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Glossary of abbreviations

CI: confidence interval

OR: odds ratio

PC-ECMO: postcardiotomy extracorporeal membrane oxygenation

VAD: ventricular assist device

VA-ECMO: venoarterial extracorporeal membrane oxygenation

Central picture legend: Hospital and on venoarterial extracorporeal membrane oxygenation (VA-ECMO) mortality rates according to increasing postcardiotomy extracorporeal membrane oxygenation 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. (Character count: 187)

Perspective statement: The use of postcardiotomy venoarterial extracorporeal membrane oxygenation (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 neurological events, aortic arch surgery and increased arterial lactate increased the risk of early death after postcardiotomy VA-ECMO. (Character count: 396)

Abstract

Objectives: The aim of this study was to identify the risk factors associated with early mortality after postcardiotomy venoarterial extracorporeal membrane oxygenation (VA-ECMO)

Methods: This is an analysis of the PC-ECMO registry, a retrospective multicenter cohort study including 781 patients aged >18 years who required VA-ECMO for cardiopulmonary failure after cardiac surgery from 2010 to 2018 at 19 cardiac surgery centers.

Results: After a mean VA-ECMO therapy of 6.9 ± 6.2 days, hospital and 1-year mortality were 64.4% and 67.2%, respectively. Hospital mortality after VA-ECMO therapy longer than 7 days was 60.5% ($p=0.105$). Centers which had treated more than 50 patients with postcardiotomy VA-ECMO had a significantly lower hospital mortality than lower volume centers (60.7% vs. 70.7%, adjusted OR 0.58, 95% CI 0.41-0.82). The PC-ECMO score was derived by assigning a weighted integer to each independent pre-VA-ECMO 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 before VA-ECMO (2 points), aortic arch surgery (4 points) and preoperative stroke/unconsciousness (5 points). The hospital mortality rates according to the PC-ECMO 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 point 89.7% ($p < 0.0001$).

Conclusions: Age, prior cardiac surgery, preoperative acute neurological events, aortic arch surgery and increased arterial lactate were associated with increased risk of early mortality after postcardiotomy VA-ECMO. Center experience with postcardiotomy VA-ECMO may contribute to improved results.

Key words: Extracorporeal membrane oxygenation; Cardiac surgery; Postcardiotomy; Venoarterial; ECMO; VA-ECMO.

Introduction

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 at 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 resources (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 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 prior to initiation of VA-ECMO which are associated with increased hospital mortality.

Methods

The 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 was collected retrospectively into an Access datasheet and underwent robust checking of its completeness and quality. Preoperative variables were defined according to the EuroSCORE II definition criteria (6).

Inclusion and exclusion criteria

Patients aged over 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 and/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 patients who required ECMO compared with patients undergoing general cardiac surgery (2).

Outcomes

The primary outcome of the present study was hospital mortality, i.e. 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, blood stream infection, renal replacement therapy, reoperation for bleeding and red blood cell transfusion.

Statistical analysis

Statistical analyses were performed using a SPSS v. 25.0 (IBM Corporation, New York, USA) and Stata v. 15.1 (StataCorp LLC, Texas, USA) statistical softwares. The Mann-Whitney *U* test, the chi-square test and the Fisher's 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 employed to identify independent risk factors for hospital death. 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 at start 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 Schneeweiss' method (7). The discrimination of the PC-ECMO risk score was evaluated by C-statistics and its calibration by the Hosmer-Lemeshow's 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%CI percentile and simple sampling as well as stratified sampling for centers. The data on arterial lactate at the start of VA-ECMO was 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. Since 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 two-sided and $p < 0.05$ was set for statistical significance.

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 1-3.

The hospital mortality was 64.4% and mortality on VA-ECMO was 46.1%. Survival rates at 1 and 5 years were 32.8% and 28.5%, respectively. The main causes of death while on VA-ECMO therapy are listed in Supplementary table 1. Adverse events occurred in a significant number of patients (Tabs. 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

184 renal replacement therapy was necessary in 53.4% of patients. Reoperations for excessive intrathoracic
 185 bleeding were performed in 42.1% of patients.

