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ORIGINAL SCIENTIFIC PAPER

Five-year survival after post-cardiotomy veno-arterial extracorporeal membrane oxygenation

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Aims Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) support for post-cardiotomy cardiogenic shock (PCS) after adult cardiac surgery is associated with satisfactory hospital survival. However, data on long-term survival of these critically ill patients are scarce.

Methods and results Between January 2010 and March 2018, 665 consecutive patients received VA-ECMO for PCS at 17 cardiac surgery centres and herein we evaluated their 5-year survival. The mean follow-up of this cohort was 1.7 ± 2.7 years (for hospital survivors, 4.6 ± 2.5 years). In this cohort, 240 (36.1%) patients survived to hospital discharge. Five-year survival of all patients was 27.7%. The PC-ECMO score was predictive of 5-year survival in these patients (0 point, 50.9%; 1 point, 44.9%; 2 points, 40.0%; 3 points, 34.7%; 4 points, 21.0%; 5 points, 17.6%; ≥6 points, 10.7%; $P < 0.0001$). Age was among factors independently associated with late survival, patients >70 years old having a remarkably poor 5-year survival (<60 years: 39.2%; 60–69 years: 29.9%; 70–79 years: 12.3%; ≥80 years: 13.0%, $P < 0.0001$). Implantation of a ventricular assist device or heart transplant was performed in 3.2% of patients and their 5-year survival was 42.9% (for heart transplant, 63.6%).

Conclusion Veno-arterial extracorporeal membrane oxygenation for PCS is associated with satisfactory 5-year survival in young patients without critical pre-ECMO conditions. The use of VA-ECMO for PCS in patients >70 years should be considered only after a judicious scrutiny of patient's life expectancy. Future studies should evaluate whether satisfactory mid-term survival of these patients translates into a good functional outcome.

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Keywords Extracorporeal membrane oxygenation • ECMO • ECLS • Post-cardiotomy • Cardiac surgery • Acute heart failure

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a salvage therapy for patients with post-cardiotomy cardiogenic shock (PCS) refractory to other therapies.[1,2] A growing body of evidence suggests that one-third of patients are expected to be salvaged by VA-ECMO.[3,4] However, in view of significant early mortality and morbidity as well as significant incremental costs,[3–6] patient's selection is a key issue to optimize resource allocation to those who may most benefit from this salvage therapy.[7] Hospital survival is the main outcome of most studies evaluating the results of VA-ECMO and only a few studies reported on survival of these patients at 5 years or later.[8] Therefore, it remains unclear whether the use of VA-ECMO translates into satisfactory long-term survival in PCS patients. In this study, we evaluated the 5-year survival of patients with PCS following adult cardiac surgery from the multicentre Post-cardiotomy Veno-arterial Extracorporeal Membrane Oxygenation (PC-ECMO) registry.

Methods

The PC-ECMO registry is a retrospective, multicentre PC-ECMO registry that enrolled patients who underwent VA-ECMO following adult cardiac surgery at 19 centres from Belgium, Czech Republic, Finland, France, Germany, Italy, Saudi Araba, Sweden, and the UK from January 2010 to March 2018. This study is registered at http://www.clinicaltrials.gov (unique identifier: NCT03508505) and was approved by local or regional Institutional Review Board. The detailed study protocol with definition criteria for baseline, operative, and post-operative variables has been published previously.[5] Seventeen participating centres agreed to collect data on late all-cause mortality of these patients, and the latter are the subjects of the present analysis.

Patients operative risk was estimated according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II risk scoring method[9] and the specific PCS VA-ECMO risk of hospital mortality according to the PC-ECMO risk score.[5] Baseline risk factors were defined according to the EuroSCORE II definition criteria and refer to patient's status before the index cardiac surgery procedure. The PC-ECMO risk score was calculated by summing weighted integers as follows: female gender, 1 point; 60–69 years, 2 points; ≥70 years, 4 points; prior cardiac surgery, 1 point; arterial lactate 6.0 mmol/L or greater before ECMO, 2 points; aortic arch surgery, 4 points; pre-operative stroke/unconsciousness, 5 points.

