Multicenter study on postcardiotomy venoarterial extracorporeal membrane oxygenation

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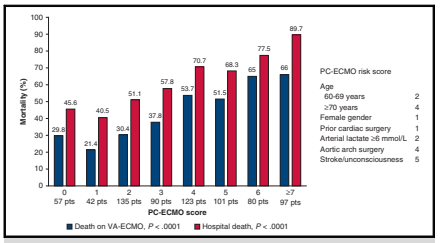
ABSTRACT

Objectives: The aim of this study was to identify the risk factors associated with early mortality after postcardiotomy venoarterial extracorporeal membrane oxygenation.

Methods: This is an analysis of the postcardiotomy extracorporeal membrane oxygenation registry, a retrospective multicenter cohort study including 781 patients aged more than 18 years who required venoarterial extracorporeal membrane oxygenation for cardiopulmonary failure after cardiac surgery from 2010 to 2018 at 19 cardiac surgery centers.

Results: After a mean venoarterial extracorporeal membrane oxygenation therapy of 6.9 ± 6.2 days, hospital and 1-year mortality were 64.4% and 67.2%, respectively. Hospital mortality after venoarterial extracorporeal membrane oxygenation therapy for more than 7 days was 60.5% ($P = .105$). Centers that had treated more than 50 patients with postcardiotomy venoarterial extracorporeal membrane oxygenation had a significantly lower hospital mortality than lower-volume centers (60.7% vs 70.7%, adjusted odds ratio, 0.58; 95% confidence interval, 0.41-0.82). The postcardiotomy extracorporeal membrane oxygenation score was derived by assigning a weighted integer to each independent pre–venoarterial extracorporeal membrane oxygenation predictors of hospital mortality as follows: female gender (1 point), advanced age (60-69 years, 2 points; ≥70 years, 4 points), prior cardiac surgery (1 point), arterial lactate 6.0 mmol/L or greater before venoarterial extracorporeal membrane oxygenation (2 points), aortic arch surgery (4 points), and preoperative stroke/unconsciousness (5 points).



Hospital and on VA-ECMO mortality rates according to increasing PC-ECMO risk scores.

Central Message

The use of postcardiotomy VA-ECMO has increased without incremental mortality. The PC-ECMO score is a simple predictive tool to stratify the risk of mortality after postcardiotomy VA-ECMO.

Perspective

The use of postcardiotomy VA-ECMO has recently increased without incremental hospital mortality. Center experience with postcardiotomy VA-ECMO may improve the results. Age, prior cardiac surgery, preoperative acute neurologic events, aortic arch surgery, and increased arterial lactate increased the risk of early death after postcardiotomy VA-ECMO.

See Commentary on page 1855.

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Abbreviations and Acronyms

CI = confidence interval
EuroSCORE = European System for Cardiac Operative Risk Evaluation
OR = odds ratio
PC-ECMO = postcardiotomy extracorporeal membrane oxygenation
VAD = ventricular assist device
VA-ECMO = venoarterial extracorporeal membrane oxygenation

Scanning this QR code will take you to the article title page to access supplementary information.

The hospital mortality rates according to the postcardiotomy extracorporeal membrane oxygenation score was 0 point, 45.6%; 1 point, 40.5%; 2 points, 51.1%; 3 points, 57.8%; 4 points, 70.7%; 5 points, 68.3%; 6 points, 77.5%; and 7 points or more, 89.7% ($P < .0001$).

Conclusions: Age, female gender, prior cardiac surgery, preoperative acute neurologic events, aortic arch surgery, and increased arterial lactate were associated with increased risk of early mortality after postcardiotomy venoarterial extracorporeal membrane oxygenation. Center experience with postcardiotomy venoarterial extracorporeal membrane oxygenation may contribute to improved results. (J Thorac Cardiovasc Surg 2020;159:1844-54)

Adult cardiac surgery is not infrequently complicated by cardiopulmonary failure requiring mechanical circulatory support. Early experience with venoarterial extracorporeal membrane oxygenation (VA-ECMO) in patients with refractory postcardiotomy cardiogenic shock demonstrated that 25% and 17% of patients survived to discharge and 1 year, respectively.[1] The widespread use of VA-ECMO in this setting led to improved results as recently documented by a pooled hospital survival of 36.1% and 1-year survival of 30.9% after postcardiotomy VA-ECMO.[2] However, VA-ECMO is associated with prolonged hospital stay, significant organizational complexity, and increased costs.[3,4] Predictors of poor outcome after postcardiotomy VA-ECMO have not been fully elucidated, and the decision of initiating VA-ECMO raises ethical issues in the absence of valid parameters contraindicating its use.[5] In this multicenter study, we sought to evaluate the current outcome with this therapy in a multicenter setting and to identify risk factors before initiation of VA-ECMO that are associated with increased hospital mortality.

MATERIALS AND METHODS

The postcardiotomy extracorporeal membrane oxygenation (PC-ECMO) registry is a retrospective, multicenter study that enrolled patients undergoing VA-ECMO after adult cardiac surgery at 19 centers of cardiac surgery 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 were collected retrospectively into an Access (Microsoft Corp, Redmond, Wash) datasheet and underwent robust checking of its completeness and quality. Preoperative variables were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II definition criteria.[6]

Inclusion and Exclusion Criteria

Patients aged more than 18 years who required VA-ECMO for refractory cardiopulmonary failure occurring during the index hospitalization after any surgical procedures on the heart valves, coronary arteries, ascending aorta/aortic arch or ventricular wall and septum, grown-up congenital heart diseases, and chronic thromboembolic pulmonary hypertension were considered for this analysis. Cardiopulmonary failure in these patients was considered not treatable with inotropes and intra-aortic balloon pump. Patients who were on any ECMO before cardiac surgery or who required VA-ECMO after implantation of a ventricular assist device (VAD) or heart transplantation were excluded from this study. Patients with VAD or heart transplant were excluded from this registry after considering the differences in terms of baseline characteristics, causes of heart failure, and outcome of heart transplant recipients who required ECMO compared with patients undergoing general cardiac surgery.[2]

Outcomes

The primary outcome of the present study was hospital mortality, that is, death from any cause occurring during the index hospitalization. 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, bloodstream infection, renal replacement therapy, reoperation for bleeding, and red blood cell transfusion.

Statistical Analysis

Statistical analyses were performed using SPSS v. 25.0 (IBM Corp, New York, NY) and Stata v. 15.1 (StataCorp LLC, College Station, Tex) statistical software. The Mann–Whitney U test, chi-square test, and Fisher exact test were used for univariate analysis of baseline and operative covariates, as well as of outcomes. Time-trend was estimated using the linear-by-linear association test. Late mortality was estimated using the Kaplan–Meier method with the log-rank test. The Youden test was used to identify the best cutoff value of continuous variables in predicting hospital death. Logistic regression was used to identify independent risk factors for hospital death. Regression models included the following risk factors preceding the initiation of VA-ECMO with P less than .05 in univariate analysis: age, female gender, estimated glomerular filtration rate, pulmonary disease, prior cardiac surgery, recent stroke or unconsciousness, aortic crossclamp time, aortic arch surgery, and arterial lactate at stat of VA-ECMO. The DeLong test was used for comparative analyses of C-statistics from different regression models and

euroSCORE II. An additive risk score, the PC-ECMO risk score, was derived by assigning a weighted integer to each independent risk factor on the basis of the coefficients of the final regression model using the method of Schneeweiss and colleagues.[7] The discrimination of the PC-ECMO risk score was evaluated by C-statistics and its calibration by the Hosmer–Lemeshow test. The limited number of patients included in this registry prevented its division into a derivation and validation dataset. Instead, internal validation of the derived risk score was performed in 1000 bootstrap samples, 95% confidence interval (CI) percentile, and simple sampling, as well as stratified sampling for centers. The data on arterial lactate at the start of VA-ECMO were missing in 56 patients; therefore, the results of logistic regression without missing replacement were confirmed using a multiple imputation method with fully conditional specification and 100 imputations. Multilevel mixed-effect logistic regression was used to evaluate any inter-institutional differences in hospital mortality. Because mixed-effect regression model confirmed the predictive covariates identified in logistic regression without considering any cluster effect, only the latter analysis was considered for the derivation of the PC-ECMO risk score. The R^2 was estimated to assess the correlation between standardized mortality ratios and centers volumes of postcardiotomy VA-ECMO. All tests were 2-sided.