186

187 *Time-trend in the use and outcome of postcardiotomy VA-ECMO*

188 During the study period, the proportion of postcardiotomy VA-ECMO differed markedly between centers
 189 (Suppl. tab. 2) and ranged from 0.2% to 2.0% between participating centers (Suppl. tab. 3). The annual rates
 190 of postcardiotomy VA-ECMO increased from 0.24% to 0.74% ($p<0.0001$) (Fig. 1), without incremental
 191 hospital mortality (Linear-by-linear association test, $p=0.167$) (Fig. 1).

192

193 *Outcome after ventricular assist device implantation and/or heart transplantation*

194 Twenty-eight patients (3.6%) underwent VAD insertion and/or heart transplantation after postcardiotomy
 195 VA-ECMO and their hospital and 1-year mortality were 42.9% and 53.6%, respectively. The following VAD
 196 devices were implanted in 21 patients: HVAD (HeartWare, Massachusetts, USA) in 14 patients, HeartMate 2
 197 (Abbott, Illinois, USA) in three patients, HeartMate 3 (Abbott, Illinois, USA) in one patient, Jarvik 2000
 198 (Jarvik Heart, New York, USA) in one patient, Berlin Heart Excor (Berlin Heart GmbH, Berlin, Germany) in
 199 one patient and Rotaflow (Getinge AB, Gothenburg, Sweden) in one patient. Fourteen patients underwent
 200 heart transplantation and their hospital and 1-year mortality after heart transplantation was 21.4% and 28.6%.
 201 Among 14 patients who underwent insertion of a VAD without heart transplantation, hospital mortality was
 202 64.3% ($p=1.000$) and 1-year mortality was 78.6% ($p=0.624$).

203

204 *Predictors of hospital mortality*

205 Pre-VA-ECMO variables associated with increased risk of hospital death are listed in Tables 1-3. Twenty-
 206 eight octogenarians had hospital and on VA-ECMO mortality rates of 82.1% ($p=0.046$) and 71.4%
 207 ($p=0.009$), respectively, which were significantly higher than in patients <80 years old. Mortality rates during
 208 VA-ECMO therapy and index hospitalization increased along with increasing deciles of arterial lactate at

initiation of VA-ECMO ($p < 0.0001$) (Suppl. fig. 1). 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 , 52.2%; 60-69, 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 at start of VA-ECMO (crude rates: 71.6% vs. 57.9%) as independent predictors of hospital death (Hosmer-Lemeshow's test: $p = 0.619$, C-statistics 0.68, 95% CI 0.64-0.72) (Suppl. tab. 4).

Similar results were observed when age and arterial lactate were included into the regression model as continuous variables (Suppl. tab. 5). These findings were confirmed in logistic regression with multiple imputation method and in mixed-effect logistic regression adjusted for the hospital cluster effect (Suppl. tab. 5). An additive PC-ECMO risk score was derived from these risk factors (Suppl. Tab. 4) The C-statistics of predicted hospital mortality was similar to that of the additive PC-ECMO score (C-statistics, 0.68, 95% CI 0.64-0.72, rho: 0.99, Suppl. Fig. 3). 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 point 89.7%. (Fig. 2). 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 points 90.5% ($p < 0.001$) (Suppl. fig. 2).

228

229 *Validation of the PC-ECMO 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 0.52-0.60,

DeLong test: $p < 0.0001$). 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, i.e. surgery on more than one heart valve, aortic surgery, repair of ventricular wall or septal defect and/or repair of complex congenital defects (C-statistics, 0.63, 95%CI 0.56-0.70).

Predictive ability of EuroSCORE II

EuroSCORE II was associated with a significant incremental risk of death on VA-ECMO and during index hospitalization (Suppl. Fig. 4). However, its discrimination ability in predicting hospital mortality was limited (C-statistics, 0.560, 95%CI 0.52-60). Only patients with EuroSCORE II $> 50\%$ had a prohibitive risk of hospital mortality (83.7%) (Suppl. Fig. 4).