The main outcome measure of this study was all-cause mortality. Secondary outcomes included death on VA-ECMO, reoperation for bleeding/tamponade, post-operative neurological and renal complications, sternal wound infection, red blood cell transfusion, and the length of stay in hospital and the intensive care unit.

Data on survival status of these patients were retrieved from national population registries, by contacting patients and their families and/or general practitioners. Follow-up was considered complete when information on the last survival status was available after January 2020.

This study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10]

Statistical analysis

Statistical analyses were conducted using Stata v. 15.1 (StataCorp LLC, TX, USA) and SPSS v. 25.0 (IBM Corporation, Armonk, NY, USA) statistical softwares. Covariates and outcomes were reported as counts and percentages, and as mean and standard deviation or median and 25–75th interquartile range (IQR). Discrimination and calibration of the PC-ECMO score in predicting hospital and 5-year mortality have been assessed using the Harrell's *C* test[11] and the slope on the log cumulative-hazard scale, respectively.[12] Survival analysis was performed using the Kaplan–Meier method with the log-rank test. Patients lost to follow-up were included in survival analyses and were considered censored at the time of their last control. Multivariate analysis was performed using the Cox proportional hazards method including covariates with $P < 0.1$ in univariate analysis. Age, estimated glomerular filtration rate, dialysis, pre-operative stoke/unconsciousness, Stanford type A aortic dissection, prior cardiac surgery, extracardiac arteriopathy, pulmonary disease, aortic cross-clamping time, aortic procedures, aortic arch repair, mitral valve surgery, coronary artery bypass grafting, central arterial cannulation, pre-ECMO arterial lactate level, and duration of VA-ECMO were included into the Cox regression model using a backward stepwise method. Landmark analyses were performed including only post-discharge patients and including covariates with $P < 0.1$ in univariate analysis. Gender and participating centres were forced in to all the regression models. Risk estimates are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Pre-VA-ECMO arterial lactate was dichotomized according to a cut-off value of 6.0 mmol/L, which has been previously estimated using the Youden's test.[5] The prognostic impact of Pre-VA-ECMO arterial lactate was further assessed by dichotomizing it with increasing cut-off values and calculating their unadjusted and adjusted HRs for 5-year mortality. A $P < 0.05$ was set for statistical significance.

Results

Patient's characteristics

Among the 665 patients, mean age was 62.5 ± 13.1 years (median 65.4 years, IQR 65.4–71.4) and 217 (32.6%) were female. Baseline characteristics of these patients are summarized in *Table 1*. Operative data are summarized in Supplementary material online, *Table S1*. The mean follow-up of the overall cohort was 1.7 ± 2.7 years (median, 0.04 years, IQR 0.1–3.2). The mean follow-up of post-discharge patients was 4.6 ± 2.5 years (median, 4.4 years, IQR 2.9–6.5). Follow-up was complete for 95.6% of patients. Twenty-nine patients had their last follow-up control before January 2020 or were lost to follow-up. The mean follow-up of the latter patients was 3.3 ± 2.1 years (median, 3.4 years, IQR 2.1–4.7).

Table 1 Baseline characteristics of patients who survived or died at 5 years[a]

