Peripheral versus Central Extracorporeal Membrane Oxygenation for Postcardiotomy Shock: Multicenter Registry, Systematic Review and Meta-analysis

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Glossary of Abbreviations

CI	= confidence interval
CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenation
ICU	= intensive care unit
IABP	= intra-aortic balloon pump
IQR	= interquartile range
OR	= odds ratio
PCS	= postcardiotomy cardiogenic shock
RBC	= red blood cell
RR	= risk ratio
SD	= standard deviation
UDPB	= universal definition of perioperative bleeding
VAD	= ventricular assist device
VA	= veno-arterial

Central message

In postcardiotomy shock, peripheral cannulation for veno-arterial extracorporeal membrane oxygenation may be associated with lower hospital mortality and complications than central cannulation.

Short legend for the central figure: In patients affected by postcardiotomy shock following cardiac surgery, the peripheral cannulation VA-ECMO cohort exhibited lower rates in terms of in-hospital mortality, reopening for bleeding, and blood transfusion.

Perspective Statement

The optimal cannulation strategy during veno-arterial extracorporeal membrane oxygenation for patients affected by postcardiotomy shock remains controversial. Our study suggests that peripheral cannulation may provide better outcome than central cannulation. These data are corroborated by current literature.

ABSTRACT

Background: We hypothesized that cannulation strategy in veno-arterial extracorporeal membrane oxygenation (VA-ECMO) could play a crucial role in the perioperative survival of patients affected by postcardiotomy shock.

Methods: Between January 2010 and March 2018, 781 adult patients receiving VA-ECMO for postcardiotomy shock at 19 cardiac surgical centers were retrieved from the PC-ECMO registry. A parallel systematic review and meta-analysis (PubMed/MEDLINE, Embase, and Cochrane Library) through December 2018 was also accomplished.

Results: Central and peripheral VA-ECMO cannulation were performed in 245 (31.4%) and 536 (68.6%) patients, respectively. Main indications for the institution VA-ECMO were failure to wean from cardiopulmonary bypass (38%), and heart failure following cardiopulmonary bypass weaning (48%).

The doubly robust analysis after inverse probability treatment weighting by propensity score demonstrated that central VA-ECMO was associated with higher hospital mortality (odds ratio 1.54; 95% confidence interval, 1.09-2.18), reoperation for bleeding/tamponade (odds ratio, 1.96; 95% confidence interval, 1.37-2.81), and transfusion of more than 9 RBC units (odds ratio, 2.42; 95% confidence interval, 1.59-3.67).

The systematic review provided a total of 2491 postcardiotomy shock individuals treated with VA-ECMO. Pooled prevalence of in-hospital/30-day mortality in overall patient population was 66.6% (95% confidence interval, 64.7-68.4%), and pooled unadjusted risk ratio analysis confirmed that patients undergoing peripheral VA-ECMO had a lower in-hospital/30-day mortality than patients undergoing central cannulation (risk ratio, 0.92; 95% confidence interval, 0.87-0.98). Adjustments for important confounders did not alter our results.

Conclusions: In patients with postcardiotomy shock treated with VA-ECMO, central cannulation was associated with higher in-hospital mortality than peripheral cannulation.

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INTRODUCTION

Postcardiotomy cardiogenic shock (PCS) is a fatal condition, affecting 0.5% to 1.5% of adult patients undergoing cardiac surgery.[1,2] Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) has been proven to be a valid rescue option for patients affected by PCS, providing temporary mechanical circulatory support, favouring cardiopulmonary recovery and treatment of the underlying cardiac disease.[3,4] However, complications following VA-ECMO support are not remote, and unfavourable outcomes are often observed.[1,2] In this context, the "central" VA-ECMO access, with direct cannulation of the ascending aorta and right atrium, and the "peripheral" access, with cannulation of the femoral artery and vein, seem to contribute significantly to the outcome of PCS patients managed with this mechanical support.[5-19] The optimal cannulation strategy remains controversial, especially for its potential impact on myocardial recovery, rate of complications and postoperative survival.[5-20]

We report the results of the large multicentre "Postcardiotomy Veno-arterial Extracorporeal Membrane Oxygenation" study (PC-ECMO), analysing the impact of VA-ECMO cannulation strategy in PCS patients. A supporting systematic review and meta-analysis of studies, which considered the relationship between central/peripheral VA-ECMO cannulation and early outcomes in PCS patients, is also presented.

METHODS

PC-ECMO Study Cohort

The PC-ECMO registry is an observational multicentre cohort study that enrolled patients undergoing VA-ECMO following adult cardiac surgery at 19 centres from Belgium, Czech Republic, Finland, France, Germany, Italy, Saudi Arabia, Sweden and the United Kingdom from January 2010 to March 2018. The present study is registered in Clinicaltrials.gov (Identifier: NCT03508505). Data were collected in a dedicated Access database (Microsoft Inc, Redmond, WA), and underwent cross-checking validation to ensure high data quality. Transcriptional discrepancies were harmonized; clinical and temporal conflicts and extreme values were corrected or removed.

The present study was approved by the Regional or Institutional Review Board of the participating centres, and it was not financially supported. The study complies with the Strengthening the Reporting

of Observational Studies in Epidemiology reporting requirements for observational studies (Sub-appendix I).[21]

Study Design and Outcome Measures

Patients aged ≥18 years who required VA-ECMO for PCS following cardiac surgery were included. Exclusion criteria encompassed patients with preoperative VA-ECMO, or those receiving VA-ECMO after implantation of ventricular assist device (VAD) or heart transplantation. Patients with an open or hybrid repair of the descending thoracic aorta were also excluded. For each patient, baseline characteristics, demographics, comorbidities, intraoperative factors, postoperative outcomes, and ECMO-related data were collected. Variables were defined according to the EuroSCORE 2 definition criteria and to the ELSO (Extracorporeal Life Support Organisation (ELSO) registry.[22,23] A cut-off of 9 units of red blood cell (RBC) as per the universal definition of perioperative bleeding (UDPB) in adult cardiac surgery was adopted as marker for massive bleeding.[24] The primary end-point was in-hospital mortality. Main secondary end-points are defined in Appendix and included death on VA-ECMO, reoperation for bleeding/tamponade, RBC transfusion, postoperative neurological, renal, cardiac and gastrointestinal complications, vascular complications, sternal wound infection, and length of stay in the intensive care unit (ICU).

Systematic Review and Meta-Analysis

The review adhered to MOOSE (MetaAnalysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) guidelines (Sub-appendixes II and III)[25,26] Complete details, including electronic search strategy, objectives, criteria for study selection, eligibility, and data collection were published online and registered in the International Registry of Systematic Reviews PROSPERO (CRD420160488140).[27] Briefly, literature searches were systematically performed with electronic databases (PubMed/MEDLINE, Embase, and Cochrane Library) without date or language restriction from inception to the end of December 2018. References of all eligible studies and review articles were also screened to identify relevant resources that were not previously recognised. Only studies comparing central versus peripheral arterial ECMO cannulation in patients affected by PCS after cardiac surgery were considered for this analysis. The primary outcome

of interest was all-cause mortality in-hospital or within 30 days from the index surgical procedure. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to the PICOS (Population, Intervention, Comparator, Outcomes, and Study design) approach (Table I in the Appendix). Year of publication, study design, country, sample size, recruitment period, number of patients in each treatment group, inclusion and exclusion criteria, measured outcomes, baseline patient demographics, cardiac status, comorbidities, and outcomes were extracted. Reasons for exclusion were also documented (Table II in the Appendix). Finally, study quality was assessed using the Newcastle-Ottawa Scale and the US Preventive Services Task Force criteria.[28,29] The Cochrane Risk of Bias tool was also used to evaluate the methodological quality of all included studies.[30]

Statistical Analysis

Analyses we conducted according to the intention-to-treat-analysis. In the PC-ECMO study, covariates and outcomes were reported as counts and percentages, and as mean and standard deviation (SD) or median and interquartile range (IQR). Unpaired *t*-test, Mann-Whitney *U*-test, Fisher's exact test, Chi-square test, and Kruskal-Wallis tests were used for univariable analyses, as appropriate.

A covariate balancing propensity score (CBPS) was developed to minimize the covariate imbalance between the central and the peripheral VA-ECMO cohorts.[31] In our study a total of 67 covariates including preoperative baseline, operative characteristics, indications for VA-ECMO and timing of ECMO insertion were used in the model. The full list of these covariates is listed in Tables 1, and Tables III and IV in the Appendix. Using the estimated propensity scores as weights, an inverse probability weighting (IPW) model was used to generate a weighted cohort.[32] C-statistics were calculated to ascertain the validity of the propensity score. Finally, to adjust for confounding related to the central and peripheral VA-ECMO insertion, a doubly robust method that combines regression model with inverse probability treatment weighting (IPTW) by propensity score was adopted to estimate the causal effect of the exposure on the outcomes of interest.[33] Statistical analyses were performed using the cobalt package of R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).[34,35]

In the meta-analysis, outcomes of interest were reported as risk ratio (RR) with a 95% confidence interval (CI), using the Mantel–Haenszel method or as pooled prevalence of adverse outcome.[36] I^2 statistic was used to estimate the percentage of total variation across studies attributed to heterogeneity

rather than chance.[37] Cochran's Q test for heterogeneity was applied.[30] Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test.[38] The impact of age, gender, pulmonary disease, coronary artery bypass grafting, prior cardiac surgery, intra-aortic balloon pump (VA-ECMO) during VA-ECMO support, and delayed VA-ECMO implantation on in-hospital/30-day mortality was evaluated by meta-regression. Finally, to account for inherent patient selection bias related with the observational design of the included studies, risk-adjusted estimates for ORs for in-hospital/30-day mortality were obtained when reported, and pooled adjusted risk estimates were computed by using log transformation and a generic inverse-variance weighting method. For the meta-analysis, analyses were conducted using the *metafor* and *meta* packages of R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).[34,39-41] $P<0.05$ was used as the level of significance for all tests.

RESULTS

PC-ECMO Study Cohort

The patient population comprised a total of 781 patients with a mean age of 63.1 ± 12.9 years (range: 18.4-86.7), and 32% were women. Baseline characteristics are detailed in Table 1 and Table III in the Appendix. Central and peripheral ECMO cannulation were performed in 245 (31.4%) and 536 (68.6%) patients, respectively. Among centers, the prevalence of peripheral and central cannulation varied from 25% to 94% and from 5% to 69%, respectively. Data regarding indications, timing and cannulation, are detailed in Table IV in the Appendix. Main indications for VA-ECMO implantation included failure to wean from cardiopulmonary bypass (CPB, 38%), and heart failure following CPB weaning (48%). A greater proportion of patients received central cannulation in case VA-ECMO was inserted immediately after surgery ($P<0.001$), and peripheral cannulation was predominantly initiated later after surgery ($P<0.01$). Left ventricular venting and IABP were more frequently adopted in the central cannulation group (18% *versus* 3.5%, $P<0.001$ and 46.5%% *versus* 30.6%, $P<0.001$, respectively). Twenty-three (9.4%) patients were switched from central to peripheral cannulation to allow definitive chest closure.

Overall, patients receiving peripheral and central VA-ECMO cannulation exhibited different demographic, clinical, and operative characteristics (Tables III and IV in the Appendix). Briefly, the

central group was younger (61.5±14.0 *versus* 63.9±12.3, *P*=0.019), and had longer CPB duration (median 220 min [IQR, 150-308 min] *versus* median 200 min [IQR, 123-280 min]; *P*=0.012).

Outcome data are summarized in Tables 2 and in Tables V in the Appendix, and full details of the overall population after exclusion of patients switched from central to peripheral cannulation are detailed in Tables VII to IX in the Appendix. As shown in the supplementary Tables VI and X, and in the supplementary Figures I to III, all the covariate of the weighted cohort resulted balanced between groups. The *C* statistics of the propensity score for VA-ECMO cannulation was 0.7499. Under the doubly robust estimation framework, the regression models demonstrated that central VA-ECMO was associated with a significantly higher risk of in-hospital mortality (OR 1.54; 95% CI, 1.09-2.18; *P*=0.02), reoperation for bleeding/tamponade (OR 1.96; 95% CI,1.37-2.81; *P*<0.001), and transfusion of more than 9 RBC units (OR 2.42; 95% CI, 1.59-3.67; *P*<0.001) (Figure 1). Peripheral VA-ECMO was instead associated with longer hospital stay (linear regression estimate, -5.79; standard error, 2.49; *P*=0.02), vascular access site infections (OR 3.98 95% CI, 1.70-9.34; *P*=0.002), liver failure (OR 1.52 95% CI, 1.09-2.33; *P*=0.02) and sepsis (OR 1.56 95% CI, 1.01-2.841; *P*=0.05). No differences were observed between the two groups with reference to peripheral vascular complications (OR, 0.80; 95% CI, 0.43-1.48, *P*=0.47) or other organ dysfunctions. Outcomes did not change after the exclusion of patients switched from central to peripheral cannulation to allow for definitive chest closure (Table IX in the Appendix), and the year of operation did not impact on mortality (range: 58% to 85%, *P*=0.26; Figure IV in the Appendix).

Finally, the relationship between hospital volume and VA-ECMO was also analyzed, and centers with larger experience with postcardiotomy VA-ECMO (>50 cases of postcardiotomy VA-ECMO during the study period) used less frequently the central cannulation approach (24.7% *versus* 42.9%, *P*<0.0001), although no differences in outcomes were observed (Table XI in the Appendix).

Sensitivity analyses and variable interactions that considered gender, age, prior cardiac surgery, preoperative left ventricular ejection fraction, coronary artery bypass grafting, history of stroke, urgent/emergent status, and arterial lactate pre-ECMO insertion ≥ 6 mmol/L showed that central cannulation impacted on in-hospital mortality in the absence of significant interactions with these

covariates (Figure 2). The timing of ECMO insertion did not interact with the cannulation strategy in influencing hospital mortality, and other secondary outcomes (Table XII and Figures II and III in the Appendix).

Systematic Review and Meta-analysis

Literature search yielded a total of 6 286 records, and 15 retrospective studies (2 multicenter, 13 single-center) published between 2005 and 2016 were finally included in the systematic review and meta-analysis (Figure V in the Appendix).[6-19] Study characteristics and collected outcomes for PCS patients undergoing VA-ECMO support are summarized in the Tables XIII-XV in the Appendix, and study quality assessment in Table XVI. Including the PC-ECMO study cohort, the final population for the meta-analysis comprised 2491 patients. Pooled prevalence of in-hospital/30-day mortality in the overall patient population was 66.6% (95% CI, 64.7-68.4%). Pooled unadjusted RRs showed that PCS patients undergoing peripheral VA-ECMO had a lower in-hospital/30-day mortality when compared with those undergoing central cannulation (RR 0.92; 95% CI 0.87–0.98; *P*=0.011; Figure 3). Low heterogeneity among studies (I^2=4%) was observed, and funnel plots revealed no evidence of publication bias (*P* =0.41; Figure VI in the Appendix). To evaluate the robustness of the associated results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary RRs. A beneficial effect of the peripheral VA-ECMO in terms of reduced in-hospital/30-day mortality was observed by removing the study of Rastan et al.,[6] an outlier in term of in-hospital mortality (Figure VII in the Appendix). Again, peripheral VA-ECMO was associated with lower in-hospital/30-day mortality than central VA-ECMO (RR 0.88; 95% CI 0.82–0.95; *P*=0.0005), but no heterogeneity was observed (I^2=0%, Figure VIII in the Appendix). Overall, 2 studies with the present one reported on adjusted effect size of VA-ECMO cannulation site on mortality (Table XV in the Appendix).[6,11] Adjusted risk estimates of in-hospital/30-day mortality reveal no differences in in-hospital/30-day mortality between the two cohorts of patients (RR 1.27; 95% CI 0.88–1.83; *P*=0.21, Figure IX in the Appendix).

Pooled estimates also demonstrated that peripheral VA-ECMO cannulation was also associated with a lower rate of reoperation for bleeding/tamponade (RR 0.63; 95% CI 0.54–0.73; I^2=0%). No differences were observed for neurological events (RR 0.79; 95% CI 0.59–1.05; I^2=0%) and lower limb

complications (RR 1.60; 95% CI 0.99–2.89; I^2=32.7%) between peripheral and central cannulation (Figures IX-XI in the Appendix). Meta-regression analysis confirmed that covariates did not represent a source of heterogeneity (Figure XII in the Appendix).

DISCUSSION

In the present cohort study, PCS patients treated with peripheral VA-ECMO had better in-hospital survival than those with central cannulation. This observation was supported by a large systematic review of 15 studies that included nearly 2500 patients from 15 countries, and by a sensitivity analyses which have also substantiated these observations in older patients, in those with severe coronary artery disease, reduced left ventricular function, pre-ECMO organ failure, and in patients requiring complex and urgent/emergent cardiac operations.

The above results are important in light of the increasing use of ECMO for refractory PCS, providing temporary circulatory support, allowing myocardial recovery as well as bridging of patients for further diagnostic and therapeutic options.[1-4] However, despite refinements in ECMO components and improvements in ICU management, mortality remains high, ranging from 43% to 85%, even in patients who were successfully weaned from VA-ECMO.[6-19] The rate of complications is also not negligible, including multiorgan failure, bleeding, vascular complications and infections.[6-19] As a consequence, several efforts have been made to identify risk factors that are most likely associated with poor outcomes following ECMO initiation. In this context, the optimal cannulation strategy for VA-ECMO in terms of in-hospital mortality and complications remains unsettled.[6-20] Central configuration favors better cardiac unloading with an antegrade flow and multiple options for left ventricular venting, although higher risks of bleeding, cerebral emboli, systemic infections and cardiac compression are often encountered.[6-20] Peripheral cannulation is faster, less invasive allowing for sternal closure, early extubation, beneficial in terms of bleeding and infections, whereas suboptimal venous drainage and LV unloading, harlequin syndrome, compromised ECMO flow, and vascular complications are the typical drawbacks.[6,20] Ko et al.[5] firstly investigated the impact of ECMO delivered by different cannulation routes in the outcomes of 76 patients affected by PCS, concluding that the underlying cardiac disease rather than the cannulation

site influenced patient outcomes. Similarly, Rastan et al.[6] reported the lack of clinical benefits exerted by the cannulation strategy in a cohort of 517 adult PCS patients treated with VA-ECMO. Consonant data have been recently observed by Raffa et al.[20] in a meta-analysis of peripheral *versus* central ECMO. However, patients affected by postcardiotomy and non-postcardiotomy shock were indistinctly included, hindering the generalizability of their results in the specific setting of refractory PCS following cardiac surgery.[20]

In our cohort study and the accompanying systematic review with meta-analysis, we included only patients who were affected by PCS following cardiac surgery and treated with VA-ECMO support. The higher rate of major bleeding, chest reopening for bleeding/tamponade, and the need for a large amount of blood product transfusions encountered in the central cannulation group seemed to play a harmful role in patient survival. Administration of large volumes of blood products is unavoidably related to the risks of transfusion-associated circulatory overload, and transfusion-related acute lung injury, both potentially fatal conditions especially in patients with an already impaired cardiac function.[42,43] In our series, 80% of the patients with central cannulation required transfusion of more than nine RBC units, and an indirect negative impact on patient outcomes has been reported even after transfusion of as little as 1 or 2 RBC units.[44] Therefore, the correlation between central cannulation and higher in-hospital mortality observed in both our cohort study and in the systematic review is not surprising. As a matter of fact, bleeding, transfusion and reopening for bleeding/tamponade have been already recognized as common complications of the central VA-ECMO strategy.[5,9] Mikus et al.[9] reported a 95% rate of reopening for bleeding/tamponade in the central group, with a median number of 39 and 18 units of RBC and fresh frozen plasma units transfused, respectively. Decreased blood component utilization in this patient population has also been proven to decrease complications and improve survival, although a conservative transfusion policy is difficult in this very critically ill patient population.[45] Therefore, the potential beneficial aspects of the central ECMO cannulation with antegrade flow, improved cardiac drainage, reduced cardiac compression (in case of open-chest), seem to be not justified by the present data, in that, these aspects have been largely overcome by the associated detrimental effects of major bleeding and blood transfusions.

