrell	2015	Australia	2007–2013	104	Retrospective, observational, case series	H
Burrell	2018	Australia	2007–2013	144	Retrospective, observational	H
Cakici	2017	Turkey	2010–2015	148	Retrospective, case series	H
de Chambrun	2016	France	2007–2015	94	Retrospective	H
den Uil	2017	Netherlands	2004–2016	132	Retrospective, database	H
Distelmaier	2016	Austria	2003–2014	385	Prospective	M
Elsharkawy	2010	USA	1995–2006	233	Retrospective	M
Flecher	2014	France	2005–2013	325	Retrospective	H
Hei	2011	China	2004–2009	68	Retrospective	M
Hsu	2010	Taiwan	2002–2006	51	Retrospective	H
Kara	2016	Netherlands	2014–2015	24	Prospective	M
Karatolios	2016	Germany	2013–2015	17	Retrospective	M
Kim	2012	Korea	2006–2010	27	Retrospective	M
Kuroki	2016	Japan	2005–2014	217	Retrospective	H
Lee	2012	Korea	2005–2010	118	Retrospective	M
Lee	2017	Korea	2010–2014	135	Retrospective, observational	M
Liden	2009	Sweden	2000–2007	33	Retrospective	M
Loforte	2014	Italy	2006–2012	228	Retrospective, multi-center	M
Loforte	2012	Italy	2007–2011	73	Retrospective, single-center	M
Loforte	2015	Italy	2004–2012	119	Retrospective, single-center	M
Lorusso	2017	USA	1992–2015	4,673	Retrospective	M
Luo	2009	China	2005–2008	45	Prospective	H
Muehrcke	1996	USA	1992–1994	23	Retrospective	M
Muller	2016	France	2008–2013	138	Retrospective, multi-center	H
Muisal	2016	Poland	2009–2015	29	Retrospective	M
Ranney	2017	USA	2009–2015	131	Retrospective	H
Russo	2010	Italy	1988–2005	15	Retrospective	M
Salna	2018	USA	2007–2016	192	Retrospective	H
Saxena	2015	USA	2003–2013	45	Retrospective	M
Schmidt	2015	USA	2003–2013	3,846	Retrospective	M
Schopka	2015	Germany	2007–2014	68	Retrospective	H
Sharma	2015	Netherlands	2007–2012	66	Retrospective	IM
Takayama	2015	USA	2007–2013	101	Retrospective	H
Takayama	2013	USA	2007–2012	90	Retrospective	H
Tsai	2017	Taiwan	2002–2011	105	Retrospective	H
Wang	2013	China	2004–2011	87	Retrospective	M
Willms	1997	USA	1986–1995	81	Retrospective	M
Yeh	2018	Taiwan	2009–2012	99	Retrospective	M
Zhong	2017	China	2009–2016	36	Retrospective	M