Variables	All patients ($n = 665$)	Survivors ($n = 191$)	Deaths ($n = 474$)	*P*-value
Age Mean (years)	62.5 (13.2)	57.5 (13.9)	64.4 (12.3)	<0.0001
Median	65.4 (56.0–71.4)	60.4 (51.5–67.3)	67.0 (58.9–72.9)	
Age >70 years	203 (30.5)	28 (14.7)	175 (36.9)	<0.0001
Females	217 (32.6)	57 (29.8)	160 (33.8)	0.201
Body mass index,				
Mean (kg/m^2)	27.2 (5.1)	27.0 (5.1)	27.3 (5.1)	0.609
Median	26.7 (23.9–30.0)	26.8 (23.7–29.4)	26.6 (23.9–30.1)	
Presentation and cardiac status				
Urgent/emergent procedure	377 (56.7)	107 (56.0)	270 (57.0)	0.740
Critical preoperative state	232 (34.9)	66 (34.6)	166 (35.0)	0.858
Pre-operative stroke/unconsciousness	26 (3.9)	3 (1.6)	23 (4.9)	0.007
Active endocarditis	77 (11.6)	20 (10.5)	57 (12.0)	0.616
Stanford type A aortic dissection	52 (7.8)	11 (5.8)	51 (8.6)	0.008
Prior cardiac surgery	164 (24.7)	36 (18.8)	128 (27.0)	0.056
Recent myocardial infarction	207 (31.1)	51 (26.7)	156 (32.9)	0.114
LVEF ≤ 50%	374 (56.4)	112 (58.9)	262 (55.4)	0.430
Comorbidities				
Diabetes	157 (23.6)	39 (20.4)	118 (24.9)	0.884
Haemoglobin				
Mean (mg/L)	125 (21)	127 (23)	125 (20)	0.297
Median	127 (110–140)	130 (110–144)	126 (110–140)	
eGFR				
Mean (mL/min/1.73 m^2)	68 (30)	74 (31)	66 (30)	0.003
Median	67 (49–84)	73 (54–73)	64 (47–83)	
Dialysis	30 (4.5)	4 (2.1)	26 (5.5)	0.081
Stroke	47 (7.1)	16 (8.4)	31 (6.5)	0.694
Extracardiac arteriopathy	89 (13.4)	17 (8.9)	72 (15.2)	0.012
Pulmonary disease	93 (14.0)	21 (11.0)	72 (15.2)	0.024
Atrial fibrillation	160 (24.1)	40 (20.9)	120 (25.3)	0.307
PC-ECMO				
Mean score	3.9 (2.5)	2.8 (2.1)	4.3 (2.5)	<0.0001
Median	4.0 (2.0–4.0)	2.0 (1.8–4.0)	4 .0 (2.0–6.0)	
EuroSCORE II				
Mean score (%)	15.1 (17.3)	11.6 (13.2)	16.7 (18.5)	<0.0001
Median	8.5 (3.1–20.8)	6.3 (2.5–16.9)	9.2 (3.3–23.1)	

[a]Baseline risk factors were defined according to the EuroSCORE II definition criteria and refer to patient's status before the index cardiac surgery procedure. Continuous data are presented as mean and standard deviation as well as median and 25–75th interquartile range; categorical variables as number and percentages.
eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; PC-ECMO, post-cardiotomy extracorporeal membrane oxygenation.

Outcomes

In this cohort, 240 (36.1%) patients survived to hospital discharge. Early complications are summarized in *Table 2*. Five-year survival of all patients was 27.7% (*Figure 1*). The PC-ECMO score was predictive of 5-year survival in these patients (0 point, 50.9%; 1 point, 44.9%; 2 points, 40.0%; 3 points, 34.7%; 4 points, 21.0%; 5 points, 17.6%; ≥6 points, 10.7%; log-rank test, $P < 0.0001$) (*Figure 2*), with satisfactory discrimination (Harrell's *C* 0.625, 95% CI 0.599–0.651) and calibration (slope on the log cumulative-hazard scale, $P = 0.677$). The PC-ECMO score was predictive of 5-year survival also when adjusted for the participating centres (HR 1.196, 95% CI 1.152–1.243). The EuroSCORE II was significantly higher in patients who died at 5-year ($P < 0.0001$) (Supplementary material online).