Institutional postcardiotomy VA-ECMO volume and hospital mortality

All participating centers were tertiary referral hospitals and all but two of them were university affiliated hospitals. The frequency of postcardiotomy VA-ECMO differed between centers (Suppl. tab. 2) and ranged from 0.2% to 2.0% between participating centers (Suppl. tab. 3). 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 (Suppl. tab. 3). Nine centers treated more than 30 patients and six centers treated more than 50 patients with postcardiotomy VA-ECMO (Suppl. Tab. 3).

Lower observed/expected ratios were observed in centers with higher volumes of postcardiotomy VA-ECMO (R^2 : 0.20, Suppl. Fig. 5). 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: $p = 0.0004$). Such a cluster

effect was observed also in multilevel mixed-effect logistic regression (between-institution variance: 0.64, 95%CI 0.04-0.57, this model vs. logistic regression: $p=0.0049$; Suppl. tab. 5).

Centers which had treated >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%, $p=0.009$). Such a difference remained significant also 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 at start of VA-ECMO (OR 0.58, 95%CI 0.41-0.82).

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

Duration of VA-ECMO 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 significantly longer on VA-ECMO therapy 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, $p<0.001$). The distribution of hospital survivors and hospital deaths according to the duration of VA-ECMO therapy is summarized in Figure 3. Most of patients who survived to discharge were on VA-ECMO for at least 3 days, whilst many patients who died were on VA-ECMO treatment ≤ 3 days. Postcardiotomy VA-ECMO seems to be a valid salvage therapy also when used for a prolonged period (Fig. 3). When the duration of VA-ECMO therapy was >7 days, the crude hospital mortality was 60.5% compared to 66.4% in patients in whom VA-ECMO therapy lasted ≤ 7 days ($p=0.10$). Center volume tended to correlate with longer VA-ECMO therapy ($\rho: 0.383$, $p=0.11$, Suppl. fig. 6).

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 rates compared to 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; 7) the complexity of cardiac surgery in patients with prior cardiac operations and aortic arch surgery is a determinant of poor outcome; 8) acute neurological 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 of 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 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 four-fold increase of the use of postcardiotomy VA-ECMO during the last 8 years without incremental mortality (Fig 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. Indeed, in the present series hospital mortality was 82.1% among the 28 octogenarians. Furthermore, the risk of in-hospital death was three-fold higher in patients aged ≥ 70 years than in younger patients. Our data are consistent with previous studies

311 (1,2,12,13), suggesting that in the elderly the indications for VA-ECMO after cardiac surgery should be
312 judiciously scrutinized and the presence of significant comorbidities may contraindicate its use.

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

323 In this study, acute neurological events were associated with increased hospital mortality. Acute pre-ECMO
324 end-organ failures have been shown to predict poor outcome after VA-ECMO (8). However, the assessment
325 of neurological, renal, pulmonary and liver function is often not feasible in postcardiotomy acute
326 cardiopulmonary failure requiring mechanical circulatory support. This is the case of patients who cannot be
327 weaned from cardiopulmonary bypass and in those with sudden cardiogenic shock after an apparently
328 normal postoperative recovery. Indeed, clinicians are often called upon to decide whether to insert VA-
329 ECMO without knowledge of the reversibility, or lack thereof, of the myocardial or other end-organ
330 damages. Increased pre-VA-ECMO levels of arterial lactate may provide valuable prognostic information in
331 this setting (2,11,14-18) as they suggest tissue hypoxia secondary to an imbalance between oxygen demand
332 and supply and is considered a valid hemodynamic marker (19-21). Increased lactate levels may prompt the
333 early insertion of VA-ECMO instead of a conservative approach with inotropes, which may aggravate the
334 imbalance between oxygen demand and supply. Previous studies have reported on different cutoff values of
335 blood lactate for prediction of early mortality (11,14-18). In the present study, analyses suggested a cutoff of
336 6 mmol/L for pre-VA-ECMO lactate. Importantly, arterial lactate level >14 mmol/L is associated with a

337 hospital mortality of 81.7% (Suppl. fig. 1) and, in presence of other critical comorbidities, this may
338 contraindicate the use of VA-ECMO.