Interestingly, although peripheral cannulation was associated with a higher risk of vascular site infections, this did not translate into reduced in-hospital survival. This observation is consistent with other published studies,[5,10,13] where the routine use of small cannula size, distal perfusion cannulas, and insertion of vascular grafts played a beneficial role. Another interesting finding from our study is the lack of differences in terms of hemodynamics and end-organ dysfunction between the two ECMO cannulation strategies. Saeed et al.[46] investigated the influence of femoro-femoral *versus* atrio-aortic ECMO on metabolic and hemodynamic data in a series of 52 patients affected by cardiogenic shock, respiratory distress syndrome, and pulmonary embolism. No differences in terms of hemodynamics, arterial blood gas values, and end-organ function were observed between groups.[46] Kanji et al.[47] confirmed similar mean peak lactate levels in both the peripheral and central cannulation populations. Finally, despite we did not document any significant difference in terms of neurologic, renal, and lung complications between the two cannulation strategies, an increased risk of liver failure was observed in the peripheral ECMO cannulation cohort possibly due to the associated suboptimal venous drainage and compromised ECMO flow as opposed to central venous drainage.[6] Similarly, a higher rate of sepsis, probably driven by vascular access site infections, was also observed in the peripheral patient cohort.

Our cohort study is not exempted from several limitations, although it is the largest registry evaluating the impact of ECMO cannulation strategy in the PCS setting. First, because of the observational nature of our registry, the present analysis is subjected to all limitations inherent to a non-randomized study. Nevertheless, the PC-ECMO registry included a large number of baseline and ECMO-related parameters as well as a consecutive series of patients treated in teaching and regional tertiary hospitals from different countries. This allowed the capture of a more inclusive patient population in centers with different referral pathways, preoperative selection criteria, and treatment strategies, rendering these results generalizable in different healthcare systems. Second, the limited number of patients in each subgroup prevented an adequate analysis of interinstitutional differences in terms of ECMO management and weaning protocols. Similarly, the impact of variables such as the axillary cannulation, the conversion from central to peripheral cannulation to allow primary chest closure on outcomes, and the LV unloading impact were not addressed in the present analysis; a limitation shared with all previously published experiences.[5-19] Third, we do not have data on whether the decision to leave the chest open and maintain

central cannulation was dictated by poorer patient conditions or excessive edema of the intrathoracic organs. Similarly, the meta-analysis has its own limitations. Principally, we were able to include a limited number of studies focusing on the impact of ECMO cannulation strategies among those effectively screened. The heterogeneity of the populations included, and the unclear inclusion/exclusion criteria prevented us from conducting a large study analysis.[5–19] Finally, owing to the emergent nature of PCS, no randomized trials of peripheral *versus* central ECMO cannulation were retrieved, therefore limiting our qualitative and quantitative analysis to observational studies only, often with limited sample size. The meta-analysis also had limitations. Principally, only a limited number of studies focusing on the outcome differences between central and peripheral VA-ECMO was included. Despite risk-adjusted estimates were obtained, we cannot exclude the presence of residual confounding factors between the peripheral and central VA-ECMO cohorts.

In summary, in the context of refractory PCS following cardiac surgery, peripheral VA-ECMO cannulation was associated with reduced in-hospital mortality, lower risk of reoperation for bleeding/tamponade, perioperative bleeding and blood transfusion requirements. Peripheral and central accesses in VA-ECMO revealed comparable results in terms of neurological, renal, pulmonary, and other complications.

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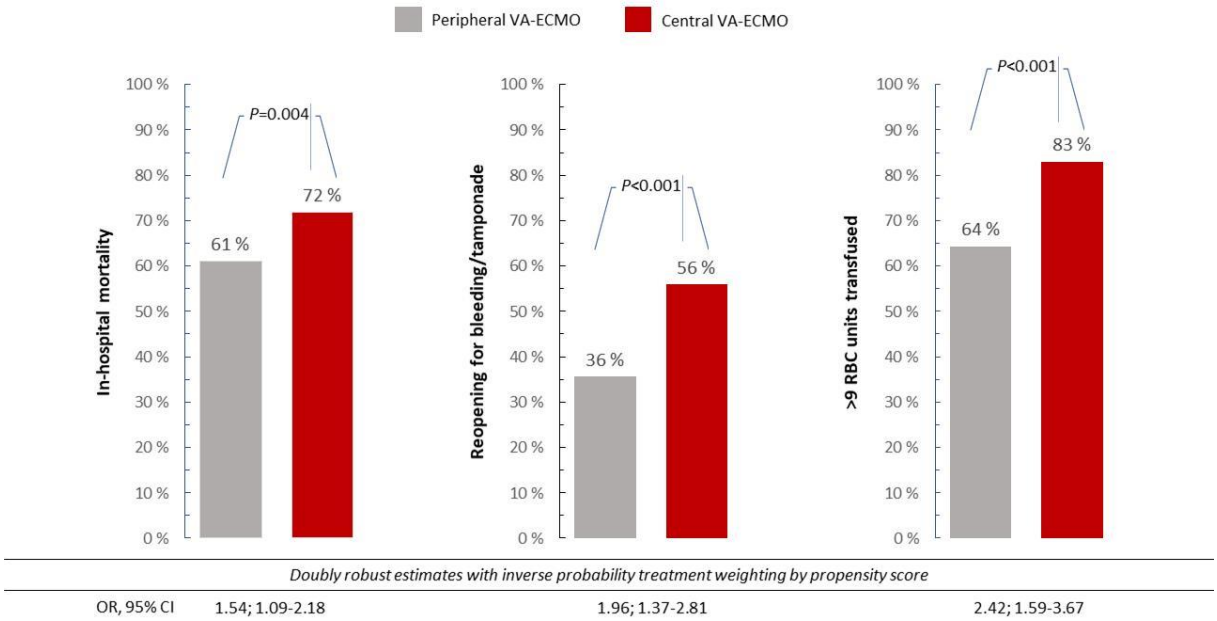


Figure 1. Central veno-arterial extracorporeal membrane oxygenation is associated with higher in-hospital mortality, reopening for bleeding, and blood transfusion than peripheral cannulation in patients affected by postcardiotomy shock following cardiac surgery. The obtained doubly robust estimates (odds ratio and 95% confidence intervals) with inverse probability treatment weighting by propensity score are shown for the main outcomes (group of reference: central cannulation). CI indicates confidence intervals; OR, odds ratio; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

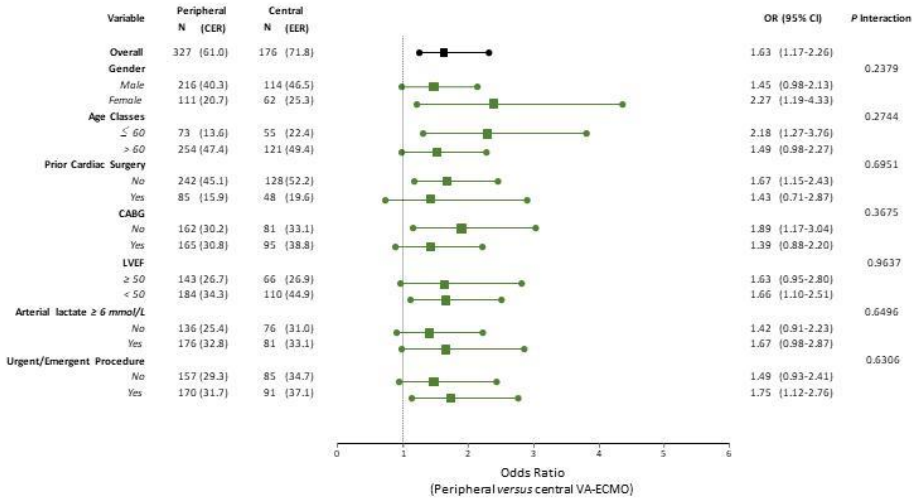


Figure 2. Sub-group analysis with reference to in-hospital mortality. Comparison is made between peripheral (reference group) and central VA-ECMO cannulation. CI indicates confidence interval; CABG, coronary artery bypass grafting; CER, control event rate; EER, experimental event rate; LVEF, left ventricular ejection fraction; OR, odds ratio.

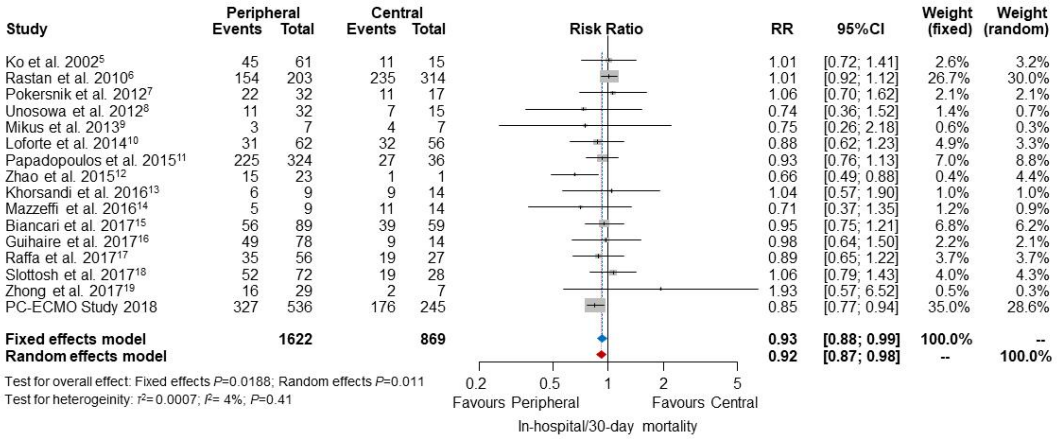


Figure 3. Forest plot with risk estimates for in-hospital/30-day mortality. CI indicates confidence interval; RR, risk ratio.

TABLE 1. Baseline characteristics patients receiving peripheral and central cannulation in the overall series*

Variables†	Overall series		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 245 pts	*P* value
Age, y	63.9 ± 12.3	61.5 ± 14.1	0.019
Female	172 (32.1)	77 (31.4)	0.92
BMI, kg/m^2	26.7 [23.9-30.0]	26.5 [23.3-29.8]	0.53
BMI>30 kg/m^2	136 (25.4)	61 (24.9)	0.96
Presentation and cardiac status			
Urgent/emergent procedure	288 (53.7)	127 (51.8)	0.68
Preoperative IABP	41 (7.6)	21 (8.6)	0.76
Prior cardiac surgery	123 (22.9)	63 (25.7)	0.45
CCS angina class IV	99 (18.5)	54 (22.0)	0.29
NYHA class III-IV	354 (66.0)	152 (62.0)	0.31
Prior MI	181 (33.8)	96 (39.2)	0.17
Prior PCI	105 (19.6)	41 (16.7)	0.39
LVEF 21-30%	89 (16.6)	47 (19.2)	0.44
LVEF <21%	41 (7.6)	26 (10.6)	0.22
Comorbidities			
Diabetes	131 (24.4)	69 (28.2)	0.31
Haemoglobin, g/L	125.6 ± 21.5	124.6 ± 22.7	0.54
eGFR, mL/min/1.73 m^2	66.5 [49.1-85.3]	65.0 [45.1-82.8]	0.31
Dialysis	25 (4.7)	7 (2.9)	0.32
Stroke	39 (7.3)	21 (8.6)	0.63
Extracardiac arteriopathy	77 (14.4)	43 (17.6)	0.29
Pulmonary disease	73 (13.6)	37 (15.1)	0.66
Atrial fibrillation	143 (26.7)	49 (20.0)	0.055
EuroSCORE 2, score	9.05 [3.63-9.48]	9.02 [3.37-26.83]	0.42

BMI, body mass index; *CCS*, Canadian Cardiovascular Society (class); *CPB*, cardiopulmonary bypass; *eGFR*, estimated glomerular filtration rate; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NYHA*, New York Heart Association (class); *PCI*, percutaneous coronary intervention; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Full baseline characteristics and operative data with standardized differences for the overall series are detailed in Table III in the Appendix.

†Continuous data are presented as mean ± standard deviation or median [interquartile range]; categorical variables as number (percent).

Table 2. Outcomes between patients receiving peripheral/central cannulation, and the doubly robust matching estimators for confounding adjustment*

Variables†	Overall series			Doubly robust adjustment‡		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 245 pts	*P* value	Odds Ratio	95% CI	*P* value
Primary end-point						
In-hospital mortality	327 (61.0)	176 (71.8)	0.004	1.54	1.09-2.18	0.02
Secondary end-points						
Reoperation for bleeding/tamponade	191 (35.6)	137 (55.9)	<0.001	1.96	1.37-2.81	<0.001
Stroke	93 (17.4)	55 (22.4)	0.11	1.11	0.72-1.71	0.65
Dialysis	286 (53.4)	123 (50.2)	0.29	0.84	0.60-1.19	0.34
Liver failure	205 (38.2)	60 (24.5)	<0.001	0.63	0.43-0.92	0.02
Multiorgan failure	279 (52.1)	111 (45.3)	0.09	0.85	0.60-1.21	0.37
DSWI	19 (3.5)	10 (4.1)	0.87	1.00	0.41-2.43	0.99
Vascular access site infection	60 (11.2)	7 (2.9)	<0.001	0.25	0.11-0.59	0.002
Sepsis	140 (26.1)	39 (15.9)	0.002	0.64	0.42-0.99	0.05
Peripheral vascular complications	49 (9.1)	20 (8.2)	0.76	0.80	0.43-1.48	0.47
RBC units transfused, u	15.0 [7.0-28.0]	21.0 [12.0-38.0]	<0.001	5.56§	2.07§	0.007§
More than 9 RBC units transfused	344 (64.2)	203 (82.9)	<0.001	2.42	1.59-3.67	<0.001
Chest drains 24 h output, mL	780 [500-1450]	1389 [750-2500]	<0.001	622.52§	132.76§	<0.001§
ICU stay, d	12.0 [5.0-24.0]	11.0 [5.0-21.0]	0.31	-1.26§	1.57§	0.42§
Hospital stay, d	17.0 [5.8-35.0]	13.0 [5.0-27.0]	0.04	-5.79§	2.49§	0.02§
More than 10 days on VA-ECMO	128 (23.9)	57 (23.3)	0.92	0.83	0.55-1.27	0.40
Successful weaning from VA-ECMO	271 (50.6)	108 (44.1)	0.11	0.74	0.53-1.06	0.10
Postoperative VAD or heart transplant	17 (3.2)	12 (4.9)	0.33	1.79	0.82-3.93	0.14

CI, confidence interval; *DSWI*, deep sternal wound infection; *ICU*, intensive care unit; *RBC*, red blood cell; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Full outcomes data in the overall series and the doubly robust matching estimators for confounding adjustment are detailed in Table V in the Appendix.

†Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

‡Reference for the events: central VA-ECMO group.

§Linear regression has been expressed as standard regression coefficient, standard error and *P* value.

ONLINE-ONLY DATA SUPPLEMENT

Peripheral versus Central Extracorporeal Membrane Oxygenation for Postcardiotomy Shock: Multicenter Registry, Systematic Review and Meta-analysis

Giovanni Mariscalco, Antonio Salsano, Antonio Fiore, Magnus Dalén, Vito G. Ruggieri, Diyar Saeed, Kristján Jónsson, Giuseppe Gatti, Svante Zipfel, Angelo M. Dell'Aquila, Andrea Perrotti, Antonio Loforte, Ugolino Livi, Marek Pol, Cristiano Spadaccio, Matteo Pettinari, Sigurdur Ragnarsson, Khalid Alkhamees, Zein El-Dean, Karl Bounader, Fausto Biancari, and the PC-ECMO group.

This supplementary material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTAL METHODS

Literature search strategy

Our keywords and MeSH terms pertinent to the exposure of interest were used in relevant combinations and they are showed below.

PubMed

Website	https://www.ncbi.nlm.nih.gov/pubmed
Access	December 31, 2018
Filters	none
Fields	Title, Abstract
Search terms	"extracorporeal membrane oxygenation" "extracorporeal life support" "ECLS" "ECMO" "cardiac surgery" "postcardiotomy" "cardiogenic shock" "outcomes" "mortality"
Number of articles	**4107** (3347+760)

Search 3347

("extracorporeal membrane oxygenation" or "extracorporeal life support" or "ECMO" or "ECLS") AND ("cardiac surgery" or "postcardiotomy" or "cardiogenic shock" or "postoperative")

Search 760

("extracorporeal membrane oxygenation" or "extracorporeal life support" or "ECMO" or "ECLS") AND ("outcomes" or "all-cause mortality") AND ("cardiac surgery" or "postcardiotomy" or "cardiogenic shock" or "postoperative")

EMBASE

Website	https://hdas.nice.org.uk/
Access	December, 31 2018
Filters	none
Fields	Title, Abstract
Search terms	"extracorporeal membrane oxygenation" "extracorporeal life support" "ECLS" "ECMO" "cardiac surgery" "postcardiotomy" "cardiogenic shock" "outcomes" "mortality"

Search **1117**

"((("extracorporeal membrane oxygenation" OR "extracorporeal life support" OR "ECMO" OR "ECLS") AND ("outcomes" OR "all-cause mortality")) AND ("cardiac surgery" OR "postcardiotomy" OR "cardiogenic shock" OR "postoperative")).ti,ab"

Cochrane Library

Website	https://www.cochranelibrary.com/search
Access	December, 31 2018

Search option Search Manager - Trials
Field Title, Abstract
Search terms "extracorporeal membrane oxygenation"
"extracorporeal life support"
"ECLS"
"ECMO"
"cardiac surgery"
"postcardiotomy"
"cardiogenic shock"
"outcomes"
"mortality"

Number of articles **720** (557 + 123 + 40)

Search 557
("extracorporeal membrane oxygenation" or "extracorporeal life support" or "ECMO" or "ECLS")

Search 123
("extracorporeal membrane oxygenation" or "extracorporeal life support" or "ECMO" or "ECLS") AND ("cardiac surgery" or "postcardiotomy" or "cardiogenic shock" or "postoperative")

Search 40
("extracorporeal membrane oxygenation" or "extracorporeal life support" or "ECMO" or "ECLS") AND ("outcomes" or "all-cause mortality") AND ("cardiac surgery" or "postcardiotomy" or "cardiogenic shock" or "postoperative")

Citations identified through "first-generation" reference list.

Study (Author/Year)	**Ref.N.**
Ko et al. 2002[1]	18
Rastan et al. 20102[2]	19
Pokersnik et al. 2012[3]	25
Unosowa et al. 2012[4]	18
Mikus et al. 2013[5]	25
Loforte et al. 2014[6]	25
Papadopoulos et al. 2015[7]	24
Zhao et al. 2015[8]	31
Khorsandi et al. 2016[9]	23
Mazzeffi et al. 2016[10]	21
Biancari et al. 2017[11]	21
Guihaire et al. 2017[12]	21
Raffa et al. 2017[13]	24
Slottosh et al. 2017[14]	24
Zhong et al. 2017[15]	21
Tot.	**340**

Outcome definitions

Neurological complications were defined according to the VARC-2 criteria:[16] "as acute episodes of a focal or global neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct"

Gastrointestinal complications were defined as any intestinal complication which required surgical intervention.

