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Postcardiotomy Veno-Arterial Extracorporeal Membrane Oxygenation in Patients Aged ≥70 Years

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Running title: Postcardiotomy VA-ECMO in the elderly

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Abstract

Background: There is uncertainty whether venoarterial extracorporeal membrane oxygenation (VA-ECMO) should be used in the elderly with cardiopulmonary failure after cardiac surgery.

Methods: This is a retrospective multicenter study on 781 patients who required postcardiotomy VA-ECMO for cardiopulmonary failure after adult cardiac surgery from 2010 to 2018 at 19 cardiac surgery centers. A parallel systematic review and meta-analysis of the literature was performed.

Results: The hospital mortality in the overall PC-ECMO series was 64.4%. Two-hundred and fifty-five patients were ≥70 years old (32.7%) and their hospital mortality was significantly higher than younger patients (76.1% vs. 58.7%, adjusted OR 2.199, 95%CI 1.536-3.149). Arterial lactate >6 mmol/L before starting VA-ECMO was the only predictor of hospital mortality among patients ≥70 years old in univariate analysis (82.6% vs. 70.4%, p=0.029). Meta-analysis of the current and prior studies showed that early mortality after postcardiotomy VA-ECMO was significantly higher in patients aged ≥70 years compared with younger patients (OR 2.09, 95%CI 1.59-2.75, five studies including 1547 patients, I^2 5.9%). The pooled early mortality rate among patients aged ≥70 years was 78.8% (95%CI 74.1-83.5, six studies including 617 patients, I^2 41.8%). Two studies reported 1-year mortality (including hospital mortality) of 79.9% and 75.6%, respectively, in patients ≥70 years old.

Conclusions: Advanced age should not be considered a contraindication for postcardiotomy VA-ECMO. However, in view of the high risk of early mortality, a meaningful scrutiny is needed before using VA-ECMO after cardiac surgery in the elderly.

Key-words: Extracorporeal membrane oxygenation; Extracorporeal life support; ECMO; ECLS; Postcardiotomy; Cardiac surgery; Elderly; Septuagenarian.

Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is an effective treatment for patients with cardiopulmonary failure after cardiac surgery unresponsive to pharmacological treatment and/or intra-aortic balloon pump (1). However, only one third of patients undergoing postcardiotomy VA-ECMO survives to discharge. Advanced age is associated with increased hospital mortality and a recent pooled analysis showed that hospital survivors were significantly younger than patients who died after postcardiotomy VA-ECMO (pooled mean age, 55.7 vs. 63.6 years, p=0.015) (2). Furthermore, several studies evaluated single institutional results with postcardiotomy VA-ECMO in patients with a mean age below 60 years (3-5), which suggests that in some centers elderly are infrequently treated with VA-ECMO. Data on the outcome of elderly undergoing VA-ECMO after cardiac surgery is scarce and there is uncertainty whether the use of VA-ECMO should be contraindicated in these patients. The present study aimed to evaluate this issue from a multicenter registry and by pooling the existing data from the literature.

Patients and Methods

PC-ECMO registry

The PC-ECMO registry is a retrospective study that enrolled patients undergoing VA-ECMO after adult cardiac surgery at 19 cardiac surgery centers in Belgium, Czech Republic, Finland, France, Italy,

Germany, Saudi Arabia, Sweden and the United Kingdom, from January 2010 to March 2018. The study is registered in Clinicaltrials.gov (Identifier: NCT03508505). This study was approved by the Institutional Review Board of each participating center or the regional Ethics Review Board, where applicable. Data was collected retrospectively into an Access datasheet and underwent robust quality checking. Preoperative variables were defined according to the EuroSCORE II definition criteria (6).

Patients aged >18 years requiring VA-ECMO for severe cardiopulmonary failure refractory to pharmacological treatment and/or intra-aortic balloon pump after any cardiac surgery procedure were considered for this analysis. Patients on any type of ECMO therapy before surgery or requiring VA-ECMO after implantation of ventricular assist device or heart transplantation were excluded from this study. The study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (7) (Supplementary table 1).