RESULTS

Characteristics and Outcomes of the Study Cohort

The PC-ECMO registry included 781 consecutive patients. Baseline, operative, and VA-ECMO–related variables are summarized in Tables 1 to 3.

The hospital mortality was 64.4%, and mortality on VA-ECMO was 46.1%. Survival at 1 and 5 years was 32.8% and 28.5%, respectively. The main causes of death while on VA-ECMO therapy are listed in Table E1. Adverse events occurred in a significant number of patients (Tables 3 and 4) and resulted in a mean stay in the intensive care unit of 17.2 ± 18.3 days (27.9 ± 21.6 days among hospital survivors). Additional cardiac procedures were necessary during VA-ECMO therapy in 9.3% (cardiac surgical procedures, 8.6%) of patients, stroke or global brain ischemia occurred in 18.9% of patients, and renal replacement therapy was necessary in 53.4% of patients. Reoperations for excessive intrathoracic bleeding were performed in 42.1% of patients.

Time-Trend in the Use and Outcome of Postcardiotomy Venoarterial Extracorporeal Membrane Oxygenation

During the study period, the proportion of postcardiotomy VA-ECMO differed markedly between centers (Table E2) and ranged from 0.2% to 2.0% between participating centers (Table E3). The annual rates of postcardiotomy VA-ECMO increased from 0.24% to 0.74% ($P < .0001$) (Figure 1), without incremental hospital mortality (linear-by-linear association test, $P = .167$) (Figure 1).

Outcome After Ventricular Assist Device Implantation or Heart Transplantation

Twenty-eight patients (3.6%) underwent VAD insertion or heart transplantation after postcardiotomy VA-ECMO, and their hospital and 1-year mortality were 42.9% and 53.6%, respectively. The following VAD devices were implanted in 21 patients: HVAD (HeartWare, Framingham, Mass) in 14 patients, HeartMate 2 (Abbott, Abbott Park, Ill) in 3 patients, HeartMate 3 (Abbott) in 1 patient, Jarvik 2000 (Jarvik Heart, New York, NY) in 1 patient, Berlin Heart Excor (Berlin Heart GnbH, Berlin, Germany) in 1 patient, and Rotaflow (Getinge AB, Gothenburg, Sweden) in 1 patient. Fourteen patients underwent heart transplantation, and their hospital and 1-year mortality after heart transplantation were 21.4% and 28.6%, respectively. Among 14 patients who underwent insertion of a VAD without heart transplantation, hospital mortality was 64.3% ($P = 1.000$) and 1-year mortality was 78.6% ($P = .624$).

Predictors of Hospital Mortality

Pre–VA-ECMO variables associated with increased risk of hospital death are listed in Tables 1 to 3. Twenty-eight octogenarians had hospital and on VA-ECMO mortality rates of 82.1% ($P = .046$) and 71.4% ($P = .009$), respectively, which were significantly higher than in patients aged less than 80 years. Mortality rates during VA-ECMO therapy and index hospitalization increased along with increasing deciles of arterial lactate at initiation of VA-ECMO ($P < .0001$) (Figure E1). The Youden test identified a cutoff value of arterial lactate at initiation of VA-ECMO of 5.7 mmol/L for prediction of hospital death, which was rounded to 6 mmol/L in the following analyses (sensitivity 56%, specificity 59%).

Logistic regression identified advanced age (crude rates: <60 years, 52.2%; 60-69 years, 64.4%; ≥70 years, 76.1%), female gender (crude rates: 69.5% vs 62.0%), stroke or unconsciousness immediately before surgery (crude rates: 88.9% vs 63.5%), prior cardiac surgery (crude rates: 71.5% vs 62.2%), aortic arch surgery (crude rates: 82.1% vs 63.5%), and arterial lactate level 6 mmol/L or greater at start of VA-ECMO (crude rates: 71.6% vs 57.9%) as independent predictors of hospital death (Hosmer–Lemeshow test: $P = .619$, C-statistics 0.68, 95% CI, 0.64-0.72) (Table E4).

Similar results were observed when age and arterial lactate were included in the regression model as continuous variables (Table E5). These findings were confirmed in logistic regression with the multiple imputation method and in mixed-effect logistic regression adjusted for the hospital cluster effect (Table E5). An additive PC-ECMO risk score was derived from these risk factors (Table E4) The C-statistics of predicted hospital mortality were similar to that of the additive PC-ECMO score (C-statistics, 0.68; 95% CI, 0.64-0.72; rho: 0.99). The correlation between predicted hospital mortality and additive PC-ECMO score is depicted in Figure E2. Hospital mortality according to increasing PC-ECMO scores was as follows: 0 point, 45.6%; 1 point, 40.5%; 2 points, 51.1%; 3 points, 57.8%; 4 points, 70.7%; 5 points, 68.3%; 6 points, 77.5%; and 7 or more points, 89.7% (Figure 2).

TABLE 1. Baseline characteristics of patients undergoing postcardiotomy venoarterial extracorporeal membrane oxygenation

Covariates	Overall series (781 patients)	Hospital survivors (278 patients)	Hospital deaths (503 patients)	*P* value
Age (y)	63.1 ± 12.9	59.6 ± 13.7	65.0 ± 12.1	**<.0001**
<60 y	245 (31.4)	117 (42.1)	128 (25.4)	**<.0001**
60-69 y	281 (36.0)	100 (36.0)	181 (36.0)	
≥70 y	255 (38.6)	61 (21.9)	194 (38.6)	
Female gender	249 (31.9)	76 (27.3)	173 (34.4)	**.043**
eGFR (mL/min/1.73 m^2)	68.0 ± 30.3	72.3 ± 30.1	65.6 ± 30.1	**.001**
Dialysis	32 (4.1)	7 (2.5)	25 (5.0)	.100
Anemia	366 (46.9)	121 (43.5)	245 (48.8)	.157
Preoperative antithrombotics				
Oral anticoagulant	175 (22.4)	59 (21.2)	116 (23.1)	.555
Ticagrelor/clopidogrel	106 (13.6)	36 (12.9)	70 (13.9)	.706
Diabetes	200 (25.6)	72 (25.9)	128 (25.4)	.890
Oral drugs	94 (12.0)	28 (10.1)	66 (13.1)	.223
Insulin therapy	106 (13.6)	44 (15.8)	62 (12.3)	
Recent myocardial infarction	199 (25.5)	73 (26.3)	126 (25.0)	.710
STEMI	115 (14.7)	41 (14.7)	74 (14.7)	.989
Prior stroke	60 (7.7)	23 (8.3)	37 (7.4)	.645
Atrial fibrillation	192 (22.3)	62 (22.3)	130 (25.8)	.271
Pulmonary disease	110 (14.1)	30 (10.8)	80 (15.9)	**.049**
Extracardiac arteriopathy	118 (15.1)	33 (11.9)	85 (16.9)	.060
Active endocarditis	85 (10.9)	31 (11.2)	54 (10.7)	.858
Prior PCI	146 (18.7)	48 (17.3)	98 (19.5)	.447
Prior cardiac surgery	186 (23.8)	53 (19.1)	133 (26.4)	**.020**
Valve surgery ± CABG	86 (11.0)	20 (7.2)	66 (13.1)	.093
Aortic surgery	43 (5.5)	16 (5.8)	27 (5.4)	
Isolated CABG	34 (4.4)	8 (2.9)	26 (5.2)	
Congenital cardiac surgery	17 (2.2)	7 (2.5)	10 (2.0)	
Other major cardiac surgery	6 (0.8)	2 (0.7)	4 (0.8)	
Left ventricular ejection fraction				.310
31%-50%	258 (331.1)	91 (32.9)	167 (33.3)	
21%-30%	136 (17.5)	57 (20.6)	79 (15.7)	
<21%	67 (8.6)	20 (7.2)	47 (9.4)	
Critical preoperative state	276 (35.3)	99 (35.6)	177 (35.2)	.906
Ventricular arrhythmia	37 (4.7)	9 (3.2)	28 (5.6)	.142
Aborted sudden death	15 (1.9)	4 (1.4)	11 (2.2)	.466
Preoperative IABP	62 (7.9)	24 (8.6)	38 (7.6)	.593
Stroke/unconsciousness	27 (3.5)	3 (1.1)	24 (4.8)	**.007**
Systolic pulmonary artery pressure				.974
31-55 mm Hg	237 (30.3)	86 (30.9)	151 (30.0)	
>55 mm Hg	139 (17.8)	49 (17.6)	90 (17.9)	
Missing data	40 (5.1)	13 (4.7)	27 (5.4)	
Urgency of the procedure				.748
Urgent	229 (29.3)	84 (30.2)	145 (28.8)	
Emergency	185 (23.7)	70 (25.2)	115 (22.9)	
Salvage	39 (5.0)	12 (4.3)	27 (5.4)	
EuroSCORE II (%), mean	15.6 ± 17.2	13.1 ± 14.7	17.0 ± 18.2	**.003**