Peripheral vascular injury was defined as any of the following conditions: aortic rupture, type A aortic dissection, type B aortic dissection, peripheral artery dissection, vascular perforation, arterial thrombosis and major lower limb amputation.

Renal failure was defined as any use of renal replacement therapy after surgery. In the present study, we did not considered less severe grades of acute kidney injury because most of patients were expected to experience any significant increase in creatinine level postoperatively.

Supplemental Tables

Table I. PICOS criteria for inclusion and exclusion of studies into meta-analysis.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult patients (≥18 years)	-
Intervention	VA-ECMO for postcardiotomy syndrome	VA-ECMO before index cardiac surgery VA-ECMO after HTx/VAD VV-ECMO
Comparator	VA-ECMO cannulation site	No comparison between peripheral versus central VA-ECMO
Outcomes	Primary: in-hospital/30-day mortality Secondary (postoperative): re-exploration for bleeding/tamponade; CVA; RRT/dialysis; GI complications; limb ischemia; sepsis; successful ECMO weaning.	-
Study design	Clinical randomised trials Controlled before-and-after studies Prospective and retrospective cohort studies Cross-sectional studies Case-control studies	Repeat publications of the same analysis or dataset Conference abstracts Editorials & opinion pieces Books or grey literature

CVA, cerebrovascular accident; *GI*, gastro-intestinal; *HTx*, heart transplant; *RRT*, renal replacement therapy; *ECMO*, extracorporeal membrane oxygenation; *VA*, veno-arterial (ECMO); *VAD*, ventricular assist device.

Table II. List of studies excluded with reasons from the final systematic review and meta-analysis.

Study (Author, year)	Design	Country	Study period	Pts.N.	Reason for exclusion			
					Etiology for ECMO	NO Data on cannulation	Review/Editorial	Other
Acheampong et al. 2016[17]	Retr. Monoc.	USA	2001-2013	24		X		
Ariyaratnam et al. 2014[18]	Retr. Monoc.	UK	-	14		X	X	
Aso et al. 2016[19]	Retr. Monoc.	Japan	2010-2013	1650	Cardiogenic shock	X		
Bakhtiary et al. 2007[20]	Retr. Monoc.	Germany	2003-2006	20	Cardiogenic shock			
Bartko et al. 2017[21]	Retr. Monoc.	Austria	2003-2014	240		X		
Bata et al. 2018[22]	Retr. Monoc.	France	2005-2014	46		X		
Becher et al. 2018[23]	Retr. Multic.	Germany	2007-2015	8351	Mixed (PCS=0%)	X		No PCS data
Beiras-Fernandez et al. 2011[24]	Retr. Monoc.	Germany	1996-2006	108		X		Pediatric Pts
Charlesworth et al. 2017[25]	(Review)	UK	-	-			X	
Chen et al. 2018[26]	Retr. Monoc.	China	2006-2017	60		X		
Chen et al. 2018[27]	(Editorial)	USA	-	-			X	
Distelmaier et al. 2013[28]	Retr. Monoc.	Austria	2002-2009	191		X		
Distelmaier et al. 2018[29]	Retr. Monoc.	Austria	2003-2014	354		X		
Doll et al. 2003[30]	Retr. Monoc.	Germany	1997-2000	95		X		
Doll et al. 2004[31]	Retr. Monoc.	Germany	1997-2002	219		X		
Du et al. 2018[32]	Prosp. Monoc.	China	-	17		X		
Ellouze et al. 2018[33]	Retr. Monoc.	France	2014-2016	57	Mixed (PCS=33%)	X		
Elsharkawy et al. 2010[34]	Prosp. Monoc.	USA	1995-2005	233		X		
Formica et al. 2008[35]	Retr. Monoc.	Italy	2000-2007	25	Mixed (PCS=50%)	X		
Fukuhara et al. 2016[36]	(Review)	USA	-	-			X	
Fux et al. 2018[37]	Retr. Monoc.	Sweden	2006-2015	105				90d-mortality
Golding et al. 1992[38]	Retr. Monoc.	USA	1979-1991	79		X		VAD
Hsu et al. 2010[39]	Retr. Monoc.	Taiwan	2002-2006	51		X		
Kanji et al. 2010[40]	Retr. Monoc.	Canada	2002-2006	50	Mixed (PCS=74%)			
Khorsandi et al. 2016[41]	Retr. Monoc.	UK	1995-2015	16				Duplicatio
Klotz et al. 2007[42]	Retr. Monoc.	Germany	1995-2006	183		X		VAD
Lamarche et al. 2010[43]	Retr. Monoc.	Canada	2000-2008	20	Mixed (PCS=75%)	X		
Liden et al. 2009[44]	Retr. Monoc.	Sweden	2000-2007	52	Mixed (PCS=63%)	X		
Li et al. 2015[45]	Retr. Monoc.	China	2011-2012	123		X		
Lin et al. 2017[46]	Retr. Monoc.	Taiwan	2008-2015	162		X		

Lorusso et al. 2016[47]	Prosp. Multic.	ELSO Registry	1992-2013	4522	Mixed (PCS=19%)	X		
Lorusso et al. 2017[48]	Prosp. Multic.	ELSO Registry	1992-2015	5408	Mixed (PCS=1.4%)	X		
Magovern et al. 1994[49]	Retr. Monoc.	USA	1991-1993	21		X		
Maybauer et al. 2017[50]	Retr. Monoc.	UK	2011-2016	4				Case series/VAD
Mazzeffi et al. 2016[51]	Retr. Monoc.	USA	2010-2013	132	Mixed (PCS=29%)	X		
Mohite et al. 2018[52]	Retr. Monoc.	UK	2005-2014	56		X		VAD
Muehrcke et al. 1996[53]	Retr. Monoc.	USA	1992-1994	23		X		No data on mortality
Musial et al. 2017[54]	Retr. Monoc.	Poland	2009-2016	27		X		
Norkiene et al.[55]	Retr. Monoc.	Lithuania	2009-2014	15		X		
Oshima et al. 2007[56]	Retr. Monoc.	Japan	1991-2006	13		X		
Park et al. 2014[57]	Retr. Monoc.	Korea	2005-2011	93		X		
Ranney et al. 2017[58]	Retr. Monoc.	USA	2009-2015	131	Mixed (PCS=67%)	X		
Rousse et al. 2015[59]	Retr. Monoc.	France	2006-2011	98	Mixed (PCS=30%)	X		
Russo et al. 2010[60]	Retr. Monoc.	Italy	2005-2009	15	Mixed (PCS=20%)			VAD
Ruzevich et al. 1987[61]	Retr. Monoc.	USA	1980-1987	22		X		VAD/Pediatric Pts
Ruzevich et al. 1988[62]	Retr. Monoc.	USA	1980-1987	22		X		VAD/Pediatric Pts
Saeed et al. 2014[63]	Retr. Monoc.	Germany	2009-2011	37	Mixed (PCS=87%)			
Santarpino et al. 2015[64]	Retr. Multic.	Europe	2005-2015	85		X		Preop ECMO
Saxena et al. 2015[65]	Retr. Monoc.	Australia	2003-2013	45		X		
Silvetti et al.[66]	Retr. Monoc.	Italy	2013-2017	92		X		
Slottosch et al. 2013[67]	Retr. Monoc.	Germany	2006-2010	77		X		
Teman et al. 2014[68]	Retr. Monoc.	USA	2004-2012	104		X		VAD
Wang et al. 1996[69]	Retr. Monoc.	Taiwan	1994-1995	18		X		
Wang et al. 2009[70]	Retr. Monoc.	China	2004-2008	62		X		
Wang et al. 2013[71]	Retr. Monoc.	China	2004-2011	87		X		
Wong et al. 2017[72]	Retr. Monoc.	USA	2010-2015	103		X		VV-ECMO/VAD-ECMO
Wu et al. 2010[73]	Retr. Monoc.	Taiwan	2003-2009	110		X		
Xie et al. 2017[74]	Retr. Monoc.	China	2011-2015	177		X		
Yang et al. 2018[75]	Retr. Monoc.	China	2004-2015	432		X		
Zalawadiya et al. 2016[76]	Prosp. Multic.	UNOS registry	2000-2015	157	Post-heart transplant	X		
Zhang et al. 2006[77]	Retr. Monoc.	Germany	1996-2004	32		X		

ECMO extracorporeal membrane oxygenation; *ELSO*, Extracorporeal Life Support Organization; *UNOS*, United Network for Organ Sharing; *PCS*, post-cardtomy shock; *VAD*, ventricular assist device; *V-V*, venous-venous (ECMO).

Table III. Baseline characteristics and operative data in the overall series.

Variables*	Overall series		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 245 pts	*P* value
Demographics			
Age, y	63.9 (12.3)	61.5 (14.1)	0.02
Female	172 (32.1)	77 (31.4)	0.92
BMI, kg/m^2	26.7 [23.9-30.0]	26.5 [23.3-29.8]	0.53
BMI>30 kg/m^2	136 (25.4)	61 (24.9)	0.96
Cardiac status			
Elective procedure	223 (41.6)	104 (42.4)	0.89
Urgent/emergent procedure	288 (53.7)	127 (51.8)	0.69
Salvage procedure	25 (4.7)	14 (5.7)	0.65
Critical preoperative state	197 (36.8)	79 (32.2)	0.25
Preoperative IABP	41 (7.6)	21 (8.6)	0.76
Prior cardiac surgery	123 (22.9)	63 (25.7)	0.45
CCS angina class IV	99 (18.5)	54 (22.0)	0.29
NYHA class I-II	182 (34.0)	93 (38.0)	0.31
NYHA class III-IV	354 (66.0)	152 (62.0)	0.31
Prior MI	181 (33.8)	96 (39.2)	0.17
Prior PCI	105 (19.6)	41 (16.7)	0.39
Recent myocardial infarction	128 (23.9)	71 (29.0)	0.15
LVEF >50%	228 (42.5)	90 (36.7)	0.15
LVEF 30-50%	178 (33.2)	82 (33.5)	1.00
LVEF 21-30%	89 (16.6)	47 (19.2)	0.44
LVEF <21%	41 (7.6)	26 (10.6)	0.22
Active endocarditis	53 (9.9)	32 (13.1)	0.23
PAPs> 55 mmHg	94 (17.5)	46 (18.8)	0.75
Comorbidities			
Diabetes	131 (24.4)	69 (28.2)	0.31
Diabetes type			0.49
No diabetes	405 (75.6)	176 (71.8)	
IDDM	68 (12.7)	38 (15.5)	
NIDDM	63 (11.8)	31 (12.7)	
Haemoglobin, g/L	125.6 (21.5)	124.6 (22.7)	0.54
eGFR, mL/min/1.73 m^2	66.5 [49.1-85.3]	65.0 [45.1-82.8]	0.31
Dialysis	25 (4.7)	7 (2.9)	0.32
Stroke	39 (7.3)	21 (8.6)	0.63
Extracardiac arteriopathy	77 (14.4)	43 (17.6)	0.29
Pulmonary disease	73 (13.6)	37 (15.1)	0.66
Atrial fibrillation	143 (26.7)	49 (20.0)	0.06
Poor mobility	29 (5.4)	15 (6.1)	0.82
EuroSCORE 2, score	0.09 [0.04-0.19]	0.09 [0.03-0.27]	0.42
Indications for Cardiac Surgery			
CAD	233 (43.5)	122 (49.8)	0.12
Aortic valve stenosis	93 (17.4)	50 (20.4)	0.36
Aortic valve regurgitation	94 (17.5)	33 (13.5)	0.19
Mitral valve stenosis	31 (5.8)	11 (4.5)	0.57

Mitral valve regurgitation	165 (30.8)	70 (28.6)	0.59
Tricuspid valve regurgitation	81 (15.1)	23 (9.4)	0.05
Ascending aortic aneurysm	43 (8.0)	15 (6.1)	0.43
Aortic arch aneurysm	9 (1.7)	5 (2.0)	0.95
Type A aortic dissection	43 (8.0)	19 (7.8)	1.00
Pulmonary Thromboembolism	10 (1.9)	1 (0.4)	0.20
Cardiac Procedures			
CABG	257 (47.9)	133 (54.3)	0.12
Off-pump CABG	8 (1.5)	3 (1.2)	1.00
On-pump CABG	242 (45.1)	125 (51.0)	0.15
Beating heart CABG on CPB	7 (1.3)	6 (2.4)	0.39
SIMA	162 (30.2)	78 (31.8)	0.71
BIMA	62 (11.6)	15 (6.1)	0.025
Incomplete revascularization	59 (11.0)	33 (13.5)	0.38
AVR	144 (26.9)	69 (28.2)	0.77
Aortic valve repair	6 (1.1)	1 (0.4)	0.57
MVR	129 (24.1)	48 (19.6)	0.19
Mitral valve repair	66 (12.3)	30 (12.2)	1.00
TVR	15 (2.8)	7 (2.9)	1.00
Tricuspid valve repair	60 (11.2)	18 (7.3)	0.13
Bentall-De Bono procedure	53 (9.9)	22 (9.0)	0.79
Aortic valve sparing	4 (0.7)	6 (2.4)	0.11
Ascending aortic replacement	35 (6.5)	19 (7.8)	0.64
Aortic arch replacement	28 (5.2)	11 (4.5)	0.79
PTE	10 (1.9)	0 (0.0)	0.07
Other major cardiac surgery	8 (1.5)	10 (4.1)	0.05
Intraoperative data			
ACC time, min	113.0 [75.0-158.0]	109.0 [68.0-161.0]	0.58
CPB time, min	200.0 [123.0-280.50]	220.0 [150.0-308.0]	0.01

ACC, aortic cross-clamp; *AVR*, aortic valve replacement; *BIMA*, bilateral internal mammary artery (use); *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CCS*, Canadian Cardiovascular Society (class); *CPB*, cardiopulmonary bypass; *eGFR*, estimated glomerular filtration rate; *IDDM*, insulin-dependent diabetes mellitus; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MVR*, mitral valve replacement; *NA*, not applicable; *NIDDM*, non-insulin-dependent diabetes mellitus; *NYHA*, New York Heart Association (class); *PAP*, pulmonary artery pressure; *PCI*, percutaneous coronary intervention; *SIMA*, single internal mammary artery (use); *PTE*, pulmonary thromboendarterectomy; *TVR*, tricuspid valve replacement.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

Table IV. VA-ECMO related characteristics and indications for insertion.

Variables*	Overall series		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 245 pts	*P* value
Indications for VA-ECMO			
Failure to wean from CPB	184 (34.3)	115 (46.9)	0.001
Heart failure after weaning from CPB	274 (51.1)	100 (40.8)	0.009
Ventricular arrhythmias after CPB weaning	42 (7.8)	20 (8.2)	0.99
Cardiac arrest after weaning from CPB	42 (7.8)	22 (9.0)	0.69
Respiratory failure after weaning from CPB	42 (7.8)	13 (5.3)	0.26
ARDS after weaning from CPB	22 (4.1)	1 (0.4)	0.009
Septic shock after weaning from CPB	14 (2.6)	1 (0.4)	0.07
Pulmonary embolism	1 (0.2)	4 (1.6)	0.06
Timing of ECMO insertion			
VA-ECMO inserted immediately after surgery			<0.001
No	230 (42.9)	76 (31.0)	
After weaning attempts with inotropes only	248 (46.3)	107 (43.7)	
After weaning attempts with IABP	57 (10.6)	62 (25.3)	
After weaning attempts with Impella	1 (0.2)	0 (0.0)	
VA-ECMO inserted later after surgery			0.002
No	306 (57.1)	169 (69.0)	
After weaning attempts with Inotropes only	182 (34.0)	51 (20.8)	
After weaning attempts with IABP	47 (8.8)	25 (10.2)	
After weaning attempts with Impella	1 (0.2)	0	
Timing between heart failure after CPB and ECMO[†]	1 (0.79-1.01)	0.78 (0.46-1.10)	<0.001
Cannulation ECMO data			
Primary arterial cannulation for VA-ECMO			<0.001
Ascending aorta	-	245 (100)	
Femoral artery	467 (87.1)	0 (0.0)	
Another artery	69 (12.9)	0 (0.0)	
Primary venous cannulation for VA-ECMO	523 (97.6)	84 (34.3)	<0.001
Conversion from mini- to full sternotomy	8 (1.5)	2 (0.8)	0.66
Switch from central to peripheral cannulation	0	23 (9.4)	<0.001
IABP			<0.001
No	372 (69.4)	131 (53.5)	
IABP immediately after surgery with ECMO	41 (7.6)	37 (15.1)	
IABP immediately after surgery without ECMO	46 (8.6)	27 (11.0)	
IABP inserted later after surgery with ECMO	21 (3.9)	18 (7.3)	
IABP inserted later after surgery without ECMO	15 (2.8)	11 (4.5)	
IABP preoperatively inserted	41 (7.6)	21 (8.6)	
Impella, n (%)			0.32
No	531 (99.1)	245 (100)	
Impella immediately after surgery with ECMO	3 (0.6)	0 (0.0)	
Impella inserted later after surgery with ECMO	2 (0.4)	0 (0.0)	
Left ventricular venting, n (%)			<0.001
No	517 (96.5)	201 (82.0)	
Right superior pulmonary vein	13 (2.4)	37 (15.1)	
Left ventricular apex	5 (0.9)	3 (1.2)	

Another site	1 (0.2)	4 (1.6)	
Lower leg perfusion during peripheral VA-ECMO from the arterial cannula site‡	396 (73.9)	12 (4.9)	<0.001
Other data			
Duration of ECMO support, days	6.0 [4.0-11.0]	6.0 [3.0-9.0]	0.39
Arterial pH before VA-ECMO	7.30 (0.14)	7.30 (0.13)	0.73
Arterial lactate before VA-ECMO,	6.0 [3.4-9.9]	5.6 [3.1-8.9]	0.34
Target ACT during VA-ECMO, sec	200 [180-220]	180 [150-200]	<0.001

ACT, activated clotting time; *CPB*, cardiopulmonary bypass; IABP, intra-aortic balloon pump; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

†Data expressed in days (mean and interquartile range).

‡In the central group, this refers to patients switched to peripheral cannulation.

Table V. Primary and secondary outcomes after VA-ECMO implantation and the doubly robust matching estimators for confounding adjustment.