Risk factors independently associated with 5-year all-cause mortality are summarized in *Table 3* (654 out of 665 patients included in the regression analysis). Advanced age was among predictors of poor 5-year survival. In particular, patients >70 years old had a markedly decreased 5-year survival (<60 years: 39.2%; 60–69 years: 29.9%; 70–79 years: 12.3%; ≥80 years: 13.0%, log-rank test, $P < 0.0001$) (*Figure 3*).

Pre-VA-ECMO arterial lactate was identified as independently associated with 5-year survival (*Table 3*). Its prognostic importance in terms of 5-year mortality started being statistically significant at a level

Table 2 In-hospital outcomes in patients who survived or died at 5 years

Outcomes	All patients (*n* = 665)	Survivors (*n* = 191)	Deaths (*n* = 474)	*P*-value
In-hospital mortality	425 (63.9)	—	—	—
Mortality on VA-ECMO	301 (45.3)	—	—	—
Ventricular assist device or heart transplant	21 (3.2)	9 (4.7)	12 (2.5)	0.047
Heart transplant	11 (1.7)	7 (3.7)	4 (0.8)	0.021
Stroke or global brain ischaemia	118 (17.8)	14 (7.3)	104 (22.0)	0.001
New dialysis	318 (51.1)	82 (44.6)	236 (53.9)	0.426
Pneumonia	252 (37.9)	100 (52.4)	152 (32.1)	<0.0001
Deep sternal wound infection	26 (3.9)	15 (7.9)	11 (2.3)	0.001
Reoperation for bleeding	272 (41.0)	77 (40.3)	195 (41.2)	0.888
RBC units transfused				
Mean (units)	21 (20)	19 (18)	22 (21)	0.963
Median	15 (8–28)	13 (6–26)	15 (8–30)	
RBC >9 units	448 (67.4)	118 (61.8)	330 (69.6)	0.277
Intensive care unit stay				
Mean (days)	17 (19)	26 (18)	14 (18)	<0.0001
Median	12 (5–23)	22 (13–32)	8 (3–17)	
Hospital stay				
Mean (days)	26 (33)	46 (35)	18 (29)	<0.0001
Median	15 (5–31)	34 (25–55)	9 (3–20)	

Continuous data are presented as mean and standard deviation as well as median and 25–75th interquartile range; categorical variables as counts and percentages.
RBC, red blood cells; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VAD, ventricular assist device.

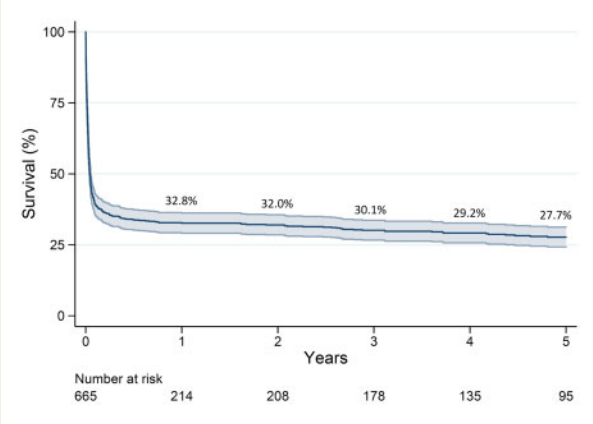

Figure 1 Five-year survival after post-cardiotomy extracorporeal membrane oxygenation.

of ≥4.0 mmol/L, and the adjusted risk estimate increased along with higher pre-VA-ECMO arterial lactate levels (Supplementary material online, *Table S2*).

The participating centre was independently associated with late all-cause mortality of these patients (*Table 3*). Centres which have treated <50 cases during the study period (13 out of 18 centres, overall 327 patients) had a significantly lower 5-year survival (24.8% vs. 30.5%, log-rank test, $P = 0.025$, adjusted HR 1.301, 95% CI 1.080–1.568). Centres without ventricular assist device and/or heart transplant program had lower 5-year survival (25.0% vs. 28.1%, log-rank test, $P = 0.018$, adjusted HR 1.301, 95% CI 1.080–1.568).