The primary outcome of this observation study was hospital death. Secondary outcomes included death on VA-ECMO, 1-year all-cause mortality, length of stay in the intensive care unit, arterial complications, tracheostomy, pancreatitis, liver failure, gastrointestinal complications requiring surgical treatment, stroke or global brain ischemia, deep sternal wound infection or mediastinitis, vascular access infection, pneumonia, blood stream infection, renal replacement therapy, reoperation for excessive bleeding and red blood cell transfusion.

Systematic Review and Meta-analysis

The protocol of this study was registered in the PROSPERO registry (CRD42019120068). Population, intervention, comparator, outcomes, and study design of this analysis are summarized in Supplementary Table 2. This meta-analysis was performed following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group guidelines (8) (Supplementary table 3). and

the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (9) Supplementary table 4).

The exposure of interest was the use of VA-ECMO during the index hospitalization after any adult cardiac surgery procedure. Studies comparing the outcome of patients aged <70 years versus patients aged ≥70 years, as well as one-arm studies including only patients aged ≥70 years were considered for this study. The primary outcome was all-cause death during hospitalization or within 30-day after the index cardiac surgery procedure.

Electronic databases of PubMed, Scopus and Google Scholar were searched on November 20, 2018 without date restriction for articles published in English language. Search criteria included different combinations of the following terms: "Extracorporeal membrane oxygenation", "ECMO", "Extracorporeal life support", "ECLS", "Cardiac surgery", "Postcardiotomy". Reference lists of pertinent articles were also reviewed. Reference lists of the retrieved articles were searched for articles of interest as well. Abstracts and full-text articles were independently reviewed and the data collected by two senior cardiac surgeons (F.B., G.M.). Discrepancies were resolved through consensus. Authors of the retrieved studies were not contacted for missing or additional data. The Quality Assessment Tool for Case Series Studies of the National Heart, Lung and Blood Institute (10) was used to assess the methodological quality of the included studies.

Statistical analysis

Statistical analyses were performed using Stata v. 15.1 (StataCorp LLC, Texas, USA), SPSS v. 25.0 (IBM Corporation, New York, USA) and Meta-analyst (http://www.cebm.brown.edu/openmeta/: accessed on December 2018) statistical softwares. The age of patients was stratified in four categories (<60 years, 60-69 years, 70-79 years and ≥80 years) and its impact on hospital mortality was evaluated

with the Linear-by-linear association test. Logistic regression was used to adjust the impact of increasing age as adjusted for all covariates listed in Table 1. All eligible patients included in the PC-ECMO registry were included in this analysis. Missing data was not replaced in these analyses. The baseline characteristics and outcomes of patients aged <70 years versus patients aged ≥70 years were then compared using the Fisher's exact tests, Chi-square tests and Mann-Whitney's test. Late mortality was estimated with the Kaplan-Meier method with the log-rank test. Logistic regression was employed to identify risk factors associated with hospital death after postcardiotomy VA-ECMO and the regression models included the following risk factors preceding the initiation of VA-ECMO with $p<0.05$ in univariate analysis: age, female gender, estimated glomerular filtration rate, pulmonary disease, prior cardiac surgery, recent stroke or unconsciousness, aortic cross-clamp time, aortic arch surgery and arterial lactate level at start of VA-ECMO. Mixed-effect logistic regression was performed to assess interinstitutional differences in hospital mortality. The outcomes of studies evaluating patients aged <70 years versus patients aged ≥70 years were pooled with the random-effects method leading to computations of odds ratios (OR) with 95% confidence intervals (CI). The outcomes of retrieved studies are reported as pooled proportions with 95%CI. I^2 statistic was used to estimate the heterogeneity of the studies, with $I^2 > 40\%$ as a threshold for significant heterogeneity. Publication bias was assessed by inspecting funnel plot asymmetry. $P<0.05$ was set for statistical significance.