Variables*	Overall series			Doubly robust adjustment[†,‡]		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 245 pts	*P* value	Odds Ratio	95% CI	*P* value
Primary end-point						
In-hospital mortality	327 (61.0)	176 (71.8)	0.004	1.54	1.09-2.18	0.02
Secondary end-points						
Reoperation for bleeding/tamponade	191 (35.6)	137 (55.9)	<0.001	1.96	1.37-2.81	<0.001
Reoperation for bleeding at cannulation site	43 (8.0)	23 (9.4)	0.62	0.81	0.42-1.57	0.53
Tracheostomy	132 (24.6)	48 (19.6)	0.15	0.76	0.49-1.17	0.21
Stroke	93 (17.4)	55 (22.4)	0.11	1.11	0.72-1.71	0.65
Dialysis			0.29	0.84	0.60-1.19	0.34
No	250 (46.6)	122 (49.8)				
Transient	231 (43.1)	92 (37.6)				
Permanent	55 (10.3)	31 (12.7)				
Pancreatitis	8 (1.5)	4 (1.6)	1.00	1.45	0.36-5.85	0.60
Liver failure	205 (38.2)	60 (24.5)	<0.001	0.63	0.43-0.92	0.02
Gastrointestinal complications requiring surgical treatment	32 (6.0)	15 (6.1)	1.00	0.93	0.45-1.92	0.84
Multiorgan failure	279 (52.1)	111 (45.3)	0.09	0.85	0.60-1.21	0.37
DSWI	19 (3.5)	10 (4.1)	0.87	1.00	0.41-2.43	0.99
Vascular access site infection	60 (11.2)	7 (2.9)	<0.001	0.25	0.11-0.59	0.002
Pneumonia	208 (38.8)	77 (31.4)	0.06	0.88	0.61-1.28	0.50
Sepsis	140 (26.1)	39 (15.9)	0.002	0.64	0.42-0.99	0.05
Other severe infections	55 (10.3)	13 (5.3)	0.03	0.57	0.35-1.34	0.27
Peripheral vascular complications	49 (9.1)	20 (8.2)	0.76	0.80	0.43-1.48	0.47
Aortic rupture	0 (0.0)	2 (0.8)				
Type A aortic dissection	6 (1.1)	2 (0.8)				
Type B aortic dissection	1 (0.2)	2 (0.8)				
Peripheral artery dissection	8 (1.5)	1 (0.4)				
Vascular perforation	3 (0.6)	4 (1.6)				
Thrombosis	32 (6.0)	11 (4.5)				
Stenosis	2 (0.4)	1 (0.4)				
Pseudoaneurysm	1 (0.2)	1 (0.4)				

Major lower limb amputation			0.37	NA		
No	530 (98.9)	239 (97.6)				
Femoral cannulation side	5 (0.9)	5 (2.0)				
Other side	1 (0.2)	1 (0.4)				
Atrial fibrillation			0.13	1.26	0.89-1.78	0. 20
No	294 (54.9)	128 (52.2)				
Paroxysmal	174 (32.5)	95 (38.8)				
Permanent	68 (12.7)	22 (9.0)				
RBC units transfused, u	15.0 [7.0-28.0]	21.0 [12.0-38.0]	<0.001	5.56§	2.07§	0.007§
More than 9 RBC units transfused	344 (64.2)	203 (82.9)	<0.001	2.42	1.59-3.67	<0.001
Chest drains output 24h after surgery, mL	780 [500- 1450]	1389 [750- 2500]	<0.001	622.52§	132.76§	<0.001§
ICU stay, d	12.0 [5.0-24.0]	11.0 [5.0-21.0]	0.31	-1.26§	1.57§	0.42§
Hospital stay, d	17.0 [5.8-35.0]	13.0 [5.0-27.0]	0.04	-5.79§	2.49§	0.02§
More than 10 days on VA-ECMO	128 (23.9)	57 (23.3)	0.92	0.83	0.55-1.27	0.40
Successful weaning from VA-ECMO	271 (50.6)	108 (44.1)	0.11	0.74	0.53-1.06	0.10
Postoperative VAD or Heart transplant	17 (3.2)	12 (4.9)	0.33	1.79	0.82-3.93	0.14
VAD from VA-ECMO	12 (2.2)	10 (4.1)	0.23	2.23	0.92-5.42	0.08
Heart transplant			0.80	NA		
No	527 (98.3)	240 (98.0)				
from VA-ECMO	5 (0.9)	2 (0.8)				
from LVAD	4 (0.7)	3 (1.2)				
Any new cardiac procedure‡	46 (8.6)	26 (0.6)	0.44	1.21	0.67-2.19	0.52
New cardiac surgery procedure during ECMO‡	44 (8.2)	23 (9.4)	0.63	1.16	0.64-2.13	0.62
Oxygenator failure for clots	58 (10.8)	11 (4.5)	0.006	0.48	0.24-0.96	0.04
Nadir arterial pH during VA-ECMO	7.22 (0.13)	7.24 (0.15)	0.07	0.01§	0.01§	0.39§
Peak arterial lactate during VA-ECMO, mmol/L	7.5 [4.6-12.0]	7.6 [4.1-13.0]	0.99	0.14§	0.55§	0.80§
Nadir postoperative haemoglobin, g/L	74.30 (10.91)	75.35 (12.64)	0.24	0.26§	1.03§	0.80§

CI, confidence interval; *CPB*, cardiopulmonary bypass; *DSWI*, deep sternal wound infection; *ICU*, intensive cardia unit; *LVAD*, left ventricular assist device; *NA,* not applicable; *RBC*, red blood cell; *LVAD*, left ventricular assist device; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

†Reference for the events: central VA-ECMO group.

§Linear regression expressed as standard regression coefficient, standard error and *P* value.

‡This include percutaneous balloon angioplasty (cardiac procedure) and bypass surgery, aortic valve replcamenet or aortic repair (new cardiac surgery).

Table VI. Covariate balance analyses in unweighted and weighted samples for VA-ECMO patients.

Variable	Unadjusted sample							Adjusted sample							
	Peripheral VA-ECMO 536 pts		Central VA-ECMO 245 pts		Balance Measures			Peripheral VA-ECMO 263.224 pts		Central VA-ECMO 245 pts		Balance Measures			
	Mean	SD	Mean	SD	Mean difference	Variance ratio	KS	Mean	SD	Mean	SD	Mean difference	Mean difference threshold	Variance ratio	KS
Age	63.846	12.323	61.514	14.059	-0.166	1.302	0.114	62.253	14.042	61.514	14.059	-0.053	<0.1	1.003	0.105
Female	0.321	0.467	0.314	0.465	-0.014			0.313	0.465	0.314	0.465	0.002	<0.1		
BMI	27.263	5.025	27.085	5.337	-0.033	1.128	0.066	27.060	4.864	27.085	5.337	0.005	<0.1	1.204	0.068
Haemoglobin	125.591	21.485	124.567	22.739	-0.045	1.120	0.033	125.202	21.257	124.567	22.739	-0.028	<0.1	1.144	0.050
eGFR	68.561	30.992	66.694	28.651	-0.065	0.855	0.061	66.995	30.709	66.694	28.651	-0.011	<0.1	0.870	0.069
Dialysis	0.047	0.211	0.029	0.167	-0.108			0.030	0.172	0.029	0.167	-0.010	<0.1		
Diabetes	0.244	0.430	0.282	0.451	0.083			0.275	0.447	0.282	0.451	0.015	<0.1		
Poor mobility	0.054	0.226	0.061	0.240	0.030			0.064	0.245	0.061	0.240	-0.010	<0.1		
Stroke	0.073	0.260	0.086	0.281	0.046			0.088	0.284	0.086	0.281	-0.009	<0.1		
Atrial fibrillation	0.267	0.443	0.200	0.401	-0.167			0.209	0.407	0.200	0.401	-0.022	<0.1		
ARDS after weaning	0.041	0.199	0.004	0.064	-0.579			0.005	0.071	0.004	0.064	-0.016	<0.1		
Extracardiac	0.144	0.351	0.176	0.381	0.084			0.175	0.381	0.176	0.381	0.001	<0.1		
Pulmonary disease	0.136	0.343	0.151	0.359	0.041			0.152	0.359	0.151	0.359	-0.002	<0.1		
Prior cardiac surgery	0.230	0.421	0.257	0.438	0.063			0.256	0.437	0.257	0.438	0.004	<0.1		
Prior MI	0.338	0.473	0.392	0.489	0.111			0.381	0.487	0.392	0.489	0.021	<0.1		
NYHA class I-II	0.340	0.474	0.380	0.486	0.082			0.373	0.485	0.380	0.486	0.014	<0.1		
LVEF >50%	0.425	0.495	0.367	0.483	-0.120			0.374	0.485	0.367	0.483	-0.013	<0.1		
LVEF 30-50%	0.332	0.471	0.335	0.473	0.006			0.337	0.474	0.335	0.473	-0.004	<0.1		
LVEF 21-30%	0.166	0.373	0.192	0.395	0.065			0.186	0.389	0.192	0.395	0.016	<0.1		
LVEF <21%	0.077	0.266	0.106	0.309	0.096			0.104	0.306	0.106	0.309	0.006	<0.1		
Elective procedure	0.416	0.493	0.425	0.495	0.017			0.425	0.495	0.425	0.495	0.000	<0.1		
Urgent/emergent	0.537	0.499	0.518	0.501	-0.038			0.526	0.500	0.518	0.501	-0.016	<0.1		
Salvage procedure	0.047	0.211	0.057	0.233	0.045			0.049	0.216	0.057	0.233	0.035	<0.1		
Prior PCI	0.196	0.397	0.167	0.374	-0.076			0.170	0.376	0.167	0.374	-0.007	<0.1		
Critical preoperative	0.368	0.483	0.322	0.468	-0.096			0.316	0.466	0.322	0.468	0.014	<0.1		
Preoperative cardiac	0.037	0.190	0.078	0.268	0.150			0.062	0.242	0.078	0.268	0.057	<0.1		
Ventricular	0.049	0.215	0.045	0.208	-0.017			0.041	0.199	0.045	0.208	0.019	<0.1		

Aborted sudden	0.024	0.154	0.008	0.090	-0.179			0.009	0.092	0.008	0.090	-0.004	<0.1		
Preoperative IABP	0.077	0.266	0.086	0.281	0.033			0.083	0.277	0.086	0.281	0.009	<0.1		
Preoperative	0.289	0.454	0.278	0.449	-0.026			0.268	0.444	0.278	0.449	0.021	<0.1		
Preoperative	0.090	0.286	0.090	0.287	0.001			0.083	0.276	0.090	0.287	0.025	<0.1		
EuroSCORE 2	0.147	0.160	0.176	0.193	0.151	1.461	0.112	0.171	0.204	0.176	0.193	0.026	<0.1	0.894	0.085
Clopidogrel or	0.140	0.347	0.127	0.333	-0.040			0.126	0.333	0.127	0.333	0.002	<0.1		
PAPs< 30 mmHg	0.502	0.501	0.551	0.498	0.099			0.545	0.499	0.551	0.498	0.012	<0.1		
PAPs 30-55 mmHg	0.323	0.468	0.261	0.440	-0.140			0.269	0.444	0.261	0.440	-0.018	<0.1		
PAPs> 55 mmHg	0.175	0.381	0.188	0.391	0.032			0.186	0.390	0.188	0.391	0.005	<0.1		
CAD	0.435	0.496	0.498	0.501	0.126			0.498	0.501	0.498	0.501	-0.001	<0.1		
Aortic valve stenosis	0.174	0.379	0.204	0.404	0.076			0.197	0.398	0.204	0.404	0.018	<0.1		
Aortic valve	0.175	0.381	0.135	0.342	-0.119			0.134	0.341	0.135	0.342	0.002	<0.1		
Mitral valve stenosis	0.058	0.234	0.045	0.208	-0.062			0.048	0.214	0.045	0.208	-0.014	<0.1		
Mitral valve	0.308	0.462	0.286	0.453	-0.049			0.295	0.457	0.286	0.453	-0.021	<0.1		
Tricuspid valve	0.151	0.359	0.094	0.292	-0.196			0.100	0.300	0.094	0.292	-0.020	<0.1		
Ascending aortic	0.080	0.272	0.061	0.240	-0.079			0.054	0.226	0.061	0.240	0.031	<0.1		
Aortic arch	0.017	0.129	0.020	0.142	0.026			0.016	0.127	0.020	0.142	0.030	<0.1		
Type A aortic	0.080	0.272	0.078	0.268	-0.010			0.081	0.273	0.078	0.268	-0.011	<0.1		
Pulmonary	0.019	0.135	0.004	0.064	-0.228			0.005	0.068	0.004	0.064	-0.008	<0.1		
Active endocarditis	0.099	0.299	0.131	0.338	0.094			0.121	0.327	0.131	0.338	0.029	<0.1		
Type of surgical	0.218	0.414	0.269	0.445	0.115			0.265	0.442	0.269	0.445	0.009	<0.1		
Type of surgical	0.216	0.412	0.196	0.398	-0.052			0.200	0.401	0.196	0.398	-0.011	<0.1		
Type of surgical	0.1026	0.304	0.090	0.287	-0.045			0.084	0.277	0.090	0.287	0.022	<0.1		
Type of surgical	0.463	0.499	0.445	0.498	-0.036			0.451	0.499	0.445	0.498	-0.012	<0.1		
ACC time	125.754	77.586	121.241	76.270	-0.059	0.966	0.054	120.534	74.936	121.241	76.266	0.009	<0.1	1.036	0.034
CPB time	219.787	116.352	241.310	122.550	0.176	1.109	0.118	239.215	122.026	241.310	122.547	0.017	<0.1	1.009	0.089
Failure to wean from	0.343	0.475	0.469	0.500	0.252			0.448	0.498	0.469	0.500	0.042	<0.1		
Heart failure after	0.511	0.500	0.408	0.493	-0.209			0.421	0.495	0.408	0.493	-0.025	<0.1		
Ventricular	0.078	0.269	0.082	0.274	0.012			0.085	0.280	0.082	0.274	-0.013	<0.1		
Cardiac arrest after	0.078	0.269	0.090	0.287	0.040			0.095	0.294	0.090	0.287	-0.018	<0.1		
Respiratory failure	0.078	0.269	0.053	0.225	-0.113			0.057	0.233	0.053	0.225	-0.018	<0.1		
Septic shock after	0.026	0.160	0.004	0.064	-0.345			0.005	0.071	0.004	0.064	-0.015	<0.1		
VA-ECMO inserted	0.429	0.495	0.310	0.464	-0.257			0.327	0.470	0.310	0.464	-0.036	<0.1		
VA-ECMO inserted	0.463	0.499	0.437	0.497	-0.052			0.443	0.498	0.437	0.497	-0.012	<0.1		
VA-ECMO inserted	0.106	0.309	0.253	0.436	0.337			0.230	0.422	0.253	0.436	0.052	<0.1		

VA-ECMO inserted	0.002	0.043	0.000	0.000			0.000	0.000	0.000	0.000	0.000	<0.1	
VA-ECMO inserted	0.340	0.474	0.208	0.407	-0.323		0.221	0.416	0.208	0.407	-0.032	<0.1	
VA-ECMO inserted	0.088	0.283	0.102	0.303	0.047		0.106	0.308	0.102	0.303	-0.012	<0.1	
VA-ECMO inserted	0.002	0.043	0.000	0.000			0.000	0.000	0.000	0.000	0.000	<0.1	

ACC, aortic cross-clamp; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CPB*, cardiopulmonary bypass; *eGFR*, estimated glomerular filtration rate; KS, Kolmogorov-Smirnov statistics; *IABP*, intraortic balloon pump; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NA*, not applicable; *NYHA*, New York Heart Association (class); *PAP*, pulmonary artery pressure; *PCI*, percutaneous coronary intervention; *SD*, standard deviation.

*other includes combined procedures and other major cardiac surgical procedures

Table VI. Baseline characteristics and operative data in the overall series after the removal of patients swiched from central to peripheral cannulation.

Variables*	Overall series		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 222 pts	*P* value
Demographics			
Age, y	63.9 (12.3)	61.3 (13.9)	<0.001
Female	172 (32.1)	30 (31.5)	0.95
BMI, kg/m^2	26.7 [23.9-30.0]	26.3 [23.0-29.8]	0.31
BMI>30 kg/m^2	136 (25.4)	54 (24.3)	0.83
Cardiac status			
Elective procedure	223 (41.6)	92 (41.4)	1.000
Urgent/emergent procedure	288 (53.7)	117 (52.7)	0.86
Salvage procedure	25 (4.7)	13 (5.9)	0.62
Critical preoperative state	197 (36.8)	75 (33.8)	0.49
Preoperative IABP	41 (7.6)	19 (8.6)	0.78
Prior cardiac surgery	123 (22.9)	58 (26.1)	0.40
CCS angina class IV	99 (18.5)	49 (22.1)	0.29
NYHA class I-II	182 (34.0)	86 (38.7)	0.24
NYHA class III-IV	354 (66.0)	136 (61.3)	0.24
Prior MI	181 (33.8)	85 (38.3)	0.27
Prior PCI	105 (19.6)	38 (16.7)	0.40
Recent myocardial infarction	128 (23.9)	63 (28.4)	0.23
LVEF >50%	228 (42.5)	81 (36.5)	0.14
LVEF 30-50%	178 (33.2)	72 (32.4)	0.91
LVEF 21-30%	89 (16.6)	46 (20.7)	0.21
LVEF <21%	41 (7.6)	23 (10.4)	0.28
Active endocarditis	53 (9.9)	30 (13.5)	0.19
PAPs> 55 mmHg	94 (17.5)	45 (20.3)	0.43
Comorbidities			
Diabetes	131 (24.4)	62 (27.9)	0.36
Diabetes type			0.56
No diabetes	405 (75.6)	160 (72.1)	
IDDM	68 (12.7)	34 (15.3)	
NIDDM	63 (11.8)	28 (12.6)	
Haemoglobin, g/L	125.6 (21.5)	124.4 (22.8)	0.51
eGFR, mL/min/1.73 m^2	66.5 [49.1-85.3]	65.0 [45.2-82.6]	0.39
Dialysis	25 (4.7)	6 (2.7)	0.29
Stroke	39 (7.3)	19 (8.6)	0.65
Extracardiac arteriopathy	77 (14.4)	38 (17.1)	0.39
Pulmonary disease	73 (13.6)	34 (15.3)	0.62
Atrial fibrillation	143 (26.7)	48 (21.6)	0.17
Poor mobility	29 (5.4)	14 (6.3)	0.75
EuroSCORE 2, score	0.09 [0.04-0.19]	0.10 [0.03-0.27]	0.26
Indications for Cardiac Surgery			
CAD	233 (43.5)	110 (49.5)	0.15
Aortic valve stenosis	93 (17.4)	43 (19.4)	0.58
Aortic valve regurgitation	94 (17.5)	33 (14.9)	0.43
Mitral valve stenosis	31 (5.8)	11 (5.0)	0.78
Mitral valve regurgitation	165 (30.8)	66 (29.7)	0.84

Tricuspid valve regurgitation	81 (15.1)	22 (9.9)	0.07
Ascending aortic aneurysm	43 (8.0)	15 (6.8)	0.66
Aortic arch aneurysm	9 (1.7)	5 (2.3)	0.81
Type A aortic dissection	43 (8.0)	19 (8.6)	0.92
Pulmonary Thromboembolism	10 (1.9)	1 (0.5)	0.25
Cardiac Procedures			
CABG	257 (47.9)	116 (52.3)	0.32
Off-pump CABG	8 (1.5)	3 (1.4)	1.00
On-pump CABG	242 (45.1)	110 (49.5)	0.31
Beating heart CABG on CPB	7 (1.3)	4 (1.8)	0.85
SIMA	162 (30.2)	66 (29.7)	0.96
BIMA	62 (11.6)	9 (4.1)	0.002
Incomplete revascularization	59 (11.0)	29 (13.1)	0.49
AVR	144 (26.9)	61 (27.5)	0.93
Aortic valve repair	6 (1.1)	1 (0.5)	0.65
MVR	129 (24.1)	46 (20.7)	0.37
Mitral valve repair	66 (12.3)	28 (12.6)	1.00
TVR	15 (2.8)	7 (3.2)	0.98
Tricuspid valve repair	60 (11.2)	17 (7.7)	0.18
Bentall-De Bono procedure	53 (9.9)	21 (9.5)	0.96
Aortic valve sparing	4 (0.7)	6 (2.7)	0.07
Ascending aortic replacement	35 (6.5)	19 (8.6)	0.41
Aortic arch replacement	28 (5.2)	11 (5.0)	1.000
PTE	10 (1.9)	0 (0.0)	0.09
Other major cardiac surgery	8 (1.5)	8 (3.6)	0.12
Intraoperative data			
ACC time, min	113.0 [75.0-158.0]	108.5 [68.0-161.0]	0.58
CPB time, min	200.0 [123.0-280.50]	220.0 [154.3-302.0]	0.02

ACC, aortic cross-clamp; *AVR*, aortic valve replacement; *BIMA*, bilateral internal mammary artery (use); *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CCS*, Canadian Cardiovascular Society (class); *CPB*, cardiopulmonary bypass; *eGFR*, estimated glomerular filtration rate; *IDDM*, insulin-dependent diabetes mellitus; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MVR*, mitral valve replacement; *NA*, not applicable; *NIDDM*, non-insulin-dependent diabetes mellitus; *NYHA*, New York Heart Association (class); *PAP*, pulmonary artery pressure; *PCI*, percutaneous coronary intervention; *SIMA*, single internal mammary artery (use); *PTE*, pulmonary thromboendarterectomy; *TVR*, tricuspid valve replacement.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

Table VIII. VA-ECMO related characteristics and indications after the removal of patients swiched from central to peripheral cannulation.