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

TABLE 2. Operative data of patients undergoing postcardiotomy venoarterial extracorporeal membrane oxygenation

Covariates	Overall series (781 patients)	Hospital survivors (278 patients)	Hospital deaths (503 patients)	*P* value
Type of cardiac procedure				
Isolated CABG	182 (23.3)	70 (25.2)	112 (22.3)	.356
Any CABG	390 (49.9)	130 (46.8)	260 (51.7)	.187
Aortic valve replacement	213 (27.3)	75 (27.0)	138 (27.4)	.891
Aortic valve repair	7 (0.9)	2 (0.7)	5 (1.0)	1.000
Mitral valve replacement	177 (22.7)	62 (22.3)	115 (22.9)	.858
Mitral valve repair	96 (12.3)	42 (15.1)	54 (10.7)	.075
Tricuspid valve replacement	22 (2.8)	8 (2.9)	14 (2.8)	.939
Tricuspid valve repair	78 (10.0)	29 (10.4)	49 (9.7)	.758
Aortic procedure	155 (19.8)	50 (18.0)	105 (20.9)	.332
Aortic arch surgery	39 (5.0)	7 (2.59)	32 (6.4)	**.017**
Ventricular wall/septal repair	29 (3.7)	9 (3.2)	20 (4.0)	.601
GUCH surgery	20 (2.6)	6 (2.2)	14 (2.8)	.596
Septal myectomy	4 (0.5)	0	4 (0.8)	.303
Maze or LAA closure	21 (2.7)	6 (2.2)	15 (3.0)	.496
Pulmonary thromboendarterectomy	10 (1.3)	4 (1.4)	6 (1.2)	.770
Other major cardiac surgery	18 (2.3)	3 (1.1)	15 (3.0)	.133
Complex cardiac surgery*	312 (39.9)	102 (36.7)	210 (41.7)	.167
No. of procedures				.623
1	439 (56.2)	166 (59.7)	273 (54.3)	
2	246 (31.5)	83 (29.9)	163 (32.4)	
3	78 (10.0)	23 (8.3)	55 (10.9)	
>3	18 (2.3)	6 (2.2)	12 (2.4)	
Arterial cannulation site at primary surgery				**.025**
Ascending aorta	662 (85.5)	236 (85.5)	426 (85.5)	
Femoral artery	62 (8.0)	29 (10.5)	33 (6.6)	
Other peripheral artery	50 (6.5)	11 (4.0)	39 (7.8)	
Venous cannulation site at primary surgery				.919
Right atrium	654 (84.6)	234 (84.8)	420 (84.5)	
Femoral vein	119 (15.49)	42 (15.2)	77 (15.5)	
Conversion from minimally invasive surgery	10 (1.3)	2 (0.7)	8 (1.6)	.508
Aortic crossclamp time, min	127 ± 101	118 ± 76	132 ± 113	**.039**
Cardiopulmonary bypass duration, min	225 ± 122	208 ± 117	233 ± 125	**.002**

Bold indicates statistical significance. 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. *Refers to surgery on more than 1 heart valve, aortic surgery, repair of ventricular wall or septal defect, and repair of complex congenital defects.

One-year mortality was as follows: 0 point, 47.6%; 1 point, 46.4%; 2 points, 52.1%; 3 points, 59.5%; 4 points, 74.6%; 5 points, 73.1%; 6 points, 78.0%; and 7 or more points, 90.5% ($P < .001$) (Figure E3).

Validation of the Postcardiotomy Extracorporeal Membrane Oxygenation Risk Score

The limited number of patients included in this series prevented the partition of the dataset into derivation and validation datasets. Therefore, an internal validation of the derived risk score was performed in 1000 bootstrap samples and resulted in a bias of −0.001 (standard error, 0.040) for simple sampling and in a bias of 0.003 (standard error, 0.040) for stratified sampling for centers. The PC-ECMO additive score had a better discrimination than the EuroSCORE II (C-statistics, 0.68, 95% CI, 0.64-0.72 vs 0.56, 95% CI, 0.52-60, DeLong test: $P < .0001$). The PC-ECMO additive score had a satisfactory discrimination in the subsets of patients who underwent isolated coronary artery bypass grafting (C-statistics, 0.69, 95% CI, 0.60-0.77), aortic surgery (C-statistics, 0.66, 95% CI, 0.57-0.75), and complex surgery, that is, surgery on more than 1 heart valve, aortic surgery, repair of ventricular wall or septal defect, or repair of complex congenital defects (C-statistics, 0.63, 95% CI, 0.56-0.70).

Predictive Ability of European System for Cardiac Operative Risk Evaluation II

The euroSCORE II was associated with a significant incremental risk of death on VA-ECMO and during

TABLE 3. Data on postcardiotomy venoarterial extracorporeal membrane oxygenation

Covariates	Overall series (781 patients)	Hospital survivors (278 patients)	Hospital deaths (503 patients)	*P* value
Chest left open at primary surgery	208 (26.7)	66 (23.7)	142 (28.3)	.164
Arterial pH at start of VA-ECMO	7.30 ± 0.14	7.32 ± 0.12	7.29 ± 0.15	.075
Arterial lactate at start of VA-ECMO*	7.30 ± 0.14	6.0 ± 4.1	7.5 ± 4.9	**<.0001**
VA-ECMO inserted at primary surgery	474 (60.7)	166 (59.7)	308 (61.2)	.677
After weaning attempt with inotropes only	354 (45.3)	124 (44.6)	230 (45.7)	.870
After weaning attempt with IABP	119 (15.2)	42 (15.1)	77 (15.3)	
After weaning attempt with Impella (Abiomed, Danvers, Mass)	1 (0.1)	0	1 (0.2)	
Central arterial VA-ECMO	245 (31.4)	69 (24.8)	176 (35.0)	**.003**
VA-ECMO arterial cannulation site				**.013**
Ascending aorta	245 (31.4)	69 (24.8)	176 (35.0)	
Femoral artery	467 (59.8)	183 (65.8)	284 (56.5)	
Other peripheral artery	69 (8.8)	26 (9.4)	43 (8.5)	
VA-ECMO venous cannulation site				**.020**
Right atrium	174 (22.3)	49 (17.6)	125 (24.9)	
Femoral vein	607 (77.7)	229 (82.4)	378 (75.1)	
Switch from central to peripheral cannulation	23 (2.9)	5 (1.8)	18 (3.6)	.189
IABP				.967
Inserted before surgery	62 (7.9)	24 (8.6)	38 (7.6)	
Inserted with VA-ECMO at primary surgery	77 (9.9)	30 (10.8)	47 (9.4)	
Inserted without VA-ECMO at primary surgery	73 (9.4)	27 (9.7)	46 (9.2)	
Inserted with VA-ECMO late after surgery	39 (5.0)	13 (4.7)	26 (5.2)	
Inserted without VA-ECMO late after surgery	26 (3.3)	9 (3.29)	17 (3.4)	
Impella	5 (0.6)	2 (0.7)	3 (0.6)	1.000
Left ventricular venting	63 (8.1)	20 (7.2)	43 (8.6)	.506
Right pulmonary vein	50 (6.4)	14 (5.0)	36 (7.2)	.457
Left ventricular apex	8 (1.0)	3 (1.1)	5 (0.4)	
Other site	5 (0.6)	3 (1.1)	2 (0.4)	
VA-ECMO duration, d	6.9 ± 6.2	7.7 ± 5.8	6.5 ± 6.4	**<.0001**
VA-ECMO duration ≥10 d	184 (23.6)	72 (25.9)	112 (22.4)	.265
Oxygenator changes because of clots	69 (8.8)	34 (12.2)	35 (7.0)	.013
Switch to VV-ECMO	2 (0.3)	0	0 (0.4)	.541
Return to VA-ECMO after weaning	26 (3.3)	5 (1.8)	21 (4.2)	.076
Cardiac procedures during VA-ECMO†	72 (9.3)	24 (8.7)	48 (9.6)	.690
Cardiac surgery procedures during VA-ECMO†	67 (8.6)	22 (8.0)	45 (9.0)	.637
VAD or heart transplantation	29 (3.7)	16 (5.8)	13 (2.6)	**.025**
VAD	22 (2.8)	11 (4.0)	11 (2.2)	.152
Left VAD	16 (2.0)	9 (3.2)	7 (1.4)	.212
Right VAD	2 (0.3)	0	2 (0.4)	
Bilateral VAD	4 (0.5)	2 (0.7)	2 (0.4)	
Heart transplantation	14 (1.8)	11 (4.0)	3 (0.6)	**.001**
From VA-ECMO	7 (0.9)	5 (1.8)	2 (0.4)	**.003**
From VAD	7 (0.9)	6 (2.2)	1 (0.2)	