Table S2 Study characteristics

Study (author)	Year	Region	Cohort (n)	Male (n)	Central ECMO (n)	Peripheral ECMO (n)	Age (survivors/non-survivors), mean ± SD/range (year)	BMI, mean ± SD (kg/m²)	BSA, mean ± SD (m²)	CPB (n)	CPB, mean ± SD (min)	CPR (n)	CPR, mean ± SD (%)	Lactate, mean ± SD (mmol/L)	Creatinine, mean ± SD (mg/dL)	Time on ECMO, mean ± SD (hours)	IABP (n)	Pre-operative LVEF, mean ± SD (%)
Aso	2016	Japan	4,658	3,399	–	–	64.8 (13.7)	–	–	–	–	–	–	–	–	–	2,830	–
Aubin	2017	Germany	160	122	–	–	56±16	–	2.02±0.24	–	–	102	30	9	1.4	96	–	–
Bakhtiary	2008	Germany	45	35	8	37	60.1±13.6	26.7±4.1	–	45	156.6±66.1	31	–	–	–	153.6±108	30	25.8±10
Bougouin	2017	France	52	38	–	–	56±10	–	–	–	–	39	–	9.2±5	–	–	–	–
Boulate	2013	France	55	44	9	46	51.2	–	1.9	–	–	–	–	1.5	99.5	192	–	15
Burrell	2015	Australia	104	72	28	76	49 [36–58]	25 [22–28]	–	–	–	–	–	6.4 (3.6–10.9)	114 [84–163]	168±120	–	–
Burrell	2018	Australia	144	95	30	114	48 [36–58]	25 [22–27]	–	–	–	126	–	6 [3–10]	118 [90–168]	168	–	–
Cakici	2017	Turkey	148	99	14	134	56.6±12	25.2±4	1.85±0.19	–	–	–	–	>200	1.72±1.03	173.28	–	25.1±4.8
de Chambrun	2016	France	94	71	–	–	50.8±11.5	26.2 (23.4–29.3)	–	–	–	–	–	–	–	96	47	–
den Uil	2017	Netherlands	132	73	5	127	47±16	–	–	–	–	–	–	8.4±5.9	147±74	144	34	–
Distelmaier	2016	Austria	385	271	39	346	65 [55–72]	27 [24–30]	–	–	–	30	20 [11–30]	–	1.3 (1.1–1.8)	–	–	–
Elsharkawy	2010	US	233	157	77	156	59.7/53.5	27.1/26.7	–	–	–	–	–	–	–	–	22	–
Flecher	2014	France	325	179	–	–	54±15	–	–	–	–	–	–	7±5	171±99	–	–	–
Hei	2011	China	68	52	–	–	47.7/52	–	–	–	–	22	22.7/33.9	8.7/9.6	–	–	11	–
Hsu	2010	Taiwan	51	36	–	–	63.0±15.7	25.1±4.1	–	–	–	–	–	–	–	180±160.8	–	40.1±17.9
Kara	2016	Netherlands	24	16	–	–	56 [20–70]	24.5 [19–37]	–	–	–	–	–	4.1 (1.1–26)	2,771	57.6	–	15
Karatolios	2016	Germany	17	15	–	17	63.39±10.50	–	–	–	–	–	–	5.51±2.1	–	–	–	25.31±0.21
Kim	2012	Korea	27	16	–	–	63.7±11.0	–	–	–	–	21	–	5.3±4.5	1.4±0.8	30.2±30.1	2	–
Kuroki	2016	Japan	217	180	–	–	58.9±15	24.0±4.9	–	–	–	188	–	10.8±5.7	1.5±1.3	77.185±79.3	146	–
Lee	2012	Korea	118	61	–	–	56.14±14.67	–	1.7±0.2	–	–	–	–	–	–	112.07±154.5	35	–
Lee	2017	Korea	135	94	0	135	59.44±16.55	24.61±3.36	–	–	–	102	54.69±39.55	10.7±5.33	1.9±2.28	99.6±103.23	22	–
Liden	2009	Sweden	33	31	21	31	52.4±12.7	–	–	–	–	–	–	–	–	–	–	–
Loforte	2014	Italy	228	123	102	126	58.3±10.5	–	–	155	214.49	185	28	13.42	–	244.8±175.2	42	–
Loforte	2012	Italy	73	54	0	73	60.3±11.6	–	–	58	205.83	65	26.6	13.63	–	244.8±175.2	16	–
Loforte	2015	Italy	119	79	64	55	57.3±12.5	–	–	73	211.26	90	27.7	13.27	–	–	44	–
Lorusso	2017	US	4,673	3,111	–	–	49.5±13.8	–	–	–	–	–	–	–	–	138±146	–	–
Luo	2009	China	45	34	4	41	49±14.1	–	–	–	–	–	–	–	–	126.7±104.3	22	–
Muehrcke	1996	US	23	17	–	–	47.3±16.4	–	1.86	–	–	–	–	–	–	70.8±103.9	17	–
Muller	2016	France	138	110	16	122	55 [46–63]	26	–	–	–	–	–	4.1	–	168	96	–
Muisal	2016	Poland	29	19	–	29	42	–	–	–	–	–	–	–	–	–	–	–
Ranney	2017	US	131	89	36	95	56.4±13.5	30.1±7.7	–	–	–	–	–	–	–	96	–	–
Russo	2010	Italy	15	10	7	8	44.7±20	–	–	–	–	–	–	–	–	276±194.4	12	–
Salna	2018	US	192	137	142	50	58 [48–67]	28.1	1.99±0.26	–	–	–	–	–	–	96	–	–
Saxena	2015	US	45	31	30	15	76.8±4.6	–	–	–	–	5	–	–	–	103.8±74.3	6	–
Schmidt	2015	US	3,846	2,548	–	–	54 [39–64]	–	–	–	–	–	–	–	–	100	410	–
Schopka	2015	Germany	68	53	–	68	53 (27.1–74.7)	27.7	–	–	–	54	–	–	–	120	–	–
Sharma	2015	Netherlands	66	39	7	59	60 [49–67]	–	–	–	–	–	–	–	–	72	–	–
Takayama	2015	US	101	67	–	–	–	29	–	–	–	–	–	5.7±4.1	1.9±1.19	–	41	–
Takayama	2013	US	90	64	–	–	53.1±13.6	28.4±7.1	–	–	–	21	–	–	–	–	54	–
Tsai	2017	Taiwan	105	70	–	–	57±14	–	–	–	–	–	–	95±65	1.71±2.17	–	–	–
Wang	2013	China	87	59	–	–	65±7	–	–	87	182±93	–	–	11.9±4.2	–	61±37	41	46±12
Willms	1997	US	81	56	–	–	62.7±13.6	–	–	–	–	–	–	–	–	–	–	–
Yeh	2018	Taiwan	99	77	–	99	76.4±6.4	–	–	–	–	–	–	–	–	124.8±124.8	–	–
Zhong	2017	China	36	33	7	29	50.4±12.2	25.4±4.25	1.82±0.23	36	279±190.25	–	–	–	–	86.4±69.6	9	–

The results presented are in weighted means, inter-quartile ranges, or n/%, ± standard deviation. Survival was considered to be at primary discharge. Characteristics were combined where presented. BMI, body mass index; BSA, body surface area; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction.