Results

PC-ECMO Registry

The age of patients who required postcardiotomy VA-ECMO in the PC-ECMO registry was distributed as follows: <60 years, 245 (31.4%); 60-69 years, 281 (36.0%); 70-79 years, 227 (29.1%); ≥80 years, 28

(3.6%). The hospital mortality rate in the overall series was 64.4% and increased along with age (<60 years, 52.2%; 60-69 years, 64.4%, 70-79 years, 75.3%; ≥80 years, 82.1%, Linear-by-linear association test, p<0.0001, adjusted OR 1.594, 95%CI 1.092-2.327; OR 2.733, 95%CI 1.779-4.200; OR 4.574, 95%CI 1.614-12.963, respectively, when compared with patients aged <60 years). Since the risk of hospital mortality increased substantially in patients ≥70 years old, the outcome of this subset of patients was compared with that of patients <70 years old.

Outcome in patients ≥70 years old

In the PC-ECMO registry, 255 patients were ≥70 years old (32.7%) and required postcardiotomy VA-ECMO. These elderly patients had a significantly increased operative risk compared to younger patients (EuroSCORE II, mean 20.5±20.8 vs. 13.2±14.5%, p<0.0001) as well as decreased estimated glomerular filtration rate (p<0.0001), higher prevalence of atrial fibrillation (p<0.0001), extracardiac arteriopathy (p<0.0001), prior stroke (p=0.016) and less frequently underwent surgery of the ascending aorta (p=0.005) and for repair of congenital defects (p=0.029). The other baseline covariates did not differ between the study cohorts (Tabs. 1 and 2). Regarding the VA-ECMO therapy, beside the duration of support which was shorter in the elderly patients (p<0.0001), the treatment strategy and its related complications were similar between the study cohorts (Table 3).
Hospital mortality was higher in patients ≥70 years old when compared with younger patients, also when adjusted for baseline covariates (crude rates 76.1% vs. 58.7%, p<0.0001, adjusted OR 2.199, 95%CI 1.536-3.149). They had also an increased risk of death on VA-ECMO (58.4% vs. 42.0%, p<0.0001) and higher risk of renal replacement therapy (59.2% vs. 50.6%, p=0.025) (Table 4). Patients ≥70 years old had a shorter stay in the intensive care unit (p<0.0001), which reflects their shorter duration of VA-ECMO therapy (mean, 6.2±5.4 vs. 8.3±6.6 days, p=0.043) (Table 3). Their risk to

develop other early adverse events was not increased when compared with younger patients (Table 4). Arterial lactate >6 mmol/L before starting VA-ECMO was the only predictor of hospital mortality among in patients aged ≥70 years in univariate analysis (82.6% vs. 70.4%, compared to patients with lower values, p=0.029, 25 patients (9.8%) had missing data).

One-year all-cause mortality (including early mortality) was 60.7% in patients aged <70 years and 79.9% in patients aged ≥70 years (log-rank test, p<0.0001).

Interinstitutional analysis

The proportion of patients aged ≥70 years among the participating centers ranged from 0 to 52.9% (Likelihood ratio, p<0.0001) (Supplementary figure 1) and their hospital mortality ranged from 50.0 to 100% (Likelihood ratio, p=0.091) (Supplementary figure 1). Mixed-effect logistic regression adjusted for age, pre-VA-ECMO arterial lactate level and EuroSCORE II showed that there were no significant interinstitutional differences in terms of hospital mortality among these elderly (p=0.100).