Bold indicates statistical significance. Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump; *VV-ECMO*, venovenous extracorporeal membrane oxygenation; *VAD*, ventricular assist device. *Missing data in 56 patients. †Excluding implantation of VADs and heart transplantation.

index hospitalization (Figure E4). However, its discrimination ability in predicting hospital mortality was limited (C-statistics, 0.560, 95% CI, 0.52-60). Only patients with euroSCORE II greater than 50% had a prohibitive risk of hospital mortality (83.7%) (Figure E4).

TABLE 4. Outcomes in patients who underwent postcardiotomy venoarterial extracorporeal membrane oxygenation

Covariates	Overall series (781 patients)	Hospital survivors (278 patients)	Hospital deaths (503 patients)	*P* value
Hospital death	503 (64.4)	–	–	–
Death on VA-ECMO	360 (46.1)	–	360 (71.6)	–
Intensive care unit stay, d	17.2 ± 18.3	27.9 ± 21.6	11.2 ± 12.8	**<.0001**
Arterial complications				
Aortic rupture	2 (0.3)	0	2 (0.4)	.541
Type A aortic dissection	8 (1.0)	1 (0.4)	7 (1.4)	.271
Type B aortic dissection	3 (0.4)	0	3 (0.6)	.556
Peripheral artery dissection	9 (1.2)	3 (1.1)	6 (1.2)	1.000
Vascular perforation	7 (0.9)	2 (0.7)	5 (1.0)	1.000
Arterial thrombosis	43 (5.5)	17 (6.1)	26 (5.2)	.579
Major lower-limb amputation	10 (1.3)	4 (1.4)	6 (1.2)	.551
Tracheostomy	180 (23.0)	90 (32.4)	90 (17.9)	**<.0001**
Pancreatitis	12 (1.5)	3 (1.1)	9 (1.9)	.554
Liver failure	265 (34.0)	61 (22.0)	204 (40.6)	**<.0001**
Gastrointestinal complication requiring surgery	42 (5.5)	6 (2.2)	36 (7.3)	.003
Multiorgan failure	390 (49.9)	53 (19.1)	337 (67.0)	**<.0001**
Major neurologic complications	147 (18.9)	32 (11.5)	115 (23.0)	**<.0001**
Stroke, nondisabling	28 (3.6)	16 (5.8)	12 (2.4)	**<.0001**
Stroke, disabling	61 (7.8)	15 (5.4)	46 (9.2)	
Global brain ischemia	58 (7.4)	1 (0.4)	57 (11.4)	
Infectious complications				
Deep sternal wound infection/mediastinitis	29 (3.7)	22 (7.9)	7 (1.4)	**<.0001**
Vascular access site infection	67 (8.6)	43 (15.5)	24 (4.8)	**<.0001**
Pneumonia	285 (36.5)	147 (52.9)	138 (27.4)	**<.0001**
Bloodstream infection	179 (22.9)	80 (28.8)	99 (19.7)	**.004**
Renal replacement therapy*	409 (53.4)	130 (47.4)	279 (56.7)	**.014**
Red blood transfusion, units	23.4 ± 22.0	22.0 ± 22.3	24.1 ± 21.8	.068
Red blood transfusion ≥10 units	547 (70.1)	186 (66.9)	361 (71.9)	.143
Reoperation for intrathoracic bleeding	328 (42.1)	109 (39.2)	219 (43.6)	.231
Reoperation for peripheral arterial bleeding	66 (8.5)	18 (6.5)	48 (9.5)	.140

Bold indicates statistical significance. Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation. *Excluding patients with preoperative dialysis.

Institutional Postcardiotomy Venoarterial Extracorporeal Membrane Oxygenation Volume and Hospital Mortality

All participating centers were tertiary referral hospitals, and all but 2 of them were university-affiliated hospitals. The frequency of postcardiotomy VA-ECMO differed between centers (Table E2) and ranged from 0.2% to 2.0% between participating centers (Table E3). Eleven centers had a heart transplantation program, and 14 centers had a VAD program.

During the study period, the frequency of postcardiotomy VA-ECMO ranged from 0.2% to 2.0% between participating centers (Table E3). Nine centers treated more than 30 patients, and 6 centers treated more than 50 patients with postcardiotomy VA-ECMO (Table E3).

Lower observed/expected ratios were observed in centers with higher volumes of postcardiotomy VA-ECMO (R^2: 0.20, Figure E5). When participating centers were added to the logistic regression model including other independent predictors of hospital death, the c-statistics of the regression model improved significantly (0.73, 95% CI, 0.69-0.77 vs 0.68, 95% CI, 0.64-0.72, DeLong test: $P = .0004$). Such a cluster effect also was observed in multilevel mixed-effect logistic regression (between-institution variance: 0.64, 95% CI, 0.04-0.57, this model vs logistic regression: $P = .0049$; Table E5).

Centers that had treated more than 50 patients with postcardiotomy VA-ECMO during the study period had a significantly lower hospital mortality rate than those with lower volume of postcardiotomy VA-ECMO (60.9% vs 70.2%, $P = .009$).

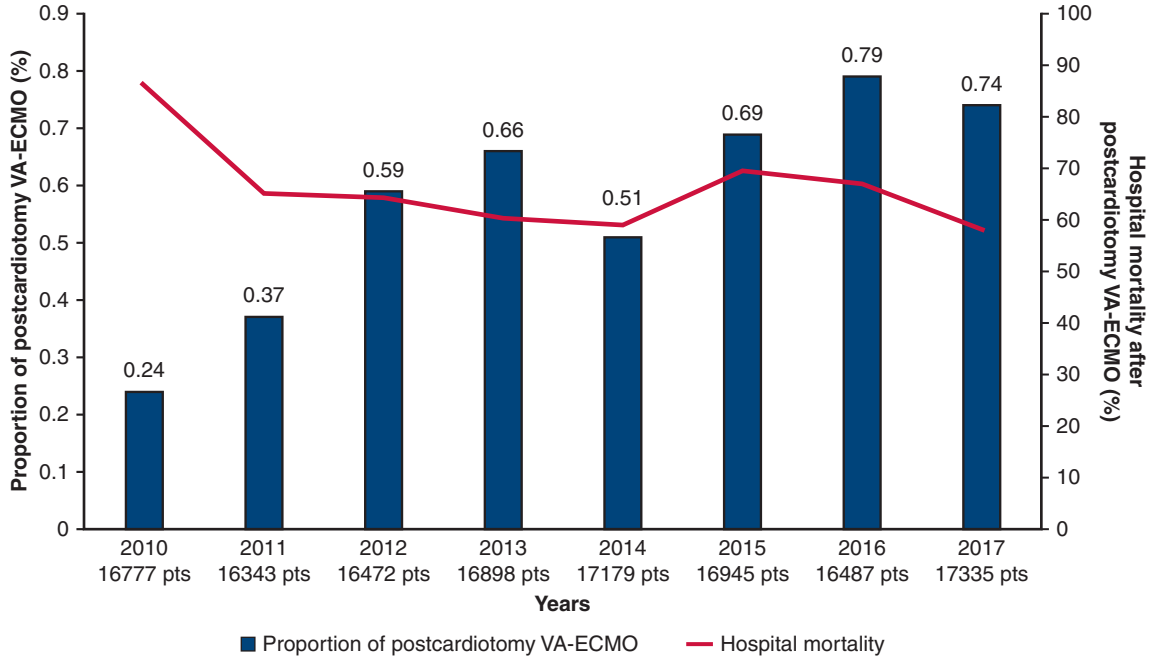

FIGURE 1. Annual rates of postcardiotomy VA-ECMO and hospital mortality rates (linear-by-linear association test, $P = .167$). The number of patients who underwent adult cardiac surgery is reported at the bottom of the bars. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

Such a difference remained significant when adjusted for age, female gender, stroke or unconsciousness immediately before surgery, prior cardiac surgery, aortic arch surgery, and arterial lactate level 6 mmol/L or greater at start of VA-ECMO (odds ratio [OR], 0.58, 95% CI, 0.41-0.82).