Study or Subgroup	Survivors Events	Total	Non–Survivors Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
1.1.1 ARDS						
Aubin, 2017	17	59	49	101	5.7%	0.43 [0.22, 0.85]
Elsharkaw, 2010	13	84	36	149	5.6%	0.57 [0.29, 1.16]
Subtotal (95% CI)		143		250	11.2%	0.50 [0.30, 0.81]
Total events	30		85			
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.1.2 AKI						
Aubin, 2017	14	59	61	101	5.5%	0.20 [0.10, 0.42]
Burrell, 2015	40	80	17	21	3.4%	0.24 [0.07, 0.76]
Elsharkaw, 2010	22	84	79	149	6.3%	0.31 [0.18, 0.56]
Hei, 2011	6	43	15	25	3.4%	0.11 [0.03, 0.35]
Wang, 2013	6	43	16	44	3.9%	0.28 [0.10, 0.82]
Subtotal (95% CI)		309		340	22.4%	0.24 [0.17, 0.35]
Total events	88		188			
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 7.48 (P < 0.00001)						
1.1.3 Liver Dysfunction						
Aubin, 2017	7	59	27	101	4.5%	0.37 [0.15, 0.91]
Burrell, 2015	16	80	12	21	4.0%	0.19 [0.07, 0.52]
Subtotal (95% CI)		139		122	8.5%	0.27 [0.14, 0.54]
Total events	23		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 3.74 (P = 0.0002)						
1.1.4 Bleeding						
Aubin, 2017	24	59	48	101	5.9%	0.76 [0.40, 1.45]
Burrell, 2015	26	80	11	21	4.2%	0.44 [0.16, 1.16]
Hei, 2011	13	43	9	25	3.9%	0.77 [0.27, 2.19]
Muller, 2016	6	65	11	73	3.9%	0.57 [0.20, 1.65]
Zhong, 2017	2	18	7	18	2.0%	0.20 [0.03, 1.13]
Subtotal (95% CI)		265		238	19.8%	0.60 [0.40, 0.92]
Total events	71		86			
Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 4 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
1.1.5 GI Bleeding						
Elsharkaw, 2010	5	84	10	149	3.7%	0.88 [0.29, 2.67]
Hei, 2011	1	43	2	25	1.1%	0.27 [0.02, 3.18]
Subtotal (95% CI)		127		174	4.8%	0.72 [0.26, 1.98]
Total events	6		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.1.6 Stroke/CVA						
Aubin, 2017	11	59	32	101	5.2%	0.49 [0.23, 1.08]
Burrell, 2015	5	80	2	21	2.0%	0.63 [0.11, 3.52]
Elsharkaw, 2010	3	84	20	149	3.2%	0.24 [0.07, 0.83]
Hei, 2011	1	43	6	25	1.4%	0.08 [0.01, 0.67]
Wang, 2013	4	43	2	44	2.0%	2.15 [0.37, 12.42]
Zhong, 2017	1	18	3	18	1.2%	0.29 [0.03, 3.14]
Subtotal (95% CI)		327		358	14.9%	0.43 [0.21, 0.88]
Total events	25		65			
Heterogeneity: Tau² = 0.22; Chi² = 7.00, df = 5 (P = 0.22); I² = 29%						
Test for overall effect: Z = 2.32 (P = 0.02)						
1.1.7 Infection						
Aubin, 2017	5	59	14	101	3.8%	0.58 [0.20, 1.69]
Elsharkaw, 2010	2	84	18	149	2.5%	0.18 [0.04, 0.79]
Hei, 2011	13	43	9	25	3.9%	0.77 [0.27, 2.19]
Muller, 2016	13	65	3	73	3.0%	5.83 [1.58, 21.53]
Wang, 2013	7	43	6	44	3.4%	1.23 [0.38, 4.02]
Zhong, 2017	2	18	3	18	1.7%	0.63 [0.09, 4.28]
Subtotal (95% CI)		312		410	18.3%	0.87 [0.37, 2.07]
Total events	42		53			
Heterogeneity: Tau² = 0.73; Chi² = 13.61, df = 5 (P = 0.02); I² = 63%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		1622		1892	100.0%	0.45 [0.34, 0.59]
Total events	285		528			
Heterogeneity: Tau² = 0.24; Chi² = 50.56, df = 27 (P = 0.004); I² = 47%						
Test for overall effect: Z = 5.65 (P < 0.00001)						
Test for subgroup differences: Chi² = 17.04, df = 6 (P = 0.009); I² = 64.8%						

Odds Ratio M–H, Random, 95% CI — scale: 0.01 0.1 1 10 100 — Favours [experimental] Favours [control]

Figure S2 Forest plot analysis: in-hospital complications. Forest plot analysis illustrating outcomes; survivors (i.e., experimental) compared to non-survivors (i.e., control). Note: survivors were less likely to have infection in this analysis, but the result is not statistically significant.