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

349 The herein derived PC-ECMO risk scoring method seems to provide a simple and clinically sound
350 stratification of the risk of patients undergoing postcardiotomy VA-ECMO. However, the observed hospital
351 mortality increased overall, but not monotonically. This is likely due to the limited size of this series and to
352 the intrinsic difficulties to identify patients at lowest and highest risk of hospital mortality. Overall, these
353 results suggest that even in low-risk patients, post-cardiotomy VA-ECMO is associated with a hospital
354 mortality of at least 40%, which confirms the severity of the conditions indicating mechanical circulatory
355 support. This excessive mortality risk is accompanied with high morbidity and prolonged postoperative care,
356 which should be considered in the decision-making process before starting postcardiotomy VA-ECMO.
357 Patients' and their families' willingness and resources to afford VA-ECMO therapy and the potentially
358 disabling effects of severe complications should play a relevant role in the clinical judgment of using this
359 therapy (22). Unfortunately, postoperative acute cardiopulmonary failure most often does not allow
360 clinicians to discuss thoroughly the ethical issues before starting VA-ECMO. In the context of uncertainty
361 regarding the use of VA-ECMO in the elderly, the present study provides insights of clinical relevance
362 because it showed that patients with advanced age, who underwent complex cardiac surgery and having
363 severe metabolic acidosis are less likely to survive after postcardiotomy VA-ECMO.

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. Secondly, 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. Thirdly, information about the nature and the 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, prior cardiac surgery, preoperative acute neurological 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 initiate this salvage therapy.

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Legend to figures

Figure 1. Annual rates of postcardiotomy extracorporeal membrane oxygenation (VA-ECMO) and hospital mortality rates (Linear-by-linear association test, $p=0.167$). Number of patients who underwent adult cardiac surgery are reported at the bottom of the bars.

Figure 2. Hospital and on venoarterial extracorporeal membrane oxygenation (VA-ECMO) mortality rates according to increasing postcardiotomy extracorporeal membrane oxygenation (PC-ECMO) risk scores.

Figure 3. Distribution of hospital survivors and hospital deaths according to the duration of venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy.

471 **Table 1.** Baseline characteristics of patients undergoing postcardiotomy VA-ECMO.

Covariates	Overall series (781 pts)	Hospital survivors (278 pts)	Hospital deaths (503 pts)	p-value
Age (years)	63.1±12.9	59.6±13.7	65.0±12.1	<0.0001
<60 years	245 (31.4)	117 (42.1)	128 (25.4)	<0.0001
60-69 years	281 (36.0)	100 (36.0)	181 (36.0)	
≥70 years	255 (38.6)	61 (21.9)	194 (38.6)	
Female gender	249 (31.9)	76 (27.3)	173 (34.4)	0.043
eGFR (mL/min/1.73 m ²)	68.0±30.3	72.3±30.1	65.6±30.1	0.001
Dialysis	32 (4.1)	7 (2.5)	25 (5.0)	0.100
Anemia	366 (46.9)	121 (43.5)	245 (48.8)	0.157
Preoperative antithrombotics				
Oral anticoagulant	175 (22.4)	59 (21.2)	116 (23.1)	0.555
Ticagrelor/clopidogrel	106 (13.6)	36 (12.9)	70 (13.9)	0.706
Diabetes	200 (25.6)	72 (25.9)	128 (25.4)	0.890
Oral drugs	94 (12.0)	28 (10.1)	66 (13.1)	0.223
Insulin therapy	106 (13.6)	44 (15.8)	62 (12.3)	
Recent myocardial infarction	199 (25.5)	73 (26.3)	126 (25.0)	0.710
STEMI	115 (14.7)	41 (14.7)	74 (14.7)	0.989
Prior stroke	60 (7.7)	23 (8.3)	37 (7.4)	0.645
Atrial fibrillation	192 (22.3)	62 (22.3)	130 (25.8)	0.271
Pulmonary disease	110 (14.1)	30 (10.8)	80 (15.9)	0.049
Extracardiac arteriopathy	118 (15.1)	33 (11.9)	85 (16.9)	0.060
Active endocarditis	85 (10.9)	31 (11.2)	54 (10.7)	0.858
Prior PCI	146 (18.7)	48 (17.3)	98 (19.5)	0.447
Prior cardiac surgery	186 (23.8)	53 (19.1)	133 (26.4)	0.020
Valve surgery +/- CABG	86 (11.0)	20 (7.2)	66 (13.1)	0.093
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				0.310
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)	0.906
Ventricular arrhythmia	37 (4.7)	9 (3.2)	28 (5.6)	0.142
Aborted sudden death	15 (1.9)	4 (1.4)	11 (2.2)	0.466
Preoperative IABP	62 (7.9)	24 (8.6)	38 (7.6)	0.593
Stroke/unconsciousness	27 (3.5)	3 (1.1)	24 (4.8)	0.007
Sys. pulmonary a. pressure				0.974
31-55 mmHg	237 (30.3)	86 (30.9)	151 (30.0)	
>55 mmHg	139 (17.8)	49 (17.6)	90 (17.9)	
Missing data	40 (5.1)	13 (4.7)	27 (5.4)	
Urgency of the procedure				0.748
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	0.003