Systematic Review and Meta-analysis of Literature Data

Of the 471 records identified (Supplementary table 5), five studies fulfilling the inclusion criteria (1,4,11-13) and the present one were the subjects of this meta-analysis (Supplementary figure 2). Their characteristics are summarized in Table 5 and Supplementary table 6. All studies reported on hospital mortality, but one which reported on 30-days mortality (11). Early mortality after postcardiotomy VA-ECMO was significantly higher in patients aged ≥70 years (patients <70 years old: 62.5%, 95%CI 54.4-70.5, five studies, 1057 patients; patients ≥70 years old 80.1%, 95%CI 74.6-85.65, five studies, 490 patients, OR 2.09, 95%CI 1.59-2.75, I^2 5.9%) (Fig. 1A). No significant publication bias was observed between the included studies (Supplementary figure fig. 3). When all studies

evaluating the outcome of patients aged ≥70 years were pooled, the early mortality rate was 78.8% (95%CI 74.1-83.5) (six studies, 617 patients, I^2 41.8%) (Fig. 1B). Among patients ≥70 years old, the study by Saxena et al. (13) and the present one reported a 1-year mortality (including hospital mortality) of 75.6% and 79.9%, respectively.

Comment

Population aging prompts the assessment of short and long-term benefits and harms of invasive cardiovascular interventions in the elderly. This issue is of importance particularly in the setting of elderlies with critical clinical conditions in view of their limited expectancy of life. Indeed, there are serious clinical and ethical concerns regarding the invasive treatment of acute cardiovascular diseases in old patients (14). The excessive morbidity and mortality associated with salvage therapies for life-threatening diseases are some of the aspects to consider in the decision-making process before starting postcardiotomy VA-ECMO. In this regard, patients' and their families' willing and possibilities to afford the short and long-term care of the potentially disabling effects of severe complications should play an important role in the clinical judgment of using VA-ECMO therapy. However, refractory cardiopulmonary failure after cardiac surgery often does not allow surgeons and anesthesiologists to discuss thoroughly the ethical issues and contextual features before starting mechanical circulatory support. In fact, the decision to start VA-ECMO is usually made at the time of weaning from cardiopulmonary bypass or during resuscitation manoeuvres outside the operating room. In the context of uncertainty regarding the use of VA-ECMO in the elderly, the present study provides insights of clinical relevance because it showed that only 20% of patients aged ≥70 years may survive after postcardiotomy VA-ECMO. Although most of these patients were alive at 1-year, such a dismal early outcome should be viewed considering the limited data on this subset of

patients, which is likely secondary to a strict patient selection and to a nihilistic approach in centres allocating VA-ECMO resources preferentially to younger patients. In fact, the significant complications, organizational efforts and excessive costs of VA-ECMO (15) prevent the use of this complex therapy to all patients with cardiopulmonary failure. The incremental costs associated with the use of ECMO and the lack of data of its cost-effectiveness (17) may speak in favour of a strict selection of elderly requiring postcardiotomy VA-ECMO in view of their short expectancy of life (15,16).

The results of this multicentre study and meta-analysis showed that this mechanical circulatory support therapy may achieve satisfactory results in patients <70 years, with a risk of hospital mortality even lower than 60%. These results further reassure about the efficacy of VA-ECMO in patients with a reasonable long expectancy of life and who may achieve a full functional recovery. On the contrary, the proportion (about 30%) of elderly patients undergoing postcardiotomy VA-ECMO in the current study may be disproportionate compared to the real benefits achieved with this expensive and complex therapy in this subset of patients. The high risk of early mortality and the frequent development of severe terminal organs and vascular complications as well as prolonged treatment in the intensive care unit in patients ≥70 years old should call for a meaningful scrutiny of the comorbidities and of the severity of cardiopulmonary failure before starting VA-ECMO therapy. Indeed, the risk and benefits of an eventual postcardiotomy VA-ECMO should be assessed also preoperatively and patients should give informed consent for its use in case of refractory postoperative cardiopulmonary failure.