Centers with a VAD or heart transplantation program (adjusted OR, 0.900, 95% CI, 0.55-1.48) and those with a heart transplantation program (adjusted OR, 0.94, 95% CI, 0.67-1.33) did not have lower hospital mortality rate after postcardiotomy VA-ECMO.

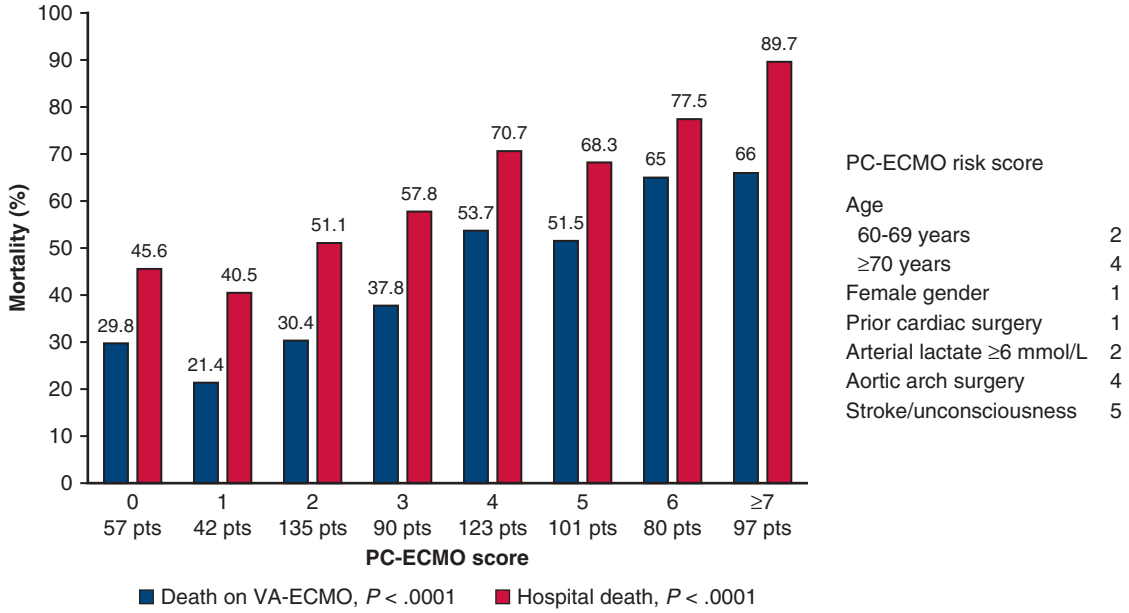

FIGURE 2. Hospital and on VA-ECMO mortality rates according to increasing PC-ECMO risk scores. *PC-ECMO*, Postcardiotomy extracorporeal membrane oxygenation; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

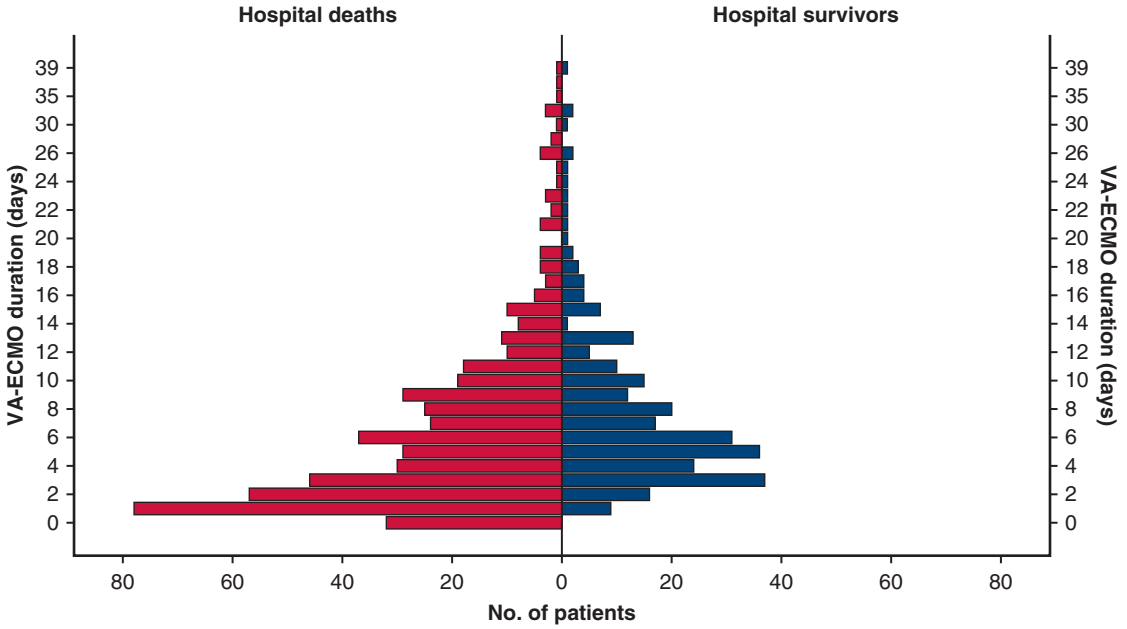

FIGURE 3. Distribution of hospital survivors and hospital deaths according to the duration of VA-ECMO therapy. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

Duration of Venoarterial Extracorporeal Membrane Oxygenation and Hospital Mortality

VA-ECMO therapy was performed for a mean of 6.9 ± 6.2 days (median, 5.3 days; range, 0-39). Hospital survivors were on VA-ECMO therapy significantly longer than those who died during the index hospitalization (mean, 7.7 ± 5.8 vs 6.5 ± 6.4 days; median, 6.0 vs 5.0 days, $P < .001$). The distribution of hospital survivors and hospital deaths according to the duration of VA-ECMO therapy is summarized in Figure 3. Most patients who survived to discharge were on VA-ECMO for at least 3 days, whereas many patients who died were on VA-ECMO treatment 3 days or less. Postcardiotomy VA-ECMO seems to be a valid salvage therapy when used for a prolonged period (Figure 3). When the duration of VA-ECMO therapy was greater than 7 days, the crude hospital mortality was 60.5% compared with 66.4% in patients in whom VA-ECMO therapy lasted 7 days or less ($P = .10$). Center volume tended to correlate with longer VA-ECMO therapy (rho: 0.383, $P = .11$, Figure E6).

DISCUSSION

The results of this multicenter study demonstrated that (1) 35.6% of the patients with refractory cardiopulmonary failure survived to hospital discharge after postcardiotomy VA-ECMO; (2) the use of postcardiotomy VA-ECMO has increased during the last years without increasing early mortality; (3) centers with high volumes of postcardiotomy VA-ECMO had better survival compared with low-volume centers; (4) a small number of patients were treated with heart transplantation, and their outcome was satisfactory; (5) advanced age is a significant risk factor for hospital death; (6) arterial lactate before initiation of VA-ECMO has significant prognostic value; (7) the complexity of cardiac surgery in patients with prior cardiac operations and aortic arch surgery is a determinant of poor outcome; (8) acute neurologic events before surgery are associated with prohibitive hospital mortality; and (9) prolonged VA-ECMO therapy may achieve good results.