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

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

Covariates	Overall series (781 pts)	Hospital survivors (278 pts)	Hospital deaths (503 pts)	p-value
Type of cardiac procedure				
Isolated CABG	182 (23.3)	70 (25.2)	112 (22.3)	0.356
Any CABG	390 (49.9)	130 (46.8)	260 (51.7)	0.187
Aortic valve replacement	213 (27.3)	75 (27.0)	138 (27.4)	0.891
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)	0.858
Mitral valve repair	96 (12.3)	42 (15.1)	54 (10.7)	0.075
Tricuspid valve replacement	22 (2.8)	8 (2.9)	14 (2.8)	0.939
Tricuspid valve repair	78 (10.0)	29 (10.4)	49 (9.7)	0.758
Aortic procedure	155 (19.8)	50 (18.0)	105 (20.9)	0.332
Aortic arch surgery	39 (5.0)	7 (2.5)	32 (6.4)	0.017
Ventricular wall/septal repair	29 (3.7)	9 (3.2)	20 (4.0)	0.601
GUCH surgery	20 (2.6)	6 (2.2)	14 (2.8)	0.596
Septal myectomy	4 (0.5)	0	4 (0.8)	0.303
Maze and/or LAA closure	21 (2.7)	6 (2.2)	15 (3.0)	0.496
Pulmonary thromboendarterectomy	10 (1.3)	4 (1.4)	6 (1.2)	0.770
Other major cardiac surgery	18 (2.3)	3 (1.1)	15 (3.0)	0.133
Complex cardiac surgery ^a	312 (39.9)	102 (36.7)	210 (41.7)	0.167
No. of procedures				0.623
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)	
Art. cannulation site at primary surgery				0.025
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				0.919
Right atrium	654 (84.6)	234 (84.8)	420 (84.5)	
Femoral vein	119 (15.4)	42 (15.2)	77 (15.5)	
Conversion from minimally invasive surgery	10 (1.3)	2 (0.7)	8 (1.6)	0.508
Aortic cross-clamp time, min	127±101	118±76	132±113	0.039
Cardiopulmonary bypass duration, min	225±122	208±117	233±125	0.002

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. ^a, it refers to surgery on more than one heart valve, aortic surgery, repair of ventricular wall or septal defect and/or repair of complex congenital defects.

498 **Table 3.** Data on postcardiotomy VA-ECMO.