In this study we were not able to identify risk factors other than arterial lactate, which may guide the decision-making process in these patients. This is likely due to the high preoperative risk of these patients (mean EuroSCORE II 20.5%), the heterogeneity of the patient population, the relatively small

size of this series and the high mortality risk observed also in patients without significant comorbidities.

The retrospective nature of the studies evaluating the outcome of postcardiotomy VA-ECMO in the elderly is a major limitation of this analysis. Secondly, the limited number of studies on this topic prevents conclusive results on the value of this therapy in old patients. Thirdly, we were not able to identify risk factors other than arterial lactate, which may be of help in the decision-making process in these critically ill and fragile patient population. Finally, we do not have data regarding the number of patients in whom VA-ECMO was denied.

Conclusions

The present findings suggest that advanced age should not be considered a contraindication for postcardiotomy VA-ECMO. However, in view of the high risk of early mortality, a meaningful scrutiny is needed before using VA-ECMO after cardiac surgery in the elderly. Further studies are needed to identify the risk factors potentially contraindicating the use of VA-ECMO in aged patients.

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Table 1. Baseline characteristics of patients who underwent postcardiotomy VA-ECMO.

Covariates	Overall series 781 pts	Age <70 years 526 pts	Age ≥70 years 255 pts	p-value
Age (years)	63.1±12.9	57.2±11.6	75.3±3.6	**<0.0001**
Female gender	249 (31.9)	165 (31.4)	84 (32.9)	0.658
Body mass index ≥30 Kg/m^2	197 (25.2)	135 (25.7)	62 (24.3)	0.683
eGFR (mL/min/1.73 m^2)	68.0±30.3	72±32	59±25	**<0.0001**
Dialysis	32 (4.1)	19 (3.6)	13 (5.1)	0.320
Anemia	366 (46.9)	236 (45.0)	130 (51.0)	0.114
Diabetes	200 (25.6)	126 (24.0)	74 (29.0)	0.128
Recent myocardial infarction	199 (25.5)	135 (25.7)	64 (25.1)	0.865
STEMI	115 (14.7)	80 (15.2)	35 (13.7)	0.583
Prior stroke	60 (7.7)	32 (6.1)	28 (11.0)	**0.016**
Atrial fibrillation	192 (22.3)	106 (20.2)	86 (33.7)	**<0.0001**
Pulmonary disease	110 (14.1)	76 (14.4)	34 (13.3)	0.674
Extracardiac arteriopathy	118 (15.1)	62 (11.8)	56 (22.0)	**<0.0001**
Active endocarditis	85 (10.9)	56 (10.6)	29 (11.4)	0.760
Prior PCI	146 (18.7)	94 (17.9)	52 (20.4)	0.593
Prior cardiac surgery	186 (23.8)	124 (23.6)	62 (24.3)	0.820
LVEF ≤50%	461 (59.2)	312 (59.5)	149 (58.4)	0.767
Critical preoperative state	276 (35.3)	191 (36.3)	85 (33.3)	0.414
Ventricular arrhythmia	37 (4.7)	26 (4.9)	11 (4.3)	0.698
Preoperative IABP	62 (7.9)	41 (7.8)	21 (8.2)	0.831
Acute stroke/unconsciousness	27 (3.5)	20 (3.8)	7 (2.7)	0.448
Sys. pulmonary a. pressure				0.386

31-55 mmHg	237 (30.3)	156 (29.7)	81 (31.8)	
>55 mmHg	139 (17.8)	89 (16.9)	50 (19.6)	
Missing data	40 (5.1)	31 (5.9)	9 (3.5)	
Urgency of the procedure				0.272
Urgent	229 (29.3)	164 (31.2)	65 (25.5)	
Emergency	185 (23.7)	124 (23.6)	61 (23.9)	
Salvage	39 (5.0)	28 (5.3)	11 (4.3)	
EuroSCORE II (%), mean	15.6±17.2	13.2±14.5	20.5±20.8	**<0.0001**

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0g/L in women and <13.0 g/L in men. PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; STEMI, ST-elevation myocardial infarction; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; EuroSCORE, European System for Cardiac Operative Risk Evaluation. Clinical variables are according to the EuroSCORE II definition criteria. In bold are statistical significances.