Only 3.2% of patients underwent implantation of a ventricular assist device or heart transplant. They had significantly higher 5-year survival (42.9% vs. 27.2%, log-rank test: $P = 0.041$; for heart transplant: 63.6% vs. 27.1%, log-rank test: $P = 0.013$) compared to those who did not undergo these treatments, but the difference was not significant in multivariate analysis (HR 1.581, 95% CI 2.879; for heart transplant: HR 0.376, 95% CI 0.137–1.036).

Post-discharge outcome

Two-hundred and forty patients survived to discharge after VA-ECMO for PCS. Among them, 1-, 3-, and 5-year survival rates were 91.1%, 83.7%, and 76.9%, respectively (Supplementary material online, *Figure S2*).

Factors independently associated with 5-year mortality were advanced age, females, recent myocardial infarction, active endocarditis, increased pre-VA-ECMO arterial lactate level, and participating centres (Supplementary material online, *Table S3*) (235 out of 240 patients included in the regression analysis).

Outcome among elderly

Cox proportional hazards analysis (*Table 3*) showed that 5-year survival was significantly reduced in patients >70 years old. Kaplan–Meier estimate of 5-year survival was 12.2% in patients >70 years old and 34.4% in younger patients (log-rank test, $P < 0.0001$, adjusted HR 1.840, 95% CI 1.522–2.224). This difference persisted also among post-discharge patients (52.0% vs. 83.0%, log-rank test, $P < 0.0001$, adjusted HR 3.080, 95% CI 1.686–5.627).

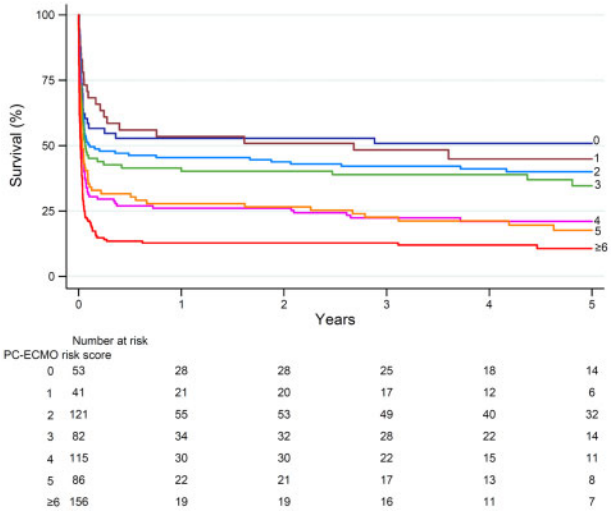

Figure 2 Five-year survival after post-cardiotomy extracorporeal membrane oxygenation according to post-cardiotomy veno-arterial extracorporeal membrane oxygenation risk scores (log-rank test, $P < 0.0001$).

Table 3 Factors independently associated with 5-year all-cause mortality in the overall cohort

Covariates	*P*-value	HR, 95% CI
Regression model with continuous variables		
Age (per each increasing year)	<0.0001	1.030, 1.021–1.039
Female	0.050	1.220, 1.000–1.489
Pre-operative stroke/unconsciousness	0.010	1.578, 1.032–2.412
Replacement of the aortic arch	0.005	1.820, 1.197–2.769
Arterial lactate before VA-ECMO (per each increasing mmol/L)	<0.0001	1.069, 1.046–1.093
Participating centre	<0.0001	–
Regression model with categorized continuous variables		
Age	<0.0001	
<60 years		Reference
60–69 years		1.531, 1.194–1.963
70–79 years		2.258, 1.748–2.915
≥80 years		2.816, 1.716–4.620
Pre-operative stroke/unconsciousness	0.003	1.949, 1.250–3.039
Replacement of the aortic arch	0.006	1.798, 1.185–2.726
Arterial lactate before VA-ECMO >6.0 mmol/L	<0.0001	1.580, 1.295–1.928
Participating centre	<0.0001	—

CI, confidence interval; HR, hazard ratio.