Covariates	Overall series (781 pts)	Hospital survivors (278 pts)	Hospital deaths (503 pts)	p-value
Chest left open at primary surgery	208 (26.7)	66 (23.7)	142 (28.3)	0.164
Arterial pH at start of VA-ECMO	7.30±0.14	7.32±0.12	7.29±0.15	0.075
Arterial lactate at start of VA-ECMO ^a	7.30±0.14	6.0±4.1	7.5±4.9	<0.0001
VA-ECMO inserted at primary surgery	474 (60.7)	166 (59.7)	308 (61.2)	0.677
after weaning attempt with inotropes only	354 (45.3)	124 (44.6)	230 (45.7)	0.870
after weaning attempt with IABP	119 (15.2)	42 (15.1)	77 (15.3)	
after weaning attempt with Impella	1 (0.1)	0	1 (0.2)	
Central arterial VA-ECMO	245 (31.4)	69 (24.8)	176 (35.0)	0.003
VA-ECMO arterial cannulation site				0.013
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				0.020
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)	0.189
IABP				0.967
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)	0.506
Right pulmonary vein	50 (6.4)	14 (5.0)	36 (7.2)	0.457
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, days	6.9±6.2	7.7±5.8	6.5±6.4	<0.0001
VA-ECMO duration ≥10 days	184 (23.6)	72 (25.9)	112 (22.4)	0.265
Oxygenator changes because of clots	69 (8.8)	34 (12.2)	35 (7.0)	0.013
Switch to VV-ECMO	2 (0.3)	0	0 (0.4)	0.541
Return to VA-ECMO after weaning	26 (3.3)	5 (1.8)	21 (4.2)	0.076
Cardiac procedures during VA-ECMO ^b	72 (9.3)	24 (8.7)	48 (9.6)	0.690
Cardiac surgery procedures during VA-ECMO ^b	67 (8.6)	22 (8.0)	45 (9.0)	0.637
VAD and/or heart transplantation	29 (3.7)	16 (5.8)	13 (2.6)	0.025
VAD	22 (2.8)	11 (4.0)	11 (2.2)	0.152
Left VAD	16 (2.0)	9 (3.2)	7 (1.4)	0.212
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)	0.001
From VA-ECMO	7 (0.9)	5 (1.8)	2 (0.4)	0.003
From VAD	7 (0.9)	6 (2.2)	1 (0.2)	

499 Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages.

500 VA-ECMO, veno-arterial extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VV-ECMO, venovenous

501 extracorporeal membrane oxygenation; VAD, ventricular assist device; ^a, missing data in 56 patients; ^b, excluding implantation of

502 ventricular assist devices and heart transplantation.

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

Covariates	Overall series (781 pts)	Hospital survivors (278 pts)	Hospital deaths (503 pts)	p-value
Hospital death	503 (64.4)	-	-	-
Death on VA-ECMO	360 (46.1)	-	360 (71.6)	-
Intensive care unit stay, days	17.2±18.3	27.9±21.6	11.2±12.8	<0.0001
Arterial complications				
Aortic rupture	2 (0.3)	0	2 (0.4)	0.541
Type A aortic dissection	8 (1.0)	1 (0.4)	7 (1.4)	0.271
Type B aortic dissection	3 (0.4)	0	3 (0.6)	0.556
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)	0.579
Major lower limb amputation	10 (1.3)	4 (1.4)	6 (1.2)	0.551
Tracheostomy	180 (23.0)	90 (32.4)	90 (17.9)	<0.0001
Pancreatitis	12 (1.5)	3 (1.1)	9 (1.9)	0.554
Liver failure	265 (34.0)	61 (22.0)	204 (40.6)	<0.0001
Gastrointestinal compl. requiring surgery	42 (5.5)	6 (2.2)	36 (7.3)	0.003
Multiorgan failure	390 (49.9)	53 (19.1)	337 (67.0)	<0.0001
Major neurological complications	147 (18.9)	32 (11.5)	115 (23.0)	<0.0001
Stroke, non-disabling	28 (3.6)	16 (5.8)	12 (2.4)	<0.0001
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)	<0.0001
Vascular access site infection	67 (8.6)	43 (15.5)	24 (4.8)	<0.0001
Pneumonia	285 (36.5)	147 (52.9)	138 (27.4)	<0.0001
Blood stream infection	179 (22.9)	80 (28.8)	99 (19.7)	0.004
Renal replacement therapy*	409 (53.4)	130 (47.4)	279 (56.7)	0.014
Red blood transfusion, units	23.4±22.0	22.0±22.3	24.1±21.8	0.068
Red blood transfusion ≥10 units	547 (70.1)	186 (66.9)	361 (71.9)	0.143
Reoperation for intrathoracic bleeding	328 (42.1)	109 (39.2)	219 (43.6)	0.231
Reoperation for peripheral arterial bleeding	66 (8.5)	18 (6.5)	48 (9.5)	0.140

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

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Supplementary material

Multicenter Study on Postcardiotomy Venoarterial Extracorporeal Membrane Oxygenation

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Legend to tables and figures

Supplementary table 1. Main causes of death in patients who died on VA-ECMO.