Table 2. Operative data of patients undergoing postcardiotomy VA-ECMO.

Covariates	Overall series 781 pts	Age <70 years 526 pts	Age ≥70 years 255 pts	p-value
Type of cardiac procedure				
Any CABG	390 (49.9)	237 (45.1)	153 (60.0)	<0.0001
Isolated CABG	182 (23.3)	118 (22.4)	64 (25.1)	0.409
Aortic valve replacement	213 (27.3)	134 (25.5)	79 (31.0)	0.105
Aortic valve repair	7 (0.9)	5 (1.0)	2 (0.8)	1.000
Mitral valve replacement	177 (22.7)	118 (22.4)	59 (23.1)	0.826
Mitral valve repair	96 (12.3)	69 (13.1)	27 (10.6)	0.313
Tricuspid valve replacement	22 (2.8)	17 (3.2)	5 (2.0)	0.365
Tricuspid valve repair	78 (10.0)	47 (8.9)	31 (12.2)	0.163
Aortic procedure	155 (19.8)	119 (22.6)	36 (14.1)	**0.005**
Aortic arch surgery	39 (5.0)	30 (5.7)	9 (3.5)	0.223
Ventricular wall/septal repair	29 (3.7)	23 (4.4)	6 (2.4)	0.162
GUCH surgery	20 (2.6)	18 (3.4)	2 (0.8)	**0.029**
Septal myectomy	4 (0.5)	2 (0.4)	2 (0.8)	0.600
Maze and/or LAA closure	21 (2.7)	13 (2.5)	8 (3.1)	0.590

Pulmonary thromboendarterectomy	10 (1.3)	5 (1.0)	1 (2.0)	0.309
Other major cardiac surgery	18 (2.3)	11 (2.1)	7 (2.7)	0.614
Aortic cross-clamp time, min	127±101	131±113	119±71	0.265
Cardiopulmonary bypass duration, min	225±122	229±128	215±112	0.290

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. CABG, coronary artery bypass grafting; GUCH, grown-up congenital heart disease; LAA, left atrial appendage; IABP, intra-aortic balloon pump; VA-ECMO veno-arterial extracorporeal membrane oxygenation. In bold are statistical significances.

Table 3. Data on postcardiotomy VA-ECMO.

Covariates	Overall series 781 pts	Age <70 years 526 pts	Age ≥70 years 255 pts	p-value
Chest left open at primary surgery	208 (26.7)	147 (28.0)	61 (24.0)	0.239
Arterial pH at start of VA-ECMO	7.30±0.14	7.29±0.13	7.31±0.15	0.253
Arterial lactate at start of VA-ECMO[a]	6.9±4.7	6.9±4.7	7.0±4.7	0.905
Arterial lactate at start of VA-ECMO >6 mmol/L[a]	359 (49.5)	244 (49.3)	115 (50.0)	0.859
VA-ECMO inserted at primary surgery	474 (60.7)	318 (60.4)	156 (61.2)	0.906
after weaning attempt with inotropes only	354 (45.3)	238 (45.2)	116 (45.5)	
after weaning attempt with IABP	119 (15.2)	79 (15.0)	40 (15.7)	
after weaning attempt with Impella	1 (0.1)	1 (0.2)	0	
Central arterial VA-ECMO	245 (31.4)	166 (31.6)	79 (31.0)	0.870