Baseline characteristics and operative data on patients >70 years old are summarized in Supplementary material online, *Tables S4* and *S5*. Among patients >70 years old, pre-ECMO arterial lactate level (HR 1.046, 95% CI 1.012–1.081) was the only factor independently associated with 5-year survival. Five-year survival was 9.9% in patients with pre-ECMO arterial lactate >6.0 mmol/L and 13.9% among patients with lower levels (log-rank test, $P = 0.045$). Lower cut-off values of arterial lactate level were not predictive of poor survival in the elderly. Participating centres did not have impact on late mortality of patients >70 years old (log-rank test, $P = 0.197$).

Discussion

In this study, we evaluated the impact of VA-ECMO on midterm survival of patients with PCS from a multicentre retrospective registry.

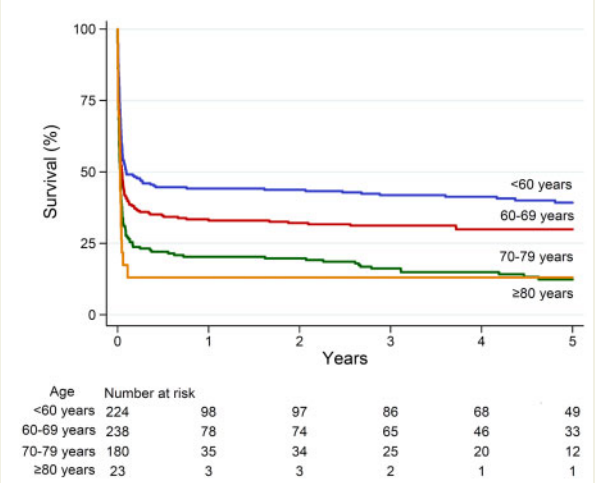

Figure 3 Five-year survival after post-cardiotomy extracorporeal membrane oxygenation according to patient's age (log-rank test, $P < 0.0001$).

The main findings of this analysis are (i) one-fourth of patients requiring VA-ECMO for PCS were alive at 5-year; (ii) only 3% of patients were treated with a ventricular assist device or heart transplant and their 5-year survival was 42.9% (for heart transplant: 63.6%); (iii) the PC-ECMO score allowed a stratification of the risk of mid-term mortality; (iv) 30% of patients treated with VA-ECMO for PCS were >70 years old and their 5-year survival was only 12%; (v) patients <60 years old or with a PC-ECMO score <3 had a 5-year survival higher than 40%.

A recent pooled analysis showed that 1-year survival after VA-ECMO for PCS was 30.9%.[3] However, data on longer term survival of these critically ill patients are scarce.[8] Chen *et al.*,[4] in 2017, reported the long-term results of 1141 patients who required ECMO after adult cardiac surgery from a nationwide administrative registry. Despite a hospital survival rate of 38.1%, 5-year survival of these patients was 17.7%. The authors did not provide the results of a multivariate analysis. Data extrapolated from survival curves showed that 5-year survival were 12% among patients aged 71–80 years and 7% among patients aged 80 years or older. It is worth noting that in this nationwide study, the proportion of patients >70 years old was 36.4%, which is comparable to that of the present cohort.

Rastan *et al.*[13] reported a hospital survival of 24.8% and 5-year survival of 13.7% in an institutional cohort of 517 patients who required VA-ECMO to treat refractory PCS. Unosawa *et al.*[14] reported a hospital survival on 29.8% and 5-year survival of 20.1% among 47 PCS VA-ECMO patients. More recently, Bonacchi *et al.*[15] evaluated the outcome of 209 PCS VA-ECMO patients with a mean follow-up of 3.2 ± 0.5 years. They reported a rather high hospital survival (42.1%), but 5-year survival was 25.2%. The investigators identified age >35 years, insulin-dependent diabetes and absence of severe coronary artery disease as risk factors for 5-year mortality.[15] Finally, Saxena *et al.*[16] reported the outcome of 45 patients >70 years old who required VA-ECMO for PCS. The hospital mortality in their cohort was 24.4% and 5-year survival was 12.6%.