Previous studies on cardiogenic shock treated with ECMO therapy did not specifically address the outcome after postcardiotomy VA-ECMO.[8,9] This salvage therapy is increasingly used with mortality rates higher than other critical conditions.[10] However, most data on postcardiotomy VA-ECMO are from institutional series of limited size usually biased by the heterogeneity of the patient population and the experience with ECMO therapy.

This study provided data on the recent use of postcardiotomy VA-ECMO from 19 centers. During the study period, the participating centers likely had a different approach toward the indications for VA-ECMO after cardiac surgery as shown by marked inter-institutional differences of its use. This study showed a 4-fold increase of the use of postcardiotomy VA-ECMO during the last 8 years without incremental mortality (Figure 1). A large registry from the United States confirmed that the increased use of this salvage therapy after cardiac surgery decreased the early mortality.[11]

The results of regression analyses documented the impact of age on the outcome after postcardiotomy VA-ECMO.

Previous studies reported that advanced age was not an absolute contraindication to ECMO,[9] but the risk of mortality among elderly patients was significantly increased. In the present series, hospital mortality was 82.1% among the 28 octogenarians. The risk of in-hospital death was 3-fold higher in patients aged 70 years or more than in younger patients. Our data are consistent with previous studies,[1,2,12,13] suggesting that in the elderly the indications for VA-ECMO after cardiac surgery should be judiciously scrutinized, and the presence of significant comorbidities may contraindicate its use.

The PC-ECMO registry includes detailed data on previous procedures and index cardiac surgery, which were rather heterogeneous. Prior cardiac surgery and aortic arch surgery were independent predictors of hospital death, suggesting that these procedures generally carry a high risk of end-organ damage requiring VA-ECMO support. However, this registry did not collect data on the possible causes of cardiopulmonary failure, such as suboptimal myocardial protection, technical errors, failure of valve prostheses, thromboembolism, or excessive bleeding. Aortic cross-clamp time was not prolonged in patients who died after VA-ECMO, which claims for a straightforward procedure in most of these patients. However, approximately 10% of patients underwent percutaneous coronary intervention or an additional cardiac surgery procedure while on VA-ECMO therapy. Furthermore, it is not known how many potentially treatable iatrogenic complications were left unrecognized or untreated in these patients.

In this study, acute neurologic events were associated with increased hospital mortality. Acute pre-ECMO end-organ failures have been shown to predict poor outcome after VA-ECMO.[8] However, the assessment of neurologic, renal, pulmonary, and liver function is often not feasible in postcardiotomy acute cardiopulmonary failure requiring mechanical circulatory support. This is the case of patients who cannot be weaned from cardiopulmonary bypass and in those with sudden cardiogenic shock after an apparently normal postoperative recovery. Indeed, clinicians are often called upon to decide whether to insert VA-ECMO without knowledge of the reversibility, or lack thereof, of the myocardial or other end-organ damages. Increased pre–VA-ECMO arterial lactate level may provide valuable prognostic information in this setting,[2,11,14-18] because it suggests tissue hypoxia secondary to an imbalance between oxygen demand and supply and is considered a valid hemodynamic marker.[19-21] Increased lactate levels may prompt the early insertion of VA-ECMO instead of a conservative approach with inotropes, which may aggravate the imbalance between oxygen demand and supply. Previous studies have reported on different cutoff values of blood lactate for prediction of early mortality.[11,14-18] In the present study, analyses suggested a cutoff of 6 mmol/L for pre–VA-ECMO lactate. Of note, arterial lactate level greater than 14 mmol/L is associated with a hospital mortality of 81.7% (Figure E1), and in the presence of other critical comorbidities, this may contraindicate the use of VA-ECMO.

A recently published pooled analysis has shown that VAD was used after VA-ECMO in only 2.3% of patients with a hospital mortality of 54.4%, whereas heart transplantation was performed in 1.9% of patients with a hospital mortality of 33.8%.[2] In the present study, 3.7% of patients underwent VAD insertion or heart transplantation, and their hospital and 1-year mortality were 44.8% and 55.2%, respectively. Hospital and 1-year mortality after heart transplantation were 21.4% and 28.6%, respectively. After VAD insertion only, hospital and 1-year mortality were 66.7% and 80.0%, respectively. The available data on VAD and heart transplantation are scarce, but they suggest that heart transplantation can achieve satisfactory early survival in patients with end-stage heart failure, who cannot be weaned from postcardiotomy VA-ECMO. Still, the satisfactory results with heart transplantation in this setting might be influenced by better clinical conditions and good expectancy of life as the strict selection criteria for heart transplantation may suggest.

The herein derived PC-ECMO risk scoring method seems to provide a simple and clinically sound stratification of the risk of patients undergoing postcardiotomy VA-ECMO. However, the observed hospital mortality increased overall, but not monotonically. This is likely due to the limited size of this series and the intrinsic difficulties to identify patients at lowest and highest risk of hospital mortality. Overall, these results suggest that even in low-risk patients, postcardiotomy VA-ECMO is associated with a hospital mortality of at least 40%, which confirms the severity of the conditions indicating mechanical circulatory support. This excessive mortality risk is accompanied with high morbidity and prolonged postoperative care, which should be considered in the decision-making process before starting postcardiotomy VA-ECMO. Patients' and their families' willingness and resources to afford VA-ECMO therapy and the potentially disabling effects of severe complications should play a relevant role in the clinical judgment of using this therapy.[22] Unfortunately, postoperative acute cardiopulmonary failure most often does not allow clinicians to discuss thoroughly the ethical issues before starting VA-ECMO. 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 patients with advanced age, who underwent complex cardiac surgery and having severe metabolic acidosis, are less likely to survive after postcardiotomy VA-ECMO.

Study Limitations

The present study is not exempted from several limitations, although it is the largest registry evaluating the

outcome of postcardiotomy VA-ECMO. The retrospective nature of the data is the main limitation of this study. However, because of the rather low frequency of PC-ECMO, a large-scale prospective study is hardly feasible. Second, the specific data on pre–VA-ECMO respiratory and hemodynamic parameters were not uniformly available for collection. This prevented any comparative analysis with available risk scores. Third, information about the nature and severity of any possible iatrogenic factors incurred perioperatively were not recorded in this registry. Finally, we do not have detailed data regarding the VA-ECMO management and the weaning strategy adopted by the participating centers.

CONCLUSIONS

This multicenter study showed that the use of postcardiotomy VA-ECMO has increased in the participating centers without incremental hospital mortality. Center experience with postcardiotomy VA-ECMO might have contributed to improved results. Advanced age, female gender, prior cardiac surgery, preoperative acute neurologic events, aortic arch surgery, and increased arterial lactate were associated with an increased risk of early mortality after refractory postcardiotomy VA-ECMO. These pre–VA-ECMO risk factors may guide the decision-making process on whether to initiate this salvage therapy.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: extracorporeal membrane oxygenation, cardiac surgery, postcardiotomy, venoarterial

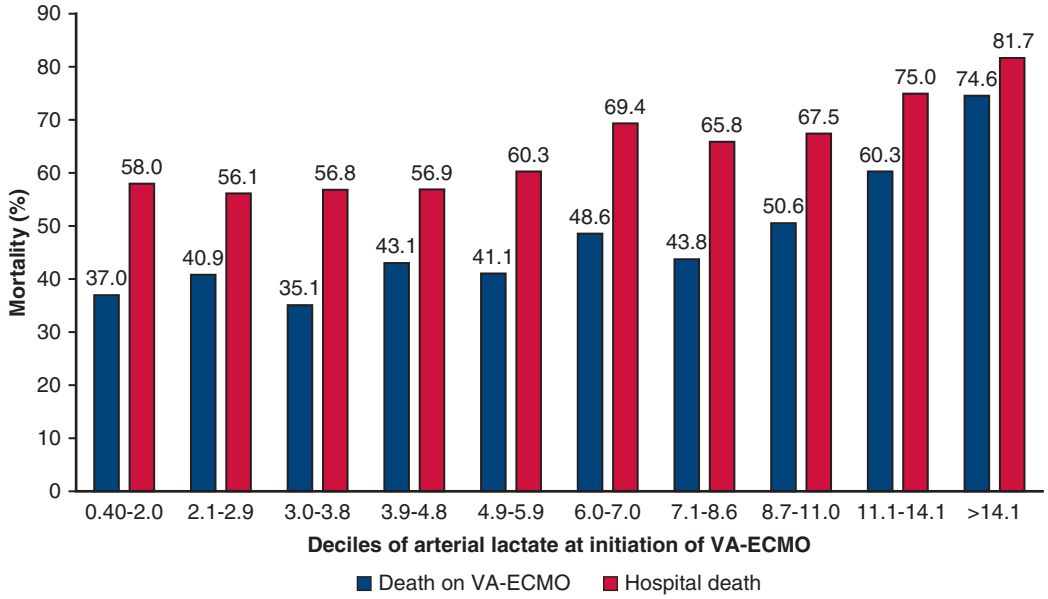


FIGURE E1. Mortality rates during VA-ECMO therapy and index hospitalization in increasing deciles of arterial lactate at initiation of VA-ECMO ($P < .0001$). *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