Variables*	Overall series		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 222 pts	*P* value
Indications for VA-ECMO			
Failure to wean from CPB	184 (34.3)	106 (47.7)	0.001
Heart failure after weaning from CPB	274 (51.1)	93 (41.9)	0.03
Ventricular arrhythmias after CPB weaning	42 (7.8)	18 (8.1)	1.00
Cardiac arrest after weaning from CPB	42 (7.8)	16 (7.2)	0.88
Respiratory failure after weaning from CPB	42 (7.8)	11 (5.0)	0.21
ARDS after weaning from CPB	22 (4.1)	0 (0)	0.005
Septic shock after weaning from CPB	14 (2.6)	1 (0.5)	0.10
Pulmonary embolism	1 (0.2)	4 (1.8)	0.05
Timing of ECMO insertion			
VA-ECMO inserted immediately after surgery			<0.001
No	230 (42.9)	68 (30.6)	
After weaning attempts with inotropes only	248 (46.3)	97 (43.7)	
After weaning attempts with IABP	57 (10.6)	57 (25.7)	
After weaning attempts with Impella	1 (0.2)	0 (0.0)	
VA-ECMO inserted later after surgery			0.001
No	306 (57.1)	154 (69.4)	
After weaning attempts with Inotropes only	182 (34.0)	43 (19.4)	
After weaning attempts with IABP	47 (8.8)	25 (11.3)	
After weaning attempts with Impella	1 (0.2)	0	
Cannulation ECMO data			
Primary arterial cannulation for VA-ECMO			<0.001
Ascending aorta	-	222 (100)	
Femoral artery	467 (87.1)	0 (0.0)	
Another artery	69 (12.9)	0 (0.0)	
Primary venous cannulation for VA-ECMO	523 (97.6)	80 (36.0)	<0.001
Conversion from mini- to full sternotomy	8 (1.5)	1 (0.5)	0.40
IABP			0.002
No	372 (69.4)	121 (54.5)	
IABP immediately after surgery with ECMO	41 (7.6)	32 (14.4)	
IABP immediately after surgery without ECMO	46 (8.6)	24 (10.8)	
IABP inserted later after surgery with ECMO	21 (3.9)	17 (7.7)	
IABP inserted later after surgery without ECMO	15 (2.8)	9 (4.1)	
IABP preoperatively inserted	41 (7.6)	19 (8.6)	
Impella, n (%)			0.35
No	531 (99.1)	222 (100)	
Impella immediately after surgery with ECMO	3 (0.6)	0 (0.0)	
Impella inserted later after surgery with ECMO	2 (0.4)	0 (0.0)	
Left ventricular venting, n (%)			<0.001
No	517 (96.5)	180 (81.1)	
Right superior pulmonary vein	13 (2.4)	36 (16.2)	
Left ventricular apex	5 (0.9)	2 (0.9)	
Another site	1 (0.2)	4 (1.8)	
Other data			

Duration of ECMO support, days	6.0 [4.0-11.0]	6.0 [3.0-9.0]	0.16
Arterial pH before VA-ECMO	7.30 (0.14)	7.30 (0.13)	0.94
Arterial lactate before VA-ECMO,	6.0 [3.4-9.9]	5.6 [3.1-8.9]	0.31
Target ACT during VA-ECMO, sec	200 [180-220]	180 [150-200]	<0.001

ACT, activated clotting time; *CPB*, cardiopulmonary bypass; IABP, intra-aortic balloon pump; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

Table IX. Principal primary and secondary outcomes after VA-ECMO implantation after the removal of patients swiched from central to peripheral cannulation.

Variables*	Overall series			Doubly robust adjustment†		
	Peripheral VA-ECMO 536 pts	Central VA-ECMO 222 pts	*P* value	Odds Ratio	95% CI	*P* value
Primary end-point						
In-hospital mortality	327 (61.0)	158 (71.2)	0.01	1.55	1.05-2.27	0.03
Secondary end-points						
Reoperation for bleeding/tamponade	191 (35.6)	122 (55.0)	<0.001	1.95	1.35-2-82	<0.001
Stroke	93 (17.4)	50 (22.5)	0.12	1.11	0.71-1.74	0.64
Dialysis	286 (53.4)	109 (49.1)	0.34	0.82	0.57-1.18	0.29
Liver failure	205 (38.2)	53 (23.9)	<0.001	0.61	0.41-0.791	0.01
Multiorgan failure	279 (52.1)	98 (44.1)	0.06	0.84	0.59-1.21	0.36
DSWI	19 (3.5)	10 (4.5)	0.68	1.05	0.42-2.61	0.91
Vascular access site infection	60 (11.2)	5 (2.3)	<0.001	0.18	0.07-0.48	<0.001
Sepsis	140 (26.1)	35 (15.8)	0.003	0.61	0.38-0.96	0.03
Peripheral vascular complications	49 (9.1)	13 (5.9)	0.18	0.51	0.25-1.02	0.06
RBC units transfused, u	15.0 [7.0-28.0]	20.5 [12.0-38.0]	<0.001	6.02§	2.15§	0.01§
More than 9 RBC units transfused	344 (64.2)	184 (82.9)	<0.001	2.49	1.61-3.84	<0.001
Chest drains output 24h after surgery, mL	780 [500- 1450]	1760 [850- 2210]	<0.001	681§	139.74§	<0.001§
ICU stay, d	12.0 [5.0-24.0]	11.0 [4.0-20.0]	0.17	-0.97§	1.63§	0.55§
Hospital stay, d	17.0 [5.8-35.0]	13.0 [5.0-25.0]	0.02	-4.64§	2.29§	0.04§
More than 10 days on VA-ECMO	128 (23.9)	49 (22.1)	0.66	0.81	0.52-1.26	0.34
Successful weaning from VA-ECMO	271 (50.6)	96 (43.2)	0.08	0.75	0.52-1.08	0.12
Postoperative VAD or Heart transplant	17 (3.2)	12 (5.4)	0.21	2.07	0.94-4.53	0.07

CI, confidence interval; *CPB*, cardiopulmonary bypass; *DSWI*, deep sternal wound infection; *ICU*, intensive cardia unit; *LVAD*, left ventricular assist device; *RBC*, red blood cell; *LVAD*, left ventricular assist device; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

†Reference for the events: central VA-ECMO group.

§Linear regression expressed as standard regression coefficient, standard error and *P* value.

Table X. Covariate balance analyses in unweighted and weighted samples for VA-ECMO patients after the removal of patients swiched from central to peripheral cannulation.

Variable	Unadjusted sample							Adjusted sample							
	Peripheral VA-ECMO 536 pts		Central VA-ECMO 222 pts		Balance Measures			Peripheral VA-ECMO 254.78 pts		Central VA-ECMO 222 pts		Balance Measures			
	Mean	SD	Mean	SD	Mean difference	Variance ratio	KS	Mean	SD	Mean	SD	Mean difference	Mean difference threshold	Variance ratio	KS
Age	63.846	12.323	61.262	13.888	-0.186	1.270	0.136	61.844	14.358	61.262	13.888	-0.042	<0.1	0.936	0.111
Female	0.321	0.467	0.315	0.466	-0.012			0.313	0.465	0.315	0.466	0.005	<0.1		
BMI	27.263	5.025	26.974	5.421	-0.053	1.164	0.087	27.017	4.963	26.974	5.421	-0.008	<0.1	1.193	0.081
Haemoglobin	125.591	21.485	124.437	22.821	-0.051	1.128	0.034	125.135	21.128	124.437	22.821	-0.031	<0.1	1.167	0.057
eGFR	68.561	30.992	66.685	27.822	-0.067	0.806	0.059	67.236	31.594	66.685	27.822	-0.020	<0.1	0.776	0.072
Dialysis	0.047	0.211	0.027	0.163	-0.121			0.028	0.164	0.027	0.163	-0.004	<0.1		
Diabetes	0.244	0.430	0.279	0.450	0.078			0.272	0.446	0.279	0.450	0.016	<0.1		
Poor mobility	0.054	0.226	0.063	0.244	0.037			0.064	0.246	0.063	0.244	-0.005	<0.1		
Stroke	0.073	0.260	0.086	0.280	0.046			0.088	0.283	0.086	0.280	-0.007	<0.1		
Atrial fibrillation	0.267	0.443	0.216	0.413	-0.123			0.223	0.417	0.216	0.413	-0.017	<0.1		
ARDS after weaning from CPB	0.041	0.199	0.000	0.000				0.000	0.000	0.000	0.000		<0.1		
Extracardiac arteriopathy	0.144	0.351	0.171	0.378	0.073			0.171	0.377	0.171	0.378	0.002	<0.1		
Pulmonary disease	0.136	0.343	0.153	0.361	0.047			0.152	0.360	0.153	0.361	0.004	<0.1		
Prior cardiac surgery	0.230	0.421	0.261	0.440	0.072			0.256	0.437	0.261	0.440	0.011	<0.1		
Prior MI	0.338	0.473	0.383	0.487	0.093			0.380	0.486	0.383	0.487	0.007	<0.1		
NYHA class I-II	0.340	0.474	0.387	0.488	0.098			0.387	0.488	0.387	0.488	0.001	<0.1		
LVEF >50%	0.425	0.495	0.365	0.483	-0.125			0.367	0.483	0.365	0.483	-0.004	<0.1		
LVEF 30-50%	0.332	0.471	0.324	0.469	-0.017			0.326	0.470	0.324	0.469	-0.004	<0.1		
LVEF 21-30%	0.166	0.373	0.207	0.406	0.101			0.206	0.405	0.207	0.406	0.003	<0.1		
LVEF <21%	0.077	0.266	0.104	0.305	0.089			0.101	0.302	0.104	0.305	0.008	<0.1		
Elective procedure	0.416	0.493	0.414	0.494	-0.003			0.420	0.495	0.414	0.494	-0.011	<0.1		
Urgent/emergent procedure	0.537	0.499	0.527	0.500	-0.021			0.525	0.500	0.527	0.500	0.004	<0.1		
Salvage procedure	0.047	0.211	0.059	0.235	0.051			0.055	0.228	0.059	0.235	0.016	<0.1		
Prior PCI	0.196	0.397	0.167	0.374	-0.078			0.173	0.379	0.167	0.374	-0.017	<0.1		
Critical preoperative state	0.368	0.483	0.338	0.474	-0.063			0.327	0.470	0.338	0.474	0.024	<0.1		
Preoperative cardiac arrest	0.037	0.190	0.081	0.274	0.160			0.066	0.249	0.081	0.274	0.055	<0.1		

Ventricular tachycardia or fibrillation	0.049	0.215	0.041	0.198	-0.040			0.035	0.185	0.041	0.198	0.027	<0.1		
Aborted sudden death	0.024	0.154	0.009	0.095	-0.161			0.009	0.095	0.009	0.095	-0.001	<0.1		
Preoperative IABP	0.077	0.266	0.086	0.280	0.032			0.083	0.277	0.086	0.280	0.009	<0.1		
Preoperative inotropes	0.289	0.454	0.293	0.456	0.008			0.279	0.449	0.293	0.456	0.030	<0.1		
Preoperative mechanical ventilation	0.090	0.286	0.095	0.293	0.017			0.086	0.281	0.095	0.293	0.029	<0.1		
EuroSCORE 2	0.147	0.160	0.181	0.198	0.173	1.530	0.117	0.175	0.207	0.181	0.198	0.033	<0.1	0.915	0.081
Clopidogrel or ticagrelor use	0.140	0.347	0.122	0.328	-0.056			0.124	0.330	0.122	0.328	-0.006	<0.1		
PAPs< 30 mmHg	0.502	0.501	0.550	0.499	0.096			0.549	0.499	0.550	0.499	0.002	<0.1		
PAPs 30-55 mmHg	0.323	0.468	0.248	0.433	-0.173			0.255	0.437	0.248	0.433	-0.016	<0.1		
PAPs> 55 mmHg	0.175	0.381	0.203	0.403	0.068			0.197	0.398	0.203	0.403	0.015	<0.1		
CAD	0.435	0.496	0.496	0.501	0.121			0.493	0.501	0.496	0.501	0.004	<0.1		
Aortic valve stenosis	0.174	0.379	0.194	0.396	0.051			0.191	0.394	0.194	0.396	0.007	<0.1		
Aortic valve regurgitation	0.175	0.381	0.149	0.357	-0.075			0.148	0.356	0.149	0.357	0.002	<0.1		
Mitral valve stenosis	0.058	0.234	0.050	0.218	-0.038			0.051	0.220	0.050	0.218	-0.006	<0.1		
Mitral valve regurgitation	0.308	0.462	0.297	0.458	-0.023			0.298	0.458	0.297	0.458	-0.001	<0.1		
Tricuspid valve regurgitation	0.151	0.359	0.099	0.300	-0.174			0.102	0.303	0.099	0.300	-0.008	<0.1		
Ascending aortic aneurysm	0.080	0.272	0.068	0.252	-0.050			0.066	0.248	0.068	0.252	0.008	<0.1		
Aortic arch aneurysm	0.017	0.129	0.023	0.149	0.039			0.024	0.153	0.023	0.149	-0.009	<0.1		
Type A aortic dissection	0.080	0.272	0.086	0.280	0.019			0.090	0.286	0.086	0.280	-0.015	<0.1		
Pulmonary Thromboembolism	0.019	0.135	0.005	0.067	-0.211			0.005	0.070	0.005	0.067	-0.005	<0.1		
Active endocarditis	0.099	0.299	0.135	0.343	0.106			0.125	0.331	0.135	0.343	0.031	<0.1		
Type of surgical procedures - isolated CABG	0.218	0.414	0.252	0.435	0.078			0.251	0.434	0.252	0.435	0.003	<0.1		
Type of surgical procedures - isolated valvular surgery	0.216	0.412	0.198	0.400	-0.046			0.194	0.396	0.198	0.400	0.011	<0.1		
Type of surgical procedures -surgery on thoracic aorta	0.103	0.304	0.099	0.300	-0.012			0.102	0.303	0.099	0.300	-0.010	<0.1		
Type of surgical procedures - other*	0.463	0.499	0.451	0.499	-0.025			0.453	0.499	0.451	0.499	-0.006	<0.1		
ACC time	125.754	77.586	120.487	72.683	-0.073	0.878	0.050	121.671	74.627	120.487	72.683	-0.016	<0.1	0.949	0.048
CPB time	219.787	116.352	238.784	116.750	0.163	1.007	0.125	238.264	120.932	238.784	116.75	0.005	<0.1	0.932	0.090
Failure to wean from CPB	0.343	0.475	0.478	0.501	0.268			0.463	0.500	0.478	0.501	0.029	<0.1		

Heart failure after weaning from CPB	0.511	0.500	0.419	0.495	-0.187		0.425	0.495	0.419	0.495	-0.012	<0.1	
Ventricular arrhythmias after weaning from CPB	0.078	0.269	0.081	0.274	0.010		0.082	0.276	0.081	0.274	-0.005	<0.1	
Cardiac arrest after weaning from CPB	0.078	0.269	0.072	0.259	-0.024		0.075	0.264	0.072	0.259	-0.013	<0.1	
Respiratory failure after weaning from CPB	0.078	0.269	0.050	0.218	-0.133		0.053	0.225	0.050	0.218	-0.018	<0.1	
Septic shock after weaning from CPB	0.026	0.160	0.005	0.067	-0.322		0.006	0.074	0.005	0.067	-0.015	<0.1	
VA-ECMO inserted immediately after surgery - No	0.429	0.495	0.306	0.462	-0.266		0.317	0.466	0.306	0.462	-0.022	<0.1	
VA-ECMO inserted immediately after surgery - After weaning attempts with inotropes only	0.463	0.499	0.437	0.497	-0.052		0.444	0.498	0.437	0.497	-0.015	<0.1	
VA-ECMO inserted immediately after surgery - After weaning attempts with IABP	0.106	0.309	0.257	0.438	0.344		0.239	0.427	0.257	0.438	0.041	<0.1	
VA-ECMO inserted immediately after surgery - After weaning attempts with Impella	0.002	0.043	0.000	0.000			0.000	0.000	0.000	0.000	0.000	<0.1	
VA-ECMO inserted later after surgery- No	0.340	0.474	0.194	0.396	-0.368		0.201	0.401	0.194	0.396	-0.018	<0.1	
VA-ECMO inserted later after surgery- After weaning attempts with Inotropes only	0.088	0.283	0.113	0.317	0.079		0.116	0.321	0.113	0.317	-0.011	<0.1	
VA-ECMO inserted later after surgery- After weaning attempts with IABP	0.002	0.043	0.000	0.000			0.000	0.000	0.000	0.000	0.000	<0.1	

ACC, aortic cross-clamp; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CPB*, cardiopulmonary bypass; *eGFR*, estimated glomerular filtration rate; KS, Kolmogorov-Smirnov statistics; *IABP*, intraortic balloon pump; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NA*, not applicable; *NYHA*, New York Heart Association (class); *PAP*, pulmonary artery pressure; *PCI*, percutaneous coronary intervention; *SD*, standard deviation..

*Other includes combined procedures and other major cardiac surgical procedures.