Supplementary table 2. Number of postcardiotomy VA-ECMO at each participating center from 2010 to 2017.

Supplementary table 3. Frequency of postcardiotomy VA-ECMO at each participating center from 2010 to 2017.

Supplementary table 4. Derivation of the PC-ECMO score.

Supplementary table 5. Independent predictors of hospital mortality after post-cardiotomy VA-ECMO according to different regression methods.

Supplementary figure 1. Mortality rates during VA-ECMO therapy and index hospitalization in increasing deciles of arterial lactate at initiation of VA-ECMO ($p < 0.0001$).

Supplementary figure 2. Kaplan-Meier estimate of all-cause mortality after postcardiotomy VA-ECMO according to increasing PC-ECMO risk scores (log-rank test: $p < 0.0001$).

Supplementary figure 3. Scatter plot of correlation between predicted hospital mortality and additive PC-ECMO score

Supplementary figure 4. Hospital and on VA-ECMO mortality rates according to increasing EuroSCORE II.

Supplementary figure 5. Scatter plot of standardized mortality ratios and institutional volumes of postcardiotomy VA-ECMO.

Supplementary figure 6. Scatter plot of institutional volumes of postcardiotomy VA-ECMO and median duration of VA-ECMO therapy.

Supplementary table 1. Main causes of death in patients who died on VA-ECMO.

Main causes of death	No. (%)
Multiorgan failure	160 (20.5)
Heart failure	103 (13.2)
Neurological 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)

Supplementary table 2. Number of postcardiotomy VA-ECMO 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

*Three and **five patients were treated after the end of the study period.

Supplementary table 3. Frequency of postcardiotomy VA-ECMO 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	12000	85 (0.7)
Rennes	10168	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	12328	31 (0.3)
Prague	9152	21 (0.2)
Glasgow	10028	22 (0.2)
Turku	3439	7 (0.2)
Leicester	8768	16 (0.2)

Supplementary table 4. Derivation of the PC-ECMO score.

Covariates	Odds ratio, 95%CI	Coefficients	Additive score
Age			
<60 years	Reference category	-	
60-69 years	1.684, 1.160-2.446	0.521	2
≥70 years	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	

Supplementary table 5. Independent predictors of hospital mortality after post-cardiotomy VA-ECMO according to different regression methods.

Covariates	
Logistic regression with age and arterial lactate as continuous variables	Odds ratio, 95%CI
Age, years	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 years	-
60-69 years	1.720, 1.199-2.468
≥70 years	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 years	-
60-69 years	1.759, 1.194-2.591
≥70 years	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=0.0049

CI, confidence interval.

Supplementary figure 1. Mortality rates during VA-ECMO therapy and index hospitalization in increasing deciles of arterial lactate at initiation of VA-ECMO ($p < 0.0001$).

Supplementary figure 2. Kaplan-Meier estimate of all-cause mortality after postcardiotomy VA-ECMO according to increasing PC-ECMO risk scores (log-rank test: $p < 0.0001$).

Supplementary figure 3. Scatter plot of correlation between predicted hospital mortality and additive PC-ECMO score

Supplementary figure 4. Hospital and on VA-ECMO mortality rates according to increasing EuroSCORE II.

Supplementary figure 5. Scatter plot of standardized mortality ratios and institutional volumes of postcardiotomy VA-ECMO.

Supplementary figure 6. Scatter plot of institutional volumes of postcardiotomy VA-ECMO and median duration of VA-ECMO therapy.