VA-ECMO venous cannulation site				**0.047**
Right atrium	174 (22.3)	128 (24.3)	46 (18.0)	
Femoral vein	607 (77.7)	398 (75.7)	209 (82.0)	
IABP	277 (35.5)	182 (34.6)	95 (37.4)	0.444
Left ventricular venting	63 (8.1)	48 (9.1)	15 (5.9)	0.279
Right pulmonary vein	50 (6.4)	37 (7.0)	13 (5.1)	
Left ventricular apex	8 (1.0)	6 (1.1)	2 (0.8)	
Other site	5 (0.6)	5 (1.0)	0	
VA-ECMO duration, days	6.9±6.2	8.3±6.6	6.2±5.4	**0.043**
VA-ECMO duration ≥10 days	184 (23.6)	131 (25.0)	53 (20.8)	0.194
Oxygenator changes because of clots	69 (8.8)	48 (9.1)	21 (8.2)	0.681
Switch to VV-ECMO	2 (0.3)	2 (0.4)	0	1.000
Return to VA-ECMO after weaning	26 (3.3)	21 (4.0)	5 (2.0)	0201
Cardiac surgery procedures during VA-ECMO[b]	67 (8.6)	47 (9.0)	20 (7.8)	0.594
VAD and/or heart transplantation	29 (3.7)	27 (5.1)	2 (0.8)	**0.002**
Heart transplantation	14 (1.8)	14 (2.7)	0	-

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. VA-ECMO, veno-arterial extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VV-ECMO, venovenous extracorporeal membrane oxygenation; VAD, ventricular assist device; [a], missing data in 56 patients; [b], excluding implantation of ventricular assist devices and heart transplantation.

Table 4. Outcomes in patients who underwent postcardiotomy VA-ECMO.

Covariates	Overall series 781 pts	Age <70 years 526 pts	Age ≥70 years 255 pts	p-value
Hospital death	503 (64.4)	309 (58.7)	194 (76.1)	**<0.0001**
Death on VA-ECMO	370 (47.4)	221 (42.0)	149 (58.4)	**<0.0001**

Intensive care unit stay, days	17.2±18.3	19.0±19.8	13.4±13.9	**<0.0001**
Arterial complications				
Aortic rupture	2 (0.3)	0	2 (0.8)	0.106
Type A aortic dissection	8 (1.0)	4 (0.8)	4 (1.6)	0.449
Type B aortic dissection	3 (0.4)	2 (0.4)	1 (0.4)	1.000
Peripheral artery dissection	9 (1.2)	8 (1.5)	1 (0.4)	0.285
Vascular perforation	7 (0.9)	6 (1.1)	1 (0.4)	0.437
Arterial thrombosis	43 (5.5)	28 (5.3)	15 (5.9)	0.748
Major lower limb amputation	12 (1.3)	11 (2.1)	1 (0.4)	0.116
Tracheostomy	180 (23.0)	124 (23.6)	56 (22.0)	0.616
Pancreatitis	12 (1.5)	10 (1.9)	2 (0.8)	0.355
Liver failure	265 (34.0)	176 (33.5)	89 (34.9)	0.703
Gastrointestinal compl. requiring surgery	42 (5.5)	27 (5.2)	15 (6.0)	0.671
Major neurological complications	147 (18.9)	103 (19.6)	44 (17.3)	0.443
Stroke, non-disabling	28 (3.6)	16 (3.0)	12 (4.7)	
Stroke, disabling	61 (7.8)	40 (7.6)	21 (8.3)	
Global brain ischemia	58 (7.4)	47 (9.0)	11 (4.3)	
Infectious complications				
Deep sternal wound infection/mediastinitis	29 (3.7)	22 (4.2)	7 (2.7)	0.319
Vascular access site infection	67 (8.6)	50 (9.5)	17 (6.7)	0.220
Pneumonia	285 (36.5)	199 (37.8)	86 (33.7)	0.264
Blood stream infection	179 (22.9)	118 (22.4)	61 (23.9)	0.643
Renal replacement therapy*	409 (53.4)	261 (50.6)	148 (59.2)	**0.025**
Red blood transfusion, units	23.4±22.0	24.0±23.1	22.2±19.4	0.776
Red blood transfusion ≥10 units	547 (70.1)	366 (69.6)	181 (71.3)	0.631
Reoperation for intrathoracic bleeding	328 (42.1)	227 (43.2)	101 (39.8)	0.368
Reoperation for peripheral arterial bleeding	66 (8.5)	41 (7.8)	25 (9.8)	0.344

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. VA-ECMO, veno-arterial extracorporeal membrane oxygenation; *, excluding patients with preoperative dialysis.