Table XI. P**rimary and secondary end-points after peripheral and central VA-ECMO implantation stratified by institutional volume.**

Variables*	Peripheral VA-ECMO			Central VA-ECMO		
	Low-volume 164 pts	High-volume† 372 pts	*P* value	Low-volume 123 pts	High-volume† 122 pts	*P* value
Primary end-point						
In-hospital mortality	110 (67.1)	217 (58.3)	0.07	93 (75.6)	83 (68.0)	0.24
Secondary end-points						
Reoperation for bleeding/tamponade	60 (36.6)	131 (35.2)	0.84	75 (61.0)	62 (50.8)	0.14
Stroke	27 (16.5)	66 (17.7)	0.81	31 (25.2)	24 (19.7)	0.38
Dialysis	65 (39.6)	221 (59.4)	<0.001	52 (42.3)	71 (58.2)	0.01
Liver failure	49 (29.9)	156 (41.9)	0.01	25 (20.3)	35 (28.7)	0.17
Multiorgan failure	87 (53.0)	192 (51.6)	0.83	64 (52.0)	47 (38.5)	0.05
DSWI	6 (3.7)	13 (3.5)	1.00	2 (1.6)	8 (6.6)	0.10
Vascular access site infection	10 (6.1)	50 (13.4)	0.02	1 (0.8)	6 (4.9)	0.12
Sepsis	23 (14.0)	117 (31.5)	<0.001	17 (13.8)	22 (18.0)	0.47
Peripheral vascular complications	9 (5.5)	40 (10.8)	0.07	9 (7.3)	11 (9.0)	0.80
RBC units transfused, u	15 [8-28]	15 [7-27]	0.47	19 [13-39]	22 [10-38]	0.65
More than 9 RBC units transfused	105 (64.0)	239 (64.2)	1.00	109 (88.6)	94 (77.0)	0.03
Chest drains output 24h after surgery, mL	1116 [610-1280]	800 [500-1341]	0.03	1790 [863-1960]	1580 [766-2385]	0.68
ICU stay, d	9.5 [4.0-22.25]	13.0 [5.0-24.25]	0.06	11.0 [5.5-19.0]	13.0 [3.0-23.0]	0.69
Hospital stay, d	13.0 [5.0-30.25]	18.0 [6.0-38.25]	0.09	13.0 [6.00-25.0]	14.0 [4.0-27.75]	0.95
More than 10 days on VA-ECMO	27 (16.5)	101 (27.2)	0.01	24 (19.5)	33 (27.0)	0.21
Successful weaning from VA-ECMO	82 (50.0)	189 (50.8)	0.94	57 (46.3)	51 (41.8)	0.56
Postoperative VAD or Heart transplant	9 (5.5)	8 (2.2)	0.08	7 (5.7)	5 (4.1)	0.78

CI, confidence interval; *CPB*, cardiopulmonary bypass; *DSWI*, deep sternal wound infection; *ICU*, intensive cardia unit; *LVAD*, left ventricular assist device; *RBC*, red blood cell; *LVAD*, left ventricular assist device; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

*Continuous data are presented as median [interquartile range]; categorical variables as number (percent).

†High-volume centers are defined as per >50 cases of postcardiotomy VA-ECMO implanted during the study period.

Table XII. Subgroup analysis for mortality and bleeding according to peripheral and central VA-ECMO with reference to timing of ECMO insertion.

Failure to wean from CPB in the operating room							
Outcomes[*]	**Peripheral VA-ECMO 184 pts**	**Central VA-ECMO 115 pts**	***P* value**	**Odds Ratio**[†]	**95% CI**	***P* value**	$P_{interaction}$[‡]
In-hospital mortality	127 (69)	90 (78.3)	0.11	2.02	1.12-3.63	0.02	0.58
Reoperation for bleeding/tamponade	77 (41.8)	62 (53.9)	0.06	1.59	0.99-2.56	0.06	0.75
More than 9 RBC units transfused	130 (70.7)	96 (83.5)	0.02	2.20	1.21-3.99	0.01	0.07
Successful weaning from VA-ECMO	80 (43.5)	44 (38.3)	0.44	0.68	0.41-1.13	0.13	0.80
Heart failure after weaning from CPB							
Outcomes[*]	**Peripheral VA-ECMO 274 pts**	**Central VA-ECMO 100 pts**	***P* value**	**Odds Ratio**[†]	**95% CI**	***P* value**	$P_{interaction}$[‡]
In-hospital mortality	155 (56.6)	68 (68.0)	0.06	2.04	1.21-3.42	0.007	0.80
Reoperation for bleeding/tamponade	88 (32.1)	55 (55.0)	<0.001	2.67	1.64-4.34	<0.001	0.88
More than 9 RBC units transfused	164 (59.9)	85 (85.0)	<0.001	3.92	2.11-7.29	<0.001	0.41
Successful weaning from VA-ECMO	154 (56.2)	50 (50.0)	0.34	0.66	0.41-1.07	0.09	0.87

CI, confidence interval; *RBC*, red blood cell; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

[*]Continuous data are presented as mean (standard deviation) or median [interquartile range]; categorical variables as number (percent).

[†]Reference for the events: central VA-ECMO group. Model adjusted for gender, age, prior cardiac surgery, preoperative left ventricular ejection fraction, coronary artery bypass grafting, history of stroke, urgent/emergent status, and arterial lactate pre-ECMO insertion ≥ 6 mmol/L.

[‡]*P*interaction: p-value for main interaction effect using likelihood ratio test fitting the models with and without interaction terms.

Table XIII. Demographic and preoperative characteristics of the studies included in the systematic review.*

Study (Author, Year)	Design	Country	Study period	Pts.N.	Age	Male	BMI	COPD	Redo	EuroSCORE II	Emergency	CABG†
Ko et al. 2002[1]	Retr. Monoc.	Taiwan	1994-2000	76	57 ± 16	63.2	-	-	-	-	-	56.6
Rastan et al. 2010[2]	Retr. Monoc.	Germany	1996-2008	517	64 ± 11	71.5	-	13.0	-	21.6 ± 20.7‡	39.7	64.5
Pokersnik et al. 2012[3]	Retr. Monoc.	USA	2005-2010	49	65 ± 13	67.3	-	12.2	55.1	-	-	67.4
Unosowa et al. 2012[4]	Retr. Monoc.	Japan	1992-2007	47	64 ± 13	74.5	23.2±3.3	-	8.5	-	46.8	51.1
Mikus et al. 2013[5]	Retr. Monoc.	Italy	2007-2011	14	52 ± 19	64.3	27.9±5.0	14.3	28.6	-	42.9	21.4
Loforte et al. 2014[6]	Retr. Multic.	Italy	2006-2012	118	61§	64.4	-	-	33.8	25.7‡,§	-	57.6
Papadopoulos et al. 2015[7]	Retr. Monoc.	Germany	2001-2013	360	62 ± 17	76.1	-	8.9	-	-	-	55.3
Zhao et al. 2015[8]	Retr. Monoc.	China	2004-2012	24	59 ± 12	79.2	-	-	-	-	-	83.3
Khorsandi et al. 2016[9]	Retr. Multic.	UK	1995-2015	23	60 ± 15	85.2	-	-	17.4	-	-	39.1
Mazzeffi et al. 2016[10]	Retr. Monoc.	USA	2010-2015	23	57 ± 15	60.9	-	-	-	-	-	30.4
Biancari et al. 2017[11]	Retr. Multic.	Europe/Arabia	2005-2016	148	65 ± 9	78.4	-	16.9	-	19.2 ± 17.7	54.1	100.0
Guihaire et al. 2017[12]	Retr. Monoc.	France	2005-2014	92	-	57.6	-	-	25.0	-	35.9	13.0
Raffa et al. 2017[13]	Retr. Monoc.	The Netherlands	2007-2017	83	65§	65.1	26.6±5.35	12.5	20.9	6.6 ± 9.9	38.4	34.2
Slottosh et al. 2017[14]	Retr. Monoc.	Germany	2008-2016	100¶	58 ± 15	76.0	26.9±4.9	9.4	20.0	-	37.0	69.0
Zhong et al. 2017[15]	Retr. Monoc.	China	2009-2016	36	50 ± 12	91.7	25.4±4.3	-	41.7	-	25.0	0.0

BMI, body mass index; *CABG*, coronary artery bypass grafting; *COPD*, chronic obstructive pulmonary disease.

*Data are expressed as mean and standard deviation for continuous variables, and as percentage for categorical variables.

†Isolated CABG or CABG with concomitant cardiac procedures are all included.

‡Expressed as Logistic EuroSCORE.

§Expressed as mean only, no standard deviation (SD) provided.

¶Patients with for postcardiotomy ECMO n=100 among a total 139 ECMO patients; other variables refer to the entire patient cohort.

Table XIV. Detailed ECMO characteristics of the studies included in the systematic review.[*]

Study (Author, Year)	Pts.N.	ECMO cannulation		ECMO at surgery	ECMO Duration (d)	Weaning Success	IABP
		Central (Aorta)	Axillary artery				
Ko et al. 2002[1]	76	19.7	0.0	51.3	4.1 ± 1.3	48.7	76.0
Rastan et al. 2010[2]	517	60.8	11.9	41.9	3.3 + 2.9	63.5	74.1
Pokersnik et al. 2012[3]	49	34.7	0.0	-	-	55.1	59.2
Unosowa et al. 2012[4]	47	31.9	0.0	70.2	2.7 ± 2.6	61.7	17.0
Mikus et al. 2013[5]	14	50.0	0.0	-	9 + 13.8	50.0	92.9
Loforte et al. 2014[6]	118	47.5	-	-	10.8*	55.1	100,0
Papadopoulos et al. 2015[6]	360	36.0	63.1	-	7 ± 1	58.1	31.1
Zhao et al. 2015[7]	24	4.2	0.0	45.8	4.8 ± 2.9	66.7	87.5
Khorsandi et al. 2016[9]	23	60.9	0.0	34.8	5.4[†]	-	39.1
Mazzeffi et al. 2016[10]	23	60.9	-	13.0	3[‡]	60.8	-
Biancari et al. 2017[11]	148	39.9	59.1	51.4	6.4 ± 5.6	-	32.0
Guihaire et al. 2017[12]	92	15.2	-	46.7	-	-	27.2
Raffa et al. 2017[13]	83	32.8	-	53.5	5.0[‡]	49.4	10.5
Slottosh et al. 2017[14]	100	28.0	0.0	60.0	4.9 ± 3.3	-	83.0
Zhong et al. 2017[15]	36	19.4	25.0	66.7	3.2 ± 1.4	-	25.0

ECMO, extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump.

[*]Data are expressed as mean and standard deviation for continuous variables, and as percentage for those categorical.

[†]Expressed as mean only, no standard deviation (SD) provided.

[‡]Expressed as median only, no mean or standard deviation provided.

Table XV. Postoperative complications following ECMO implantation in the included studies.[*]

Study (Author, Year)	Mortality	Bleeding Tamponade	CVA	GI complications	RRT	Limb ischemia[†]	Sepsis
Ko et al. 2002[1]	43.4	46.1	11.8	-	-	43.4	-
Rastan et al. 2010[2]	75.2[‡]	58.0	17.4	18.8	65.0	19.9	-
Pokersnik et al. 2012[3]	67.3	71.4	6.1	-	32.7	-	-
Unosowa et al. 2012[4]	70.2	70.2	21.3	-	31.9	25.5	-
Mikus et al. 2013[5]	50.0	64.3	14.3	-	57.1	-	42.9
Loforte et al. 2014[6]	53.4	58.4	16.9	-	55.1	5.9	22.0
Papadopoulos et al. 2015[7]	70.0[§]	41.1	11.9	16.1	61.1	13.1	-
Zhao et al. 2015[8]	66.7	16.7	8.3	20.8	29.2	8.3	45.8
Khorsandi et al. 2016[10]	65.2	8.7	21.7	-	26.0	21.7	-
Mazzeffi et al. 2016[11]	69.6	8.7	17,4	-	47.8	-	18.8
Biancari et al. 2017[11]	64.2	41.9	23.6	10.8	45.3	10.8	24.3
Guihaire et al. 2017[12]	63.0	19.6	3.3	-	-	9.8	-
Raffa et al. 2017[13]	62.8	46.4	20.2	15.5	29.8	10.7	21.4
Slottosh et al. 2017[14]	71.0	63.0	-	-	-	-	-
Zhong et al. 2017[15]	50.0	25.0	11.1	-	25.0	13.9	13.9

CVA, cerebrovascular accident; *GI*, gastro-intestinal; *RRT*, renal replacement therapy.

[*]Dara are expressed in percentages.

[†]Lower limb ischemia defined as an acute impaired circulation to the lower extremities, necessitating endovascular or surgical revascularization, and/or major surgery (i.e. amputation).

[‡]Adjusted mortality for central VA-ECMO cannulation: OR 0.91 (95%CI, 0.59-1.40, *P*=0.666).

[§]Adjusted mortality for central VA-ECMO cannulation: OR 1.5 (95% CI, 0.45-1.85, P=0.37).

Table XVI. Quality assessment of the included studies.

Study (Author/Year)	Newcastle-Ottawa Scale[78]			Cochrane Risk of Bias Analysis[79]					USPSTF design-specific quality criteria[80]
	Selection	Comparability	Outcome	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	
Ko et al. 2002[1]	**	**	***	Low	High	High	High	High	Poor
Rastan et al. 2010[2]	**	**	***	High	Low	Low	High	High	Fair
Pokersnik et al. 2012[3]	**	**	**	High	Low	Low	Low	Low	Fair
Unosowa et al. 2012[4]	**	**	**	High	High	Unclear	High	Unclear	Poor
Mikus et al. 2013[5]	**	**	***	Low	Low	Low	Low	Low	Fair
Loforte et al. 2014[6]	**	*	**	Low	Low	Low	Low	Low	Poor
Papadopoulos et al. 2015[7]	**	**	**	High	High	Low	High	High	Poor
Zhao et al. 2015[8]	**	**	**	High	High	Low	High	High	Fair
Khorsandi et al. 20169	*	*	**	High	High	Low	Low	Low	Poor
Mazzeffi et al. 2016[10]	***	***	***	High	Low	Low	Low	Low	Fair
Biancari et al. 2017[11]	***	**	***	Low	High	Low	Low	Low	Fair
Guihaire et al. 2017[12]	***	*	***	Low	High	Low	Low	Low	Fair
Raffa et al. 2017[13]	**	*	**	Low	High	High	Low	Low	Fair
Slottosh et al. 2017[14]	***	***	**	High	High	Low	High	High	Fair
Zhong et al. 2017[15]	**	**	**	High	High	Low	High	High	Poor

USPSTF indicates US Preventive Services Task Force.

Supplemental Figures

Figure I. Mirror histogram of the propensity score with distribution balance for the entire cohort of patients in the upper panel, and mirror histogram of the propensity score with distribution balance without patient crossed from peripheral to central VA-ECMO group during the study period.

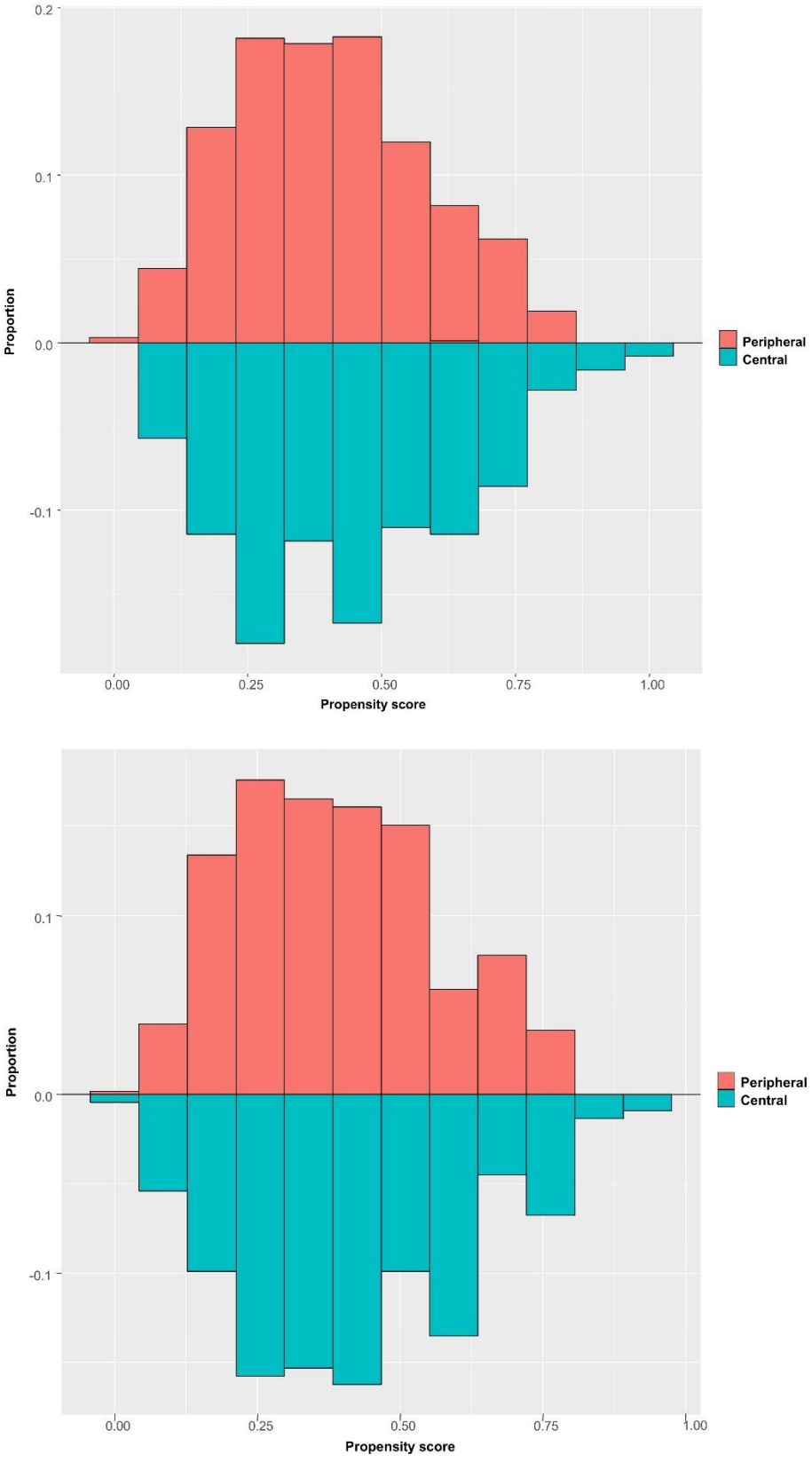


Figure II. Love plot summarizing covariate balance before and after conditioning for the entire patient cohort.