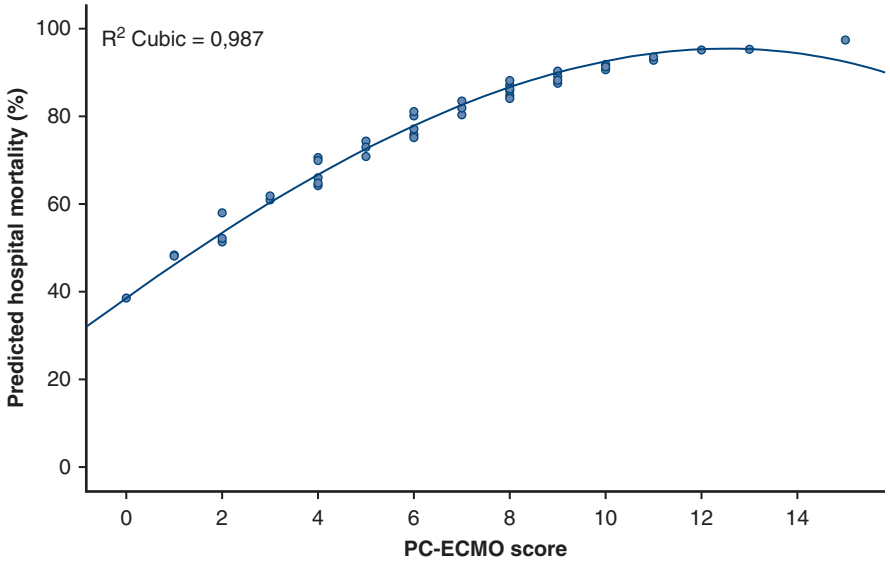
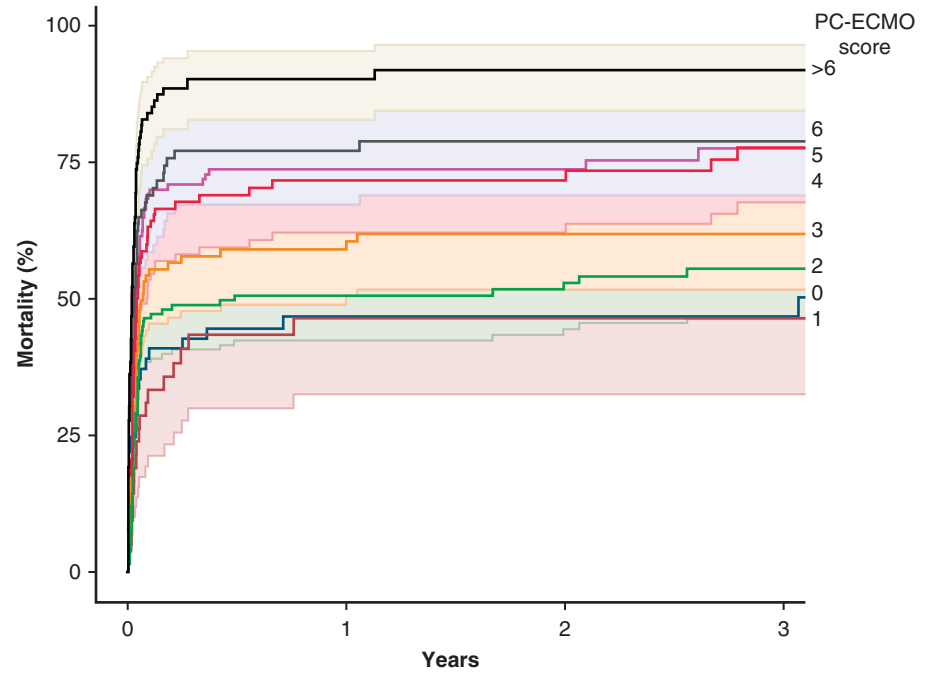


FIGURE E2. Scatter plot of correlation between predicted hospital mortality and additive PC-ECMO score. *PC-ECMO*, Postcardiotomy extracorporeal membrane oxygenation.



Patients at risk

Score				
0	57	23	19	16
1	42	16	9	7
2	133	50	40	30
3	89	30	21	16
4	119	22	16	9
5	96	20	16	9
6	77	14	9	7
>6	94	6	5	3

FIGURE E3. Kaplan–Meier estimate of all-cause mortality after postcardiotomy VA-ECMO according to increasing PC-ECMO risk scores (log-rank test: $P < .0001$). *PC-ECMO*, Postcardiotomy extracorporeal membrane oxygenation.

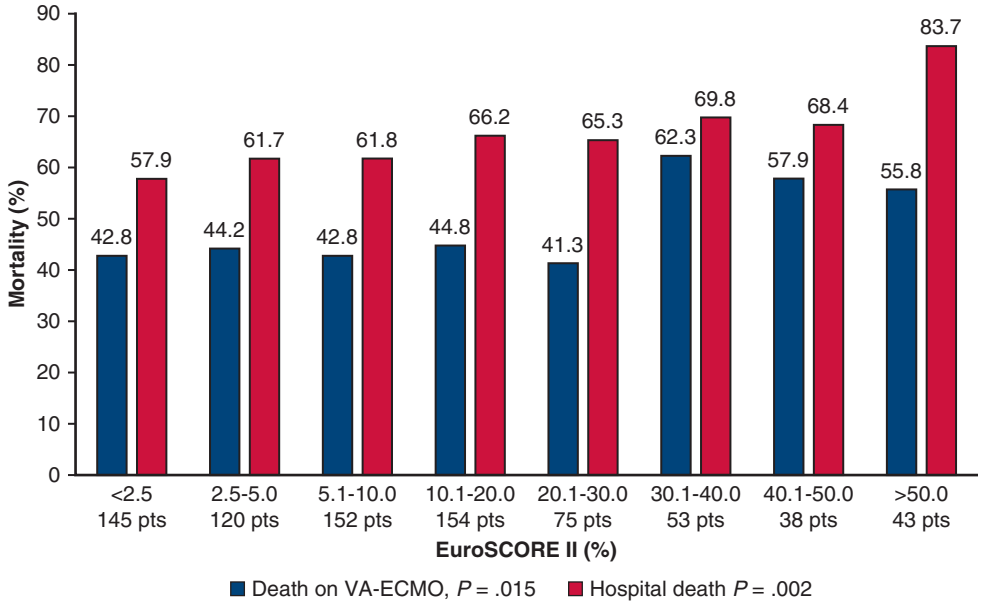


FIGURE E4. Hospital and on VA-ECMO mortality rates according to increasing euroSCORE II. *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