Table 5. Characteristics and data of the included studies.

Author	Year	Country	Study design	Quality assessment	Study period	No. of patients ≥70 years old	Proportion of patients ≥70 years old (%)	Hospital mortality in patients <70 years old (%)	Hospital mortality in patients ≥70 years old (%)
Magovern	1999	USA	R	Fair	1991-1997	12	21.8	60.5	75.0
Rastan	2010	Germany	R	Good	1996-2008	154	29.8	72.7	81.2
Saxena	2015	USA	R	Good	2003-2013	45	48.4	58.3	75.6
Pontailleur	2017	France	R	Fair	2014-2014	127	-	-	74.0*
Rubino	2018	UK	R	Good	2008-2016	24	23.8	58.4	91.7
Current study	2019	International	R	Good	2010-2018	255	32.7	58.7	76.1

CABG, coronary artery bypass grafting; R: retrospective study; *, it refers to 30-day mortality.

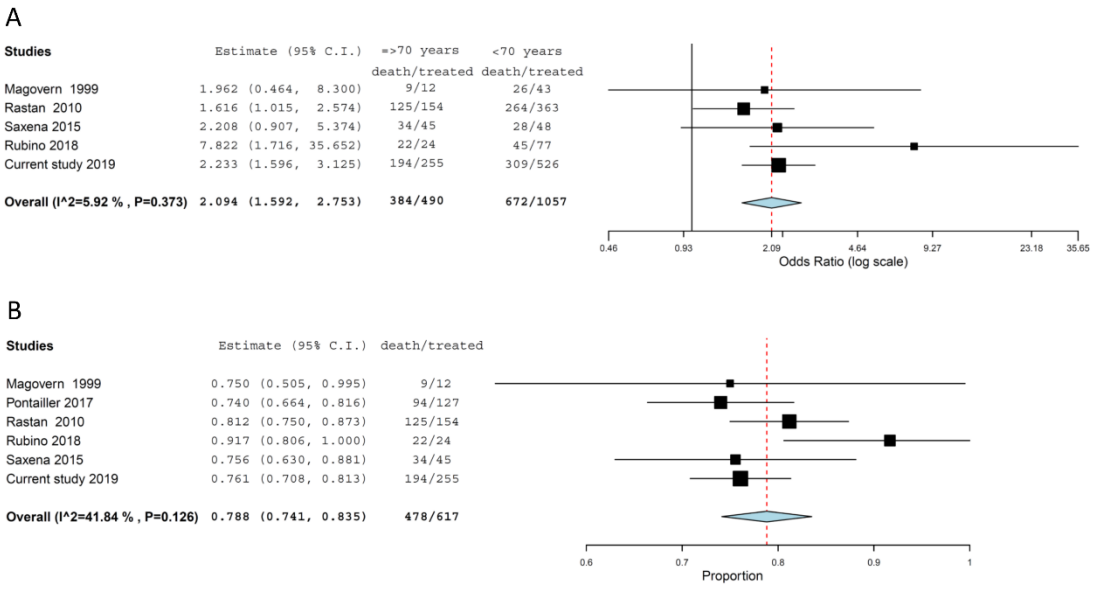

Figure 1. A. Forest plot of studies comparing hospital mortality of patients aged <70 years versus patients aged ≥70 years after postcardiotomy VA-ECMO; B. Pooled proportion of hospital mortality of patients aged ≥70 years after postcardiotomy VA-ECMO.