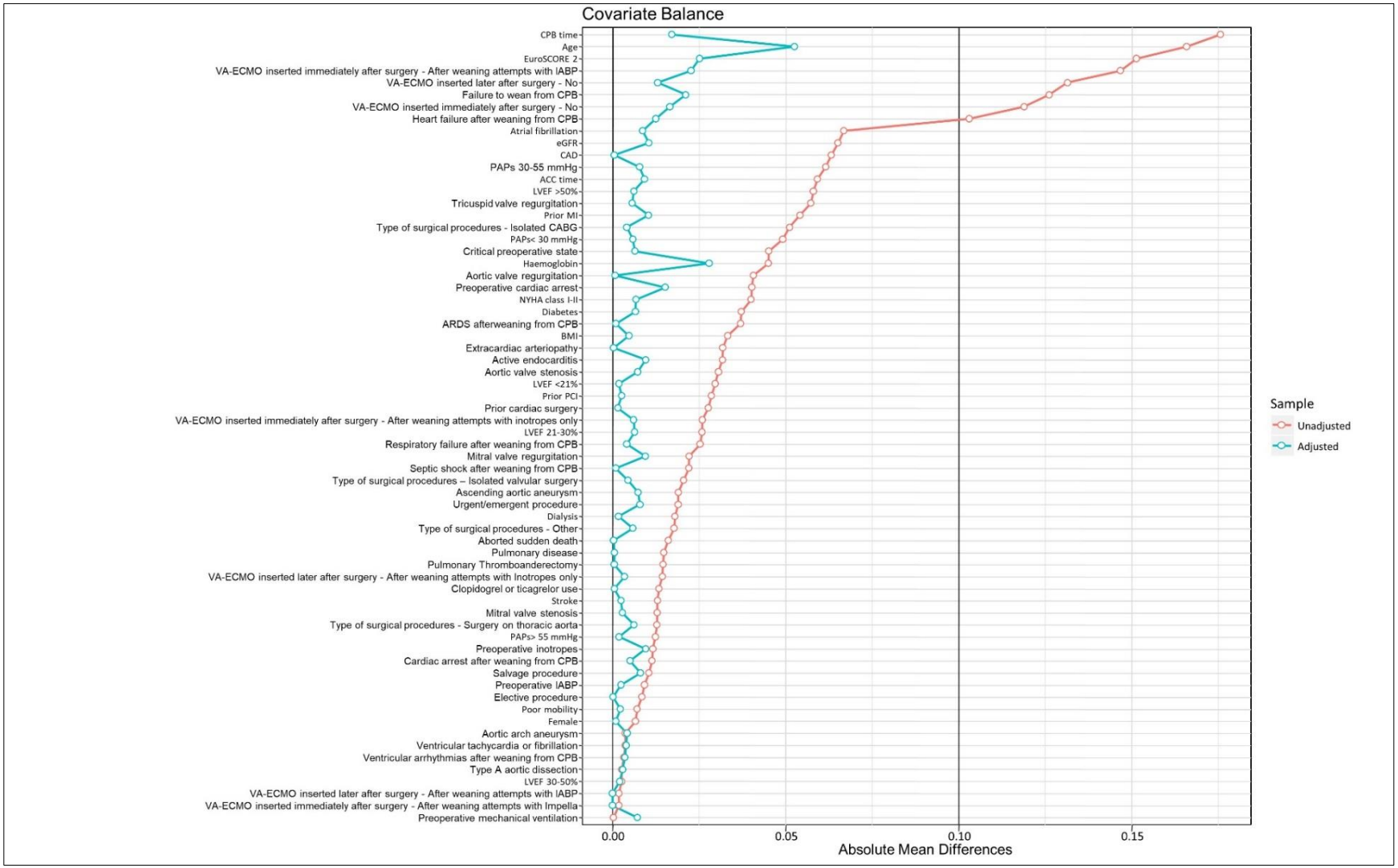


Figure III. Love plot summarizing covariate balance before and after conditioning without patient crossed from peripheral to central VA-ECMO group during the study period.

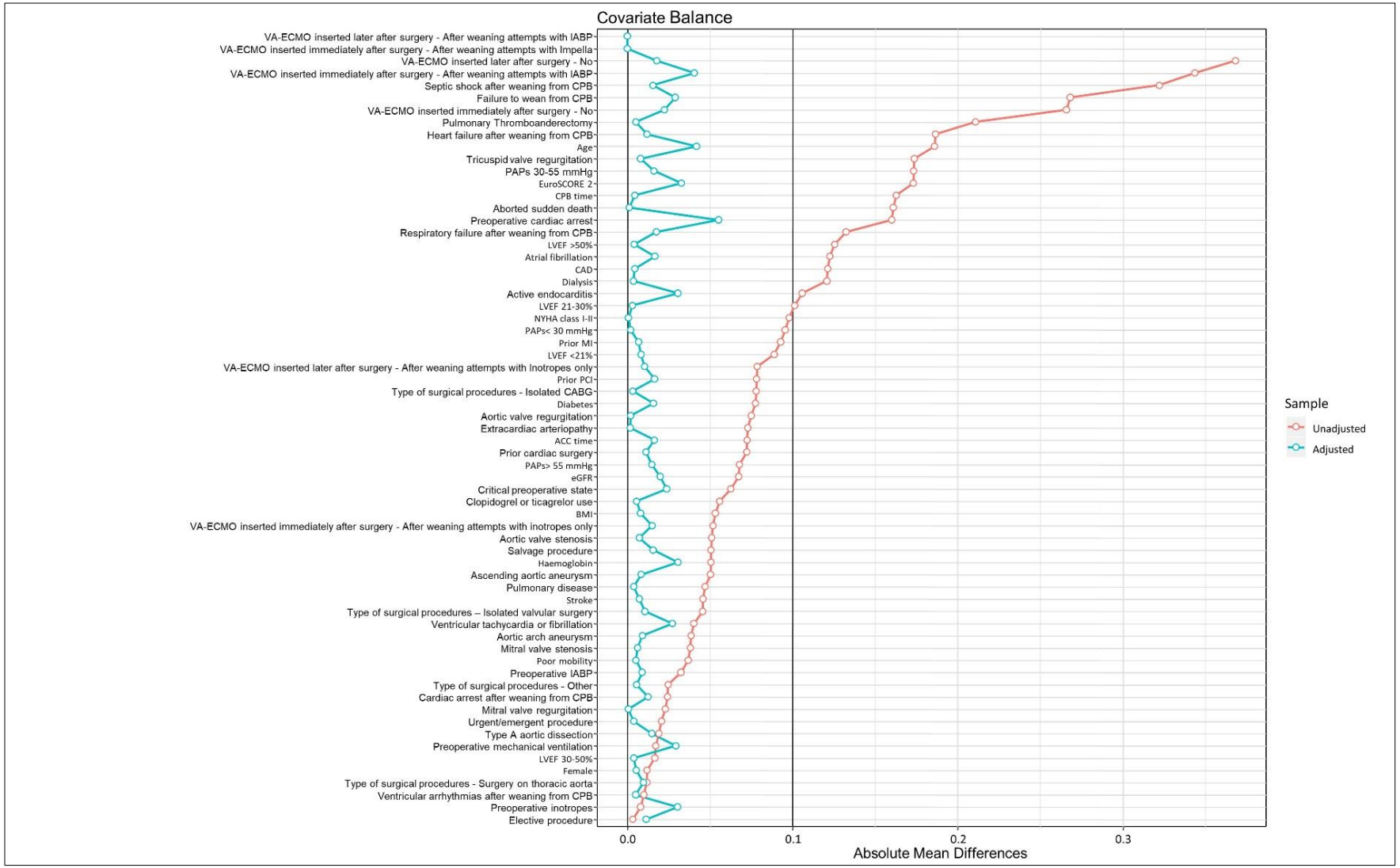


Figure IV. Hospital mortality during the entire study period (Chi-square test for independence: *P* = 0.26).

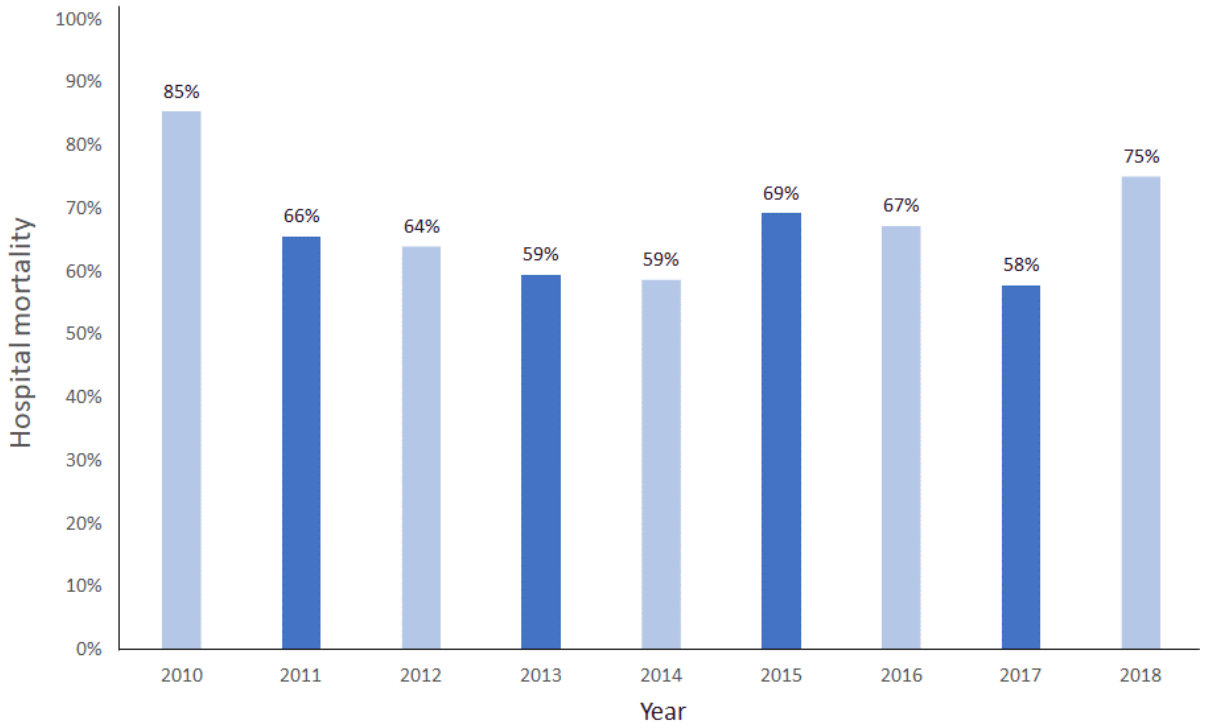


Figure V. PRISMA flow chart of search strategy.[81]

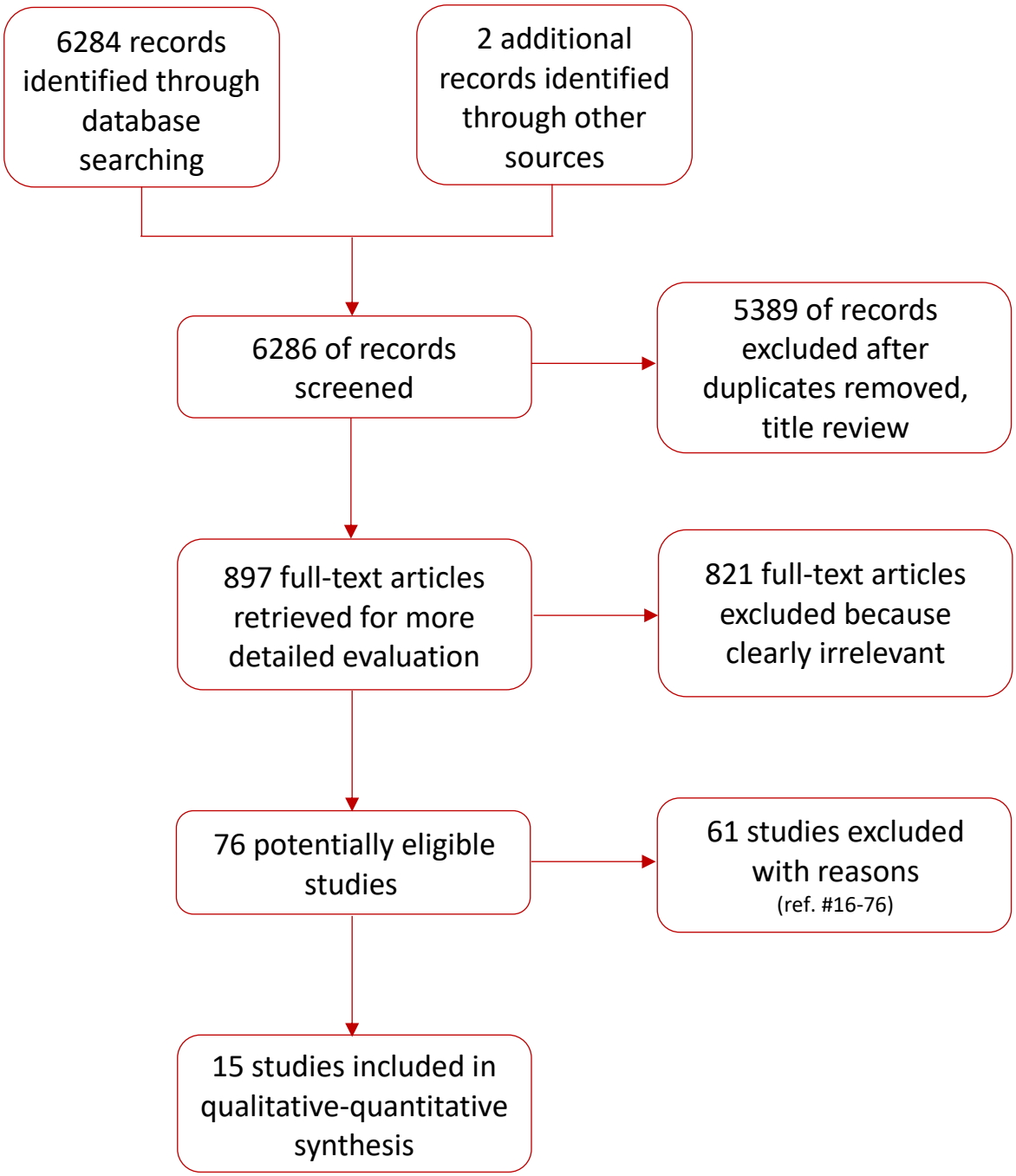
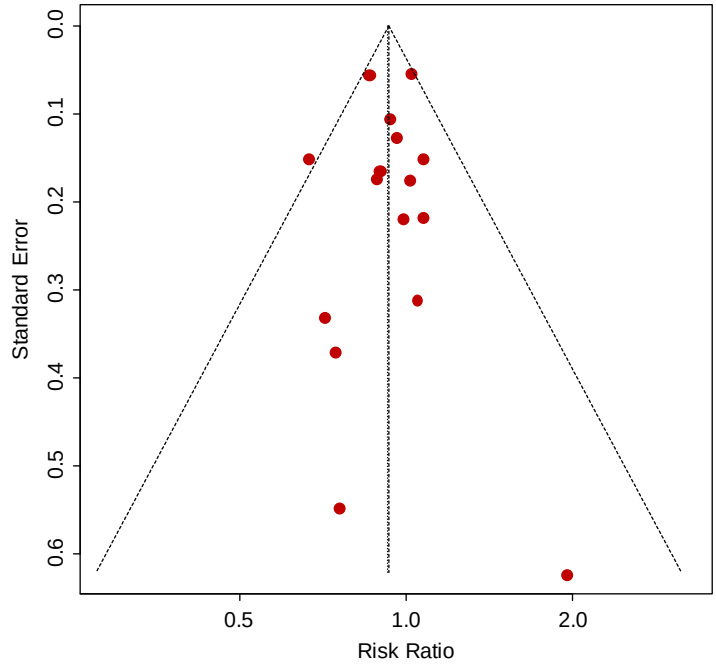


Figure VI. Funnel plot (upper panel) and radial plot (lower panel) for in-hospital/30-day mortality showing no heterogeneity among studies and evidence of publication bias (Egger's test, df = 14, *P*=0.916), respectively.



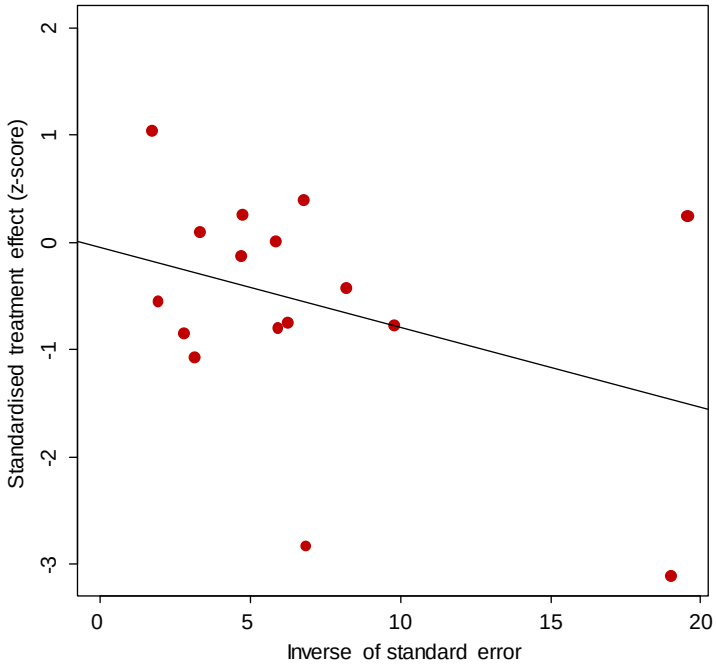
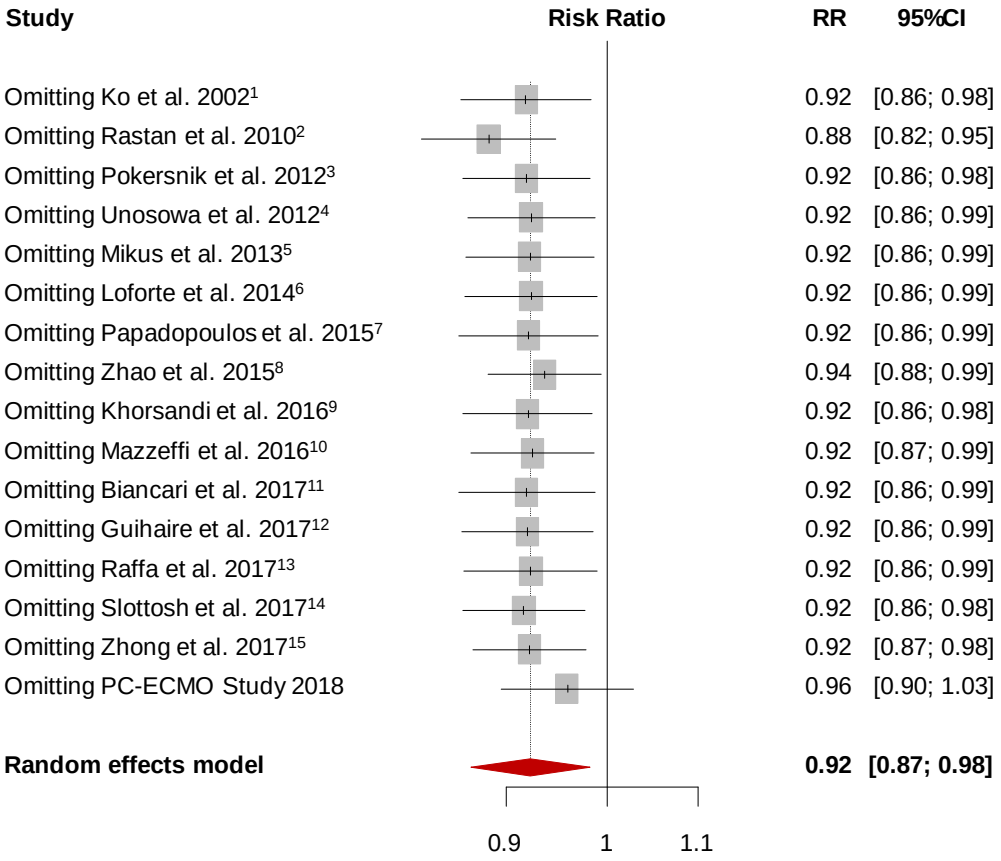


Figure VII. Leave-one-out meta-analysis (influence analysis) on in-hospital/30-day mortality (upper panel), and leave-one-out meta-analysis for sensitivity analysis on in-hospital/30-day mortality after exclusion of the study of Rastan et al.[2] (lower panel). Pooled estimates are calculated omitting one study at a time.