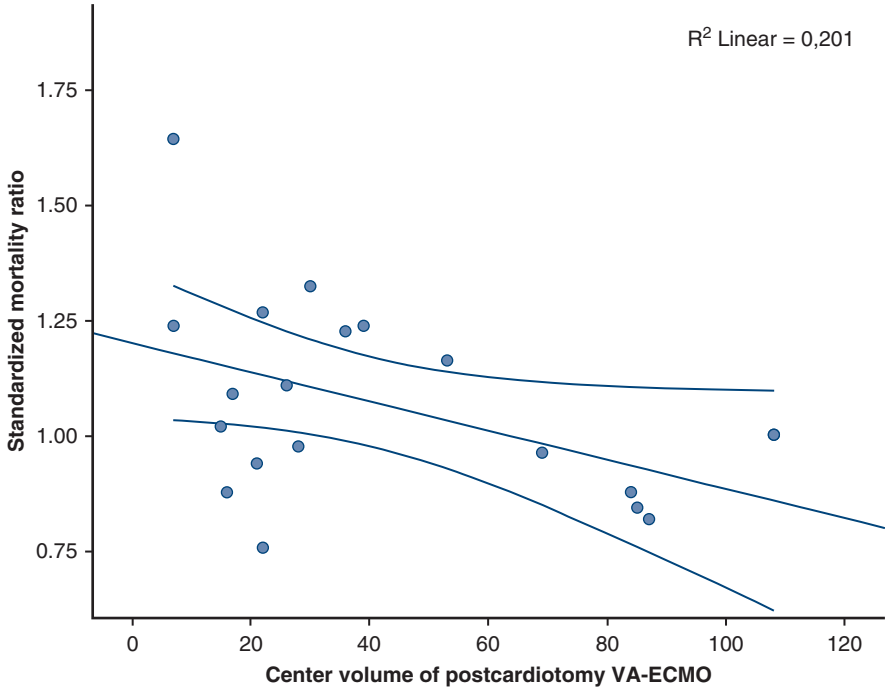


FIGURE E5. Scatter plot of standardized mortality ratios and institutional volumes of postcardiotomy VA-ECMO. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

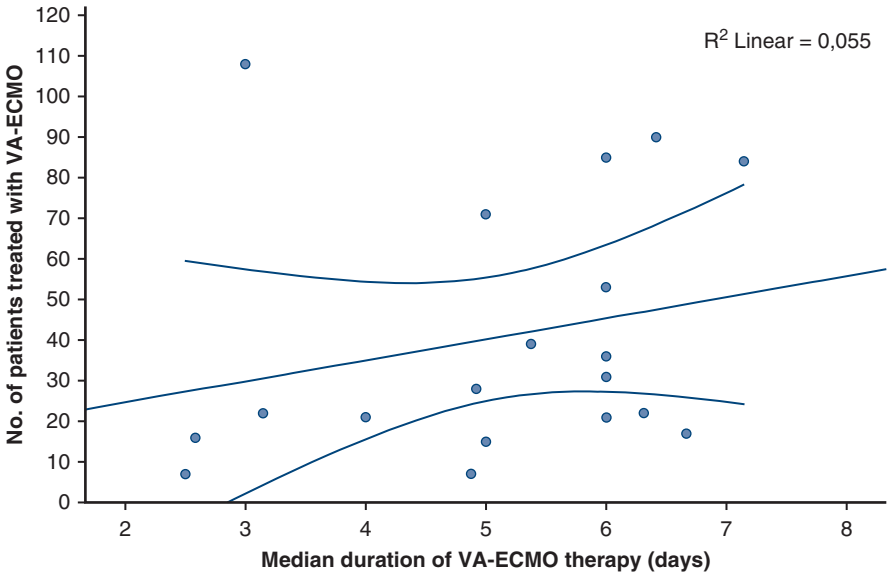


FIGURE E6. Scatter plot of institutional volumes of postcardiotomy VA-ECMO and median duration of VA-ECMO therapy. *VA-ECMO*, Venoarterial extracorporeal membrane oxygenation.

TABLE E1. Main causes of death in patients who died on venoarterial extracorporeal membrane oxygenation

Main causes of death	No. (%)
Multiorgan failure	160 (20.5)
Heart failure	103 (13.2)
Neurologic complications	40 (5.1)
Sepsis	16 (2.0)
Intractable bleeding	14 (1.8)
Mesenteric ischemia	13 (1.7)
Vasoplegia	6 (0.8)
Aortic rupture/dissection	5 (0.6)
Intracavitary cardiac thrombosis	4 (0.5)
Ventricular septal rupture	3 (0.4)
Respiratory complications	2 (0.3)
Thrombosis of the mitral valve prosthesis	2 (0.3)
Thrombosis of the tricuspid valve prosthesis	1 (0.1)
Transfusion reaction	1 (0.1)

TABLE E2. Number of postcardiotomy venoarterial extracorporeal membrane oxygenation at each participating center from 2010 to 2017

Participating center	No. of postcardiotomy VA-ECMO
Münster	108
Paris Créteil*	93
Düsseldorf	85
Stockholm	84
Rennes	71
Besançon	53
Gothenburg	39
Bologna	36
Hamburg	31
Trieste	28
Genk†	26
Glasgow	22
Lund	22
Prague	21
Udine	17
Leicester	16
Reims	15
Alhassa	7
Turku	7

VA-ECMO, Venoarterial extracorporeal membrane oxygenation. *Three patients were treated after the end of the study period. †Five patients were treated after the end of the study period.

TABLE E3. Frequency of postcardiotomy venoarterial extracorporeal membrane oxygenation at each participating center from 2010 to 2017

Participating center	No. of cardiac surgery procedures	No. of postcardiotomy VA-ECMO (%)
Paris	4603	90 (2.0)
Munster	8086	108 (1.3)
Stockholm	7300	84 (1.2)
Besançon	6065	53 (0.9)
Dusseldorf	12,000	85 (0.7)
Rennes	10,168	71 (0.7)
Trieste	4141	28 (0.7)
Genk	3760	21 (0.6)
Bologna	6764	36 (0.5)
Alhassa	1426	7 (0.5)
Gothenburg	8476	39 (0.5)
Reims	3468	15 (0.4)
Udine	5724	17 (0.3)
Lund	8740	22 (0.3)
Hamburg	12,328	31 (0.3)
Prague	9152	21 (0.2)
Glasgow	10,028	22 (0.2)
Turku	3439	7 (0.2)
Leicester	8768	16 (0.2)

VA-ECMO, Venoarterial extracorporeal membrane oxygenation.

TABLE E4. Derivation of the postcardiotomy extracorporeal membrane oxygenation score

Covariates	Odds ratio, 95% CI	Coefficients	Additive score
Age			
<60 y	Reference category	–	
60-69 y	1.684, 1.160-2.446	0.521	2
≥70 y	3.087, 2.048-4.653	1.127	4
Female gender	1.476, 1.043-2.090	0.390	1
Prior cardiac surgery	1.489, 1.012-2.192	0.398	1
Arterial lactate ≥6 mmol/L	1.737, 1.259-2.397	0.552	2
Aortic arch surgery	2.876, 1.147-7.212	1.057	4
Stroke/unconsciousness	3.877, 1.126-13.350	1.355	5
Constant		−0.467	

CI, Confidence interval.

TABLE E5. Independent predictors of hospital mortality after postcardiotomy venoarterial extracorporeal membrane oxygenation according to different regression methods

Covariates	
Logistic regression with age and arterial lactate as continuous variables	**Odds ratio, 95% CI**
Age, y	1.037, 1.024-1.050
Female gender	1.539, 1.084-2.185
Prior cardiac surgery	1.658, 1.115-2.465
Arterial lactate, mmol/L	1.080, 1.041-1.122
Aortic arch surgery	2.808, 1.041-7.079
Stroke/unconsciousness	3.555, 1.031-12.263
Logistic regression with multiple imputation method	**Odds ratio, 95% CI**
Age	
<60 y	–
60-69 y	1.720, 1.199-2.468
≥70 y	3.084, 2.086-4.560
Female gender	1.469, 1.051-2.053
Prior cardiac surgery	1.506, 1.036-2.188
Arterial lactate ≥6 mmol/L	1.660, 1.206-2.284
Aortic arch surgery	2.611, 1.104-6.175
Stroke/unconsciousness	4.074, 1.188-13.972
Mixed-effect logistic regression	**Odds ratio, 95% CI**
Age	
<60 y	–
60-69 y	1.759, 1.194-2.591
≥70 y	3.305, 2.144-5.093
Female gender	1.495, 1.047-2.136
Prior cardiac surgery	1.492, 1.003-2.220
Arterial lactate ≥6 mmol/L	1.862, 1.324-2.619
Aortic arch surgery	2.820, 1.103-7.208
Stroke/unconsciousness	4.514, 1.276-15.970
	Between-Institution variance, 95% CI
Institution	0.640, 0.037-0.568
Likelihood-ratio test for model vs logistic regression	$P = .0049$

CI, Confidence interval.