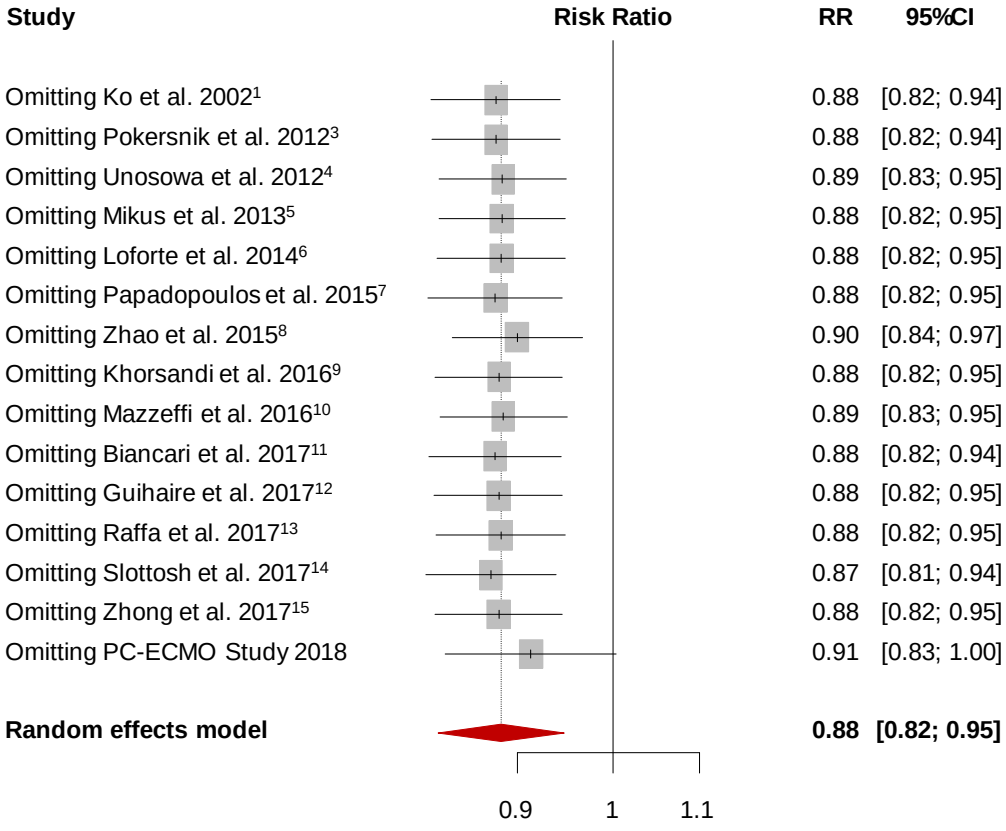


Figure VIII. Forest plots with unadjusted risk estimates for in-hospital/30-day mortality in patients who underwent peripheral *versus* central ECMO. *CI* indicates confidence interval; *RR*, risk ratio.

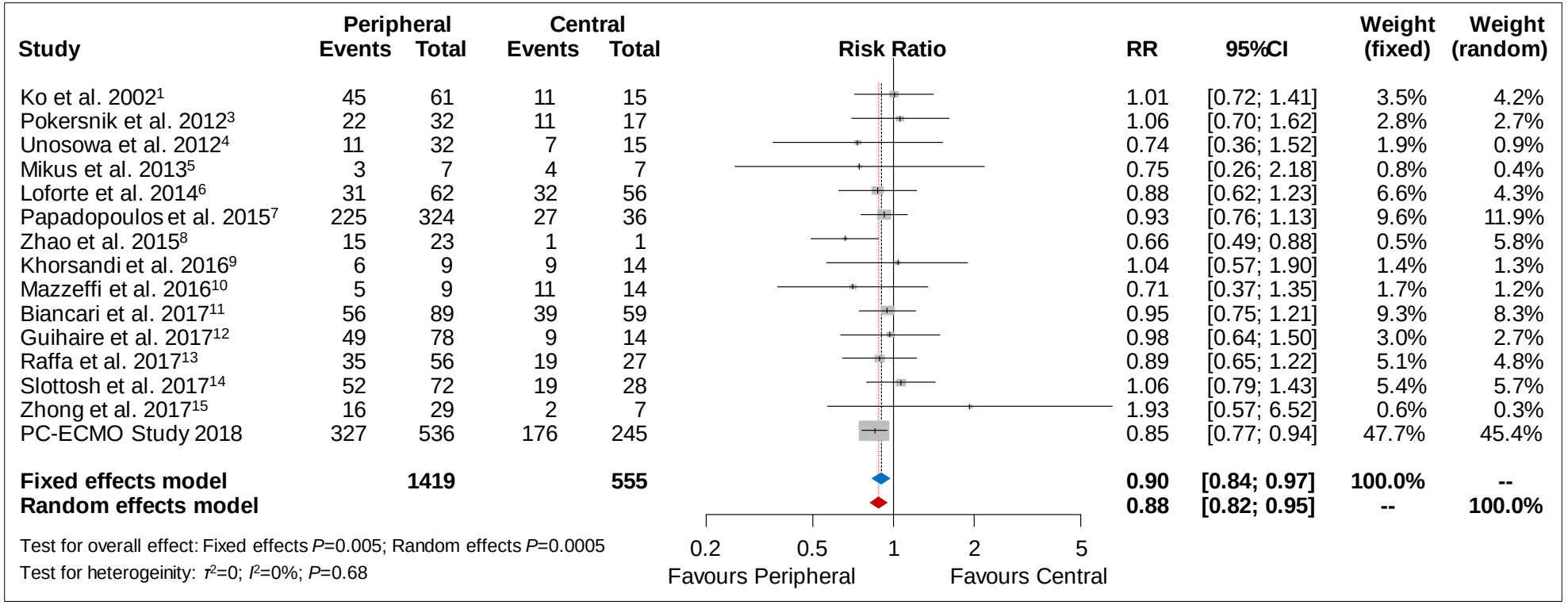


Figure IX. Forest plot with adjusted risk estimates for in-hospital/30-day mortality in patients who underwent peripheral *versus* central ECMO. *CI* indicates confidence interval; *RR*, risk ratio; *SE*, standard error.

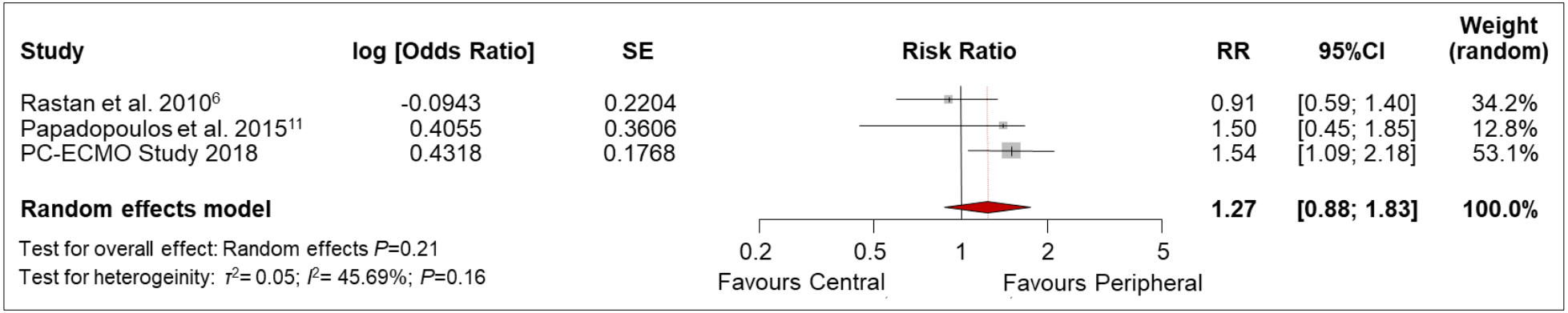


Figure X. Forest plots with unadjusted risk estimates for stroke (top), re-opening for bleeding/tamponade (central), and lower limb complications (bottom) in patients who underwent peripheral versus central arterial ECMO cannulation. CI indicates confidence interval; RR, risk ratio.

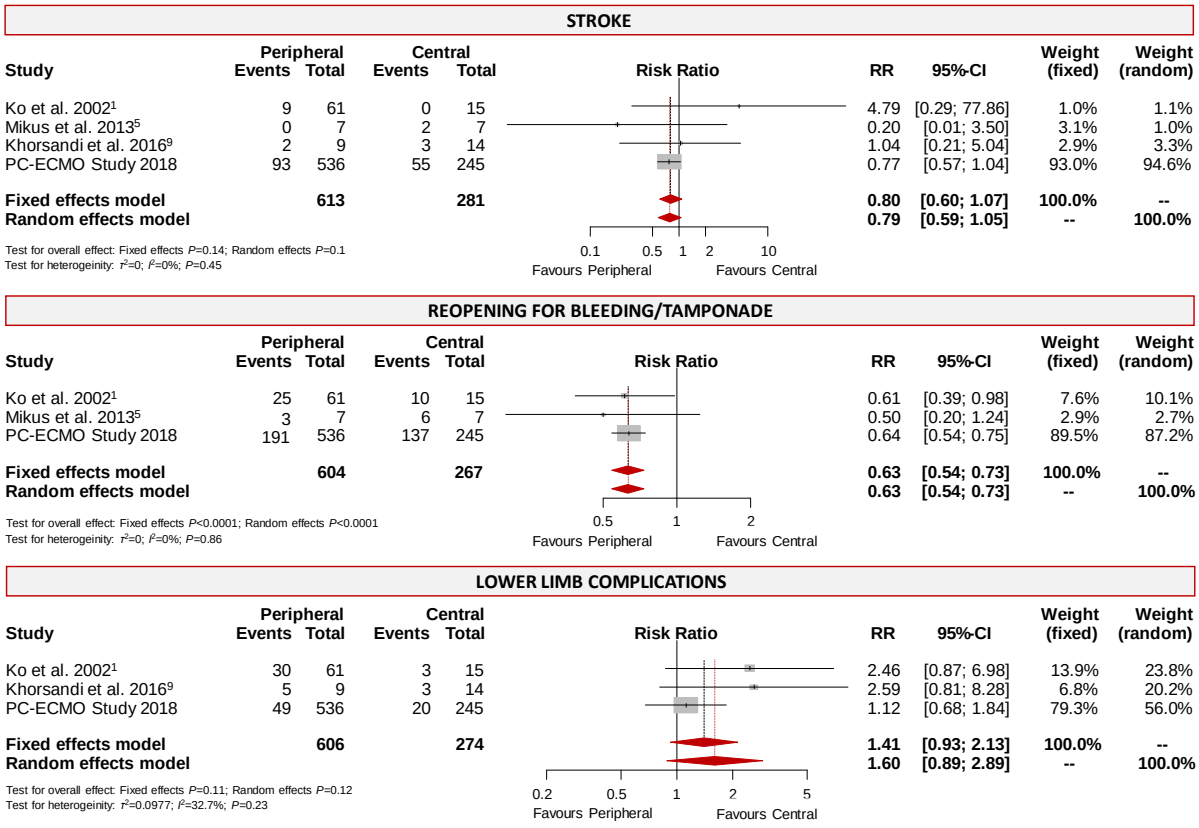
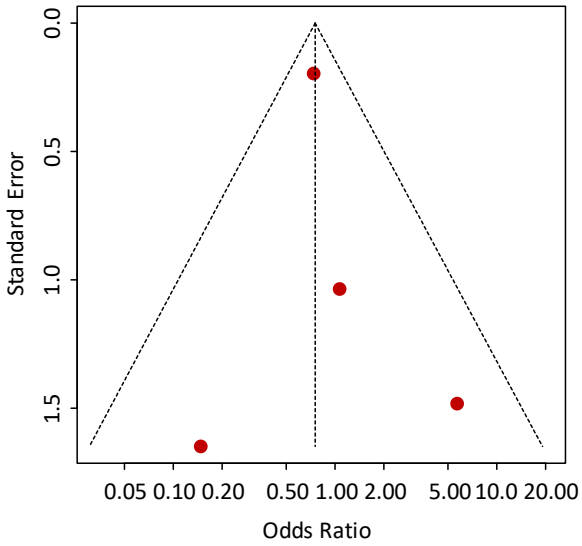


Figure XI. Funnel plots showing the absence of publication bias in secondary outcomes, stroke (top), re-opening for bleeding/tamponade (central), and leg complications (bottom).


Standard Error
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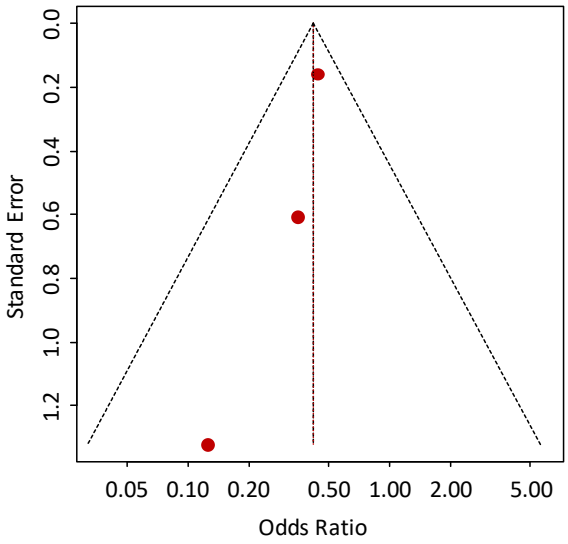
0.5
1.0
1.5
0.05 0.10 0.20 0.50 1.00 2.00 5.00 10.0 20.00
Odds Ratio


Standard Error
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0.2
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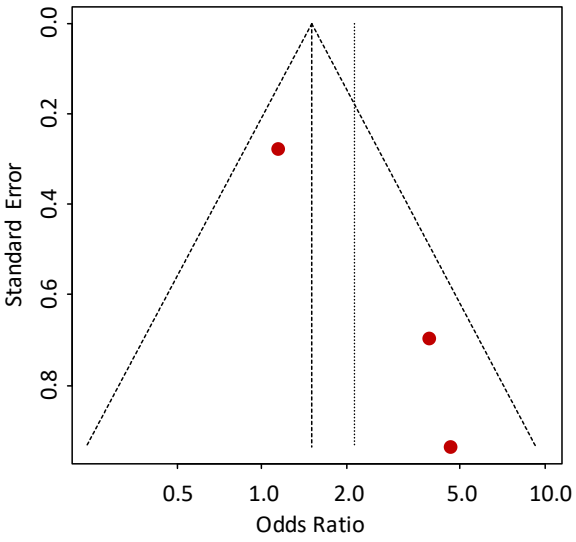
0.6
0.8
1.0
1.2
0.05 0.10 0.20 0.50 1.00 2.00 5.00
Odds Ratio


Standard Error
0.0
0.2
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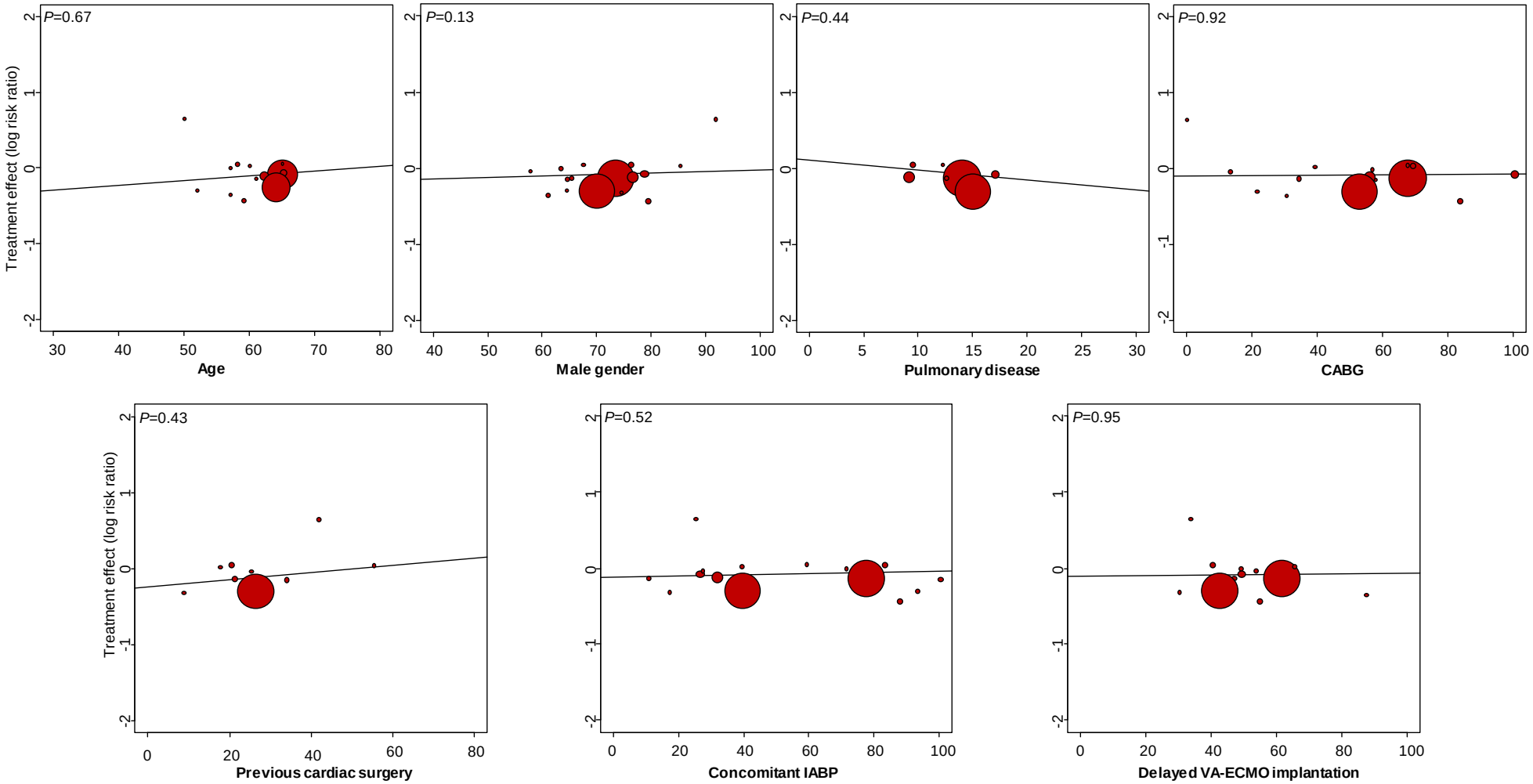
0.6
0.8
0.5 1.0 2.0 5.0 10.0
Odds Ratio

Figure XII. Meta-regression bubble plots showing the effect of age, gender (proportion of male patients), pulmonary disease, prior cardiac surgery, proportion of patients undergoing CABG, IABP, and delayed VA-ECMO implantation on cannulation site (peripheral *versus* central VA-ECMO) and in-hospital/30-day mortality. CABG indicates coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VA, veno-arterial.



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Sub-appendix

Sub-appendix I. STROBE Statement for Observational Studies.[82]

	Item No	Recommendation	Reported on Page N.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3,4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6

		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

Sub-appendix II. MOOSE Checklist for Meta-analyses of Observational Studies.[83]

Item N.	Recommendation	Reported on Page N.
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	4, Appendix
5	Type of study designs used	4,5
6	Study population	4,5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	4,5
8	Search strategy, including time period included in the synthesis and key words	4,5, Appendix
9	Effort to include all available studies, including contact with authors	4,5
10	Databases and registries searched	4, Appendix
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	Appendix
13	List of citations located and those excluded, including justification	6, Appendix
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	Appendix
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	6, Appendix
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Table 2

26	Table giving descriptive information for each study included	Appendix
27	Results of sensitivity testing (eg, subgroup analysis)	8,9
28	Indication of statistical uncertainty of findings	8,9
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	9-11
30	Justification for exclusion (eg, exclusion of non-English language citations)	9-11
31	Assessment of quality of included studies	9-11
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12
34	Guidelines for future research	12
35	Disclosure of funding source	13

Sub-appendix III. PRISMA checklist of Items to Include when Reporting a Systematic Review or Meta-analysis.[81]

Section/topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, Appendix
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5, Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4,5

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8,9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13