The present analysis confirmed that 5-year survival of septuagenarians and octogenarians after VA-ECMO for PCS is usually <15%. These results should be view also in the context of a high proportion (30%) of patients >70 years old receiving this salvage therapy. It is worth noting, that most of these patients required VA-ECMO after coronary surgery or isolated valve surgery, and the proportion of elderly who underwent complex surgery was limited. Overall, these findings showed that VA-ECMO is offered to a large number of elderly with PCS without any significant benefit in terms of mid-term survival. Despite the rather large number of patients >70 years old included in this multicentre registry, the high mortality rate in this subset of patients prevented the identification of risk factors contraindicating this salvage therapy in the elderly. Overall, these results suggest that advanced age is not an absolute contraindication to VA-ECMO for PCS, but judicious clinical scrutiny is required before starting VA-EECMO in the elderly.

This study confirmed that the PC-ECMO risk score may be a useful tool also to stratify the risk of mid-term survival in these patients and may indicate when the risk of early and late mortality is prohibitive and does contraindicate the use of this salvage therapy. Indeed, identification of patients with an expected 5-year survival lower than 20% is relevant in the decision-making process in PCS patients. However, the ability of the PC-ECMO risk score to predict mid-term survival most likely is influenced by the high hospital mortality. Survival analysis of post-discharge patients showed that advanced age, male gender, recent myocardial infarction, active endocarditis, pre-VA-ECMO arterial lactate, and participating centres were factors independently associated with 5-year all-cause mortality. These risk factors provide the clinicians with further information to estimate the life expectancy of these patients, because the presence of such comorbidities and metabolic derangement may be an argument against the use of VA-ECMO after adult cardiac surgery.

The present analysis might be biased by interinstitutional differences in practice and experience with post-cardiotomy VA-ECMO. Therefore, analyses were adjusted for participating centres, which were found being independently associated with survival. We assessed the performance of these centres by evaluating the impact of the volume of post-cardiotomy VA-ECMO using a cut-off of 50 cases treated during the study period. This analysis showed that low-volume centres had lower 5-year survival (24.8% vs. 30.5%, $P = 0.025$). Furthermore, centres without ventricular assist device and/or heart transplant program had lower 5-year survival (25.0% vs. 28.1%, $P = 0.018$). However, centre volume did not impact late survival of elderly patients.

Limitations of the study

The retrospective nature is the main limitation of this study. Second, we do not have data on the mid-term functional outcome of these patients, and this prevented conclusive results on the quality of life of this critically ill patient population. Indeed, the evaluation of functional outcome is of importance because good mid-term survival may not reflect a satisfactory quality of life.[17] Third, a number of patients were lost to follow-up. In some cases, data on their survival status was not retrievable even from national electronic registries because patients moved to abroad. Furthermore, several patients were referred to ECMO centres from other centres and this made difficult the follow-

up of patients in countries without data from National registries. Therefore, it is possible that survival of this cohort might be overestimated. Finally, despite this multicentre study included a rather large number of patients, the analysis of subsets of patients may be biased by a type II error. Indeed, the sample size of patients >70 years old having high early and late mortality, is not sufficient for a reliable identification of risk factors significantly associated with poor survival.

Conclusions

Our study showed that VA-ECMO achieved satisfactory mid-term survival in patients with cardiopulmonary insufficiency after adult cardiac surgery. However, survival benefit with this salvage therapy is evident only in young patients without critical pre-VA-ECMO conditions. In view of their poor 5-year survival, the use of VA-ECMO for PCS in patients >70 years should be considered only after a judicious scrutiny of their life expectancy. Further studies are needed to confirm the present findings and to assess whether satisfactory mid-term survival translates into a good functional outcome in these critically ill patients.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care*.

Conflict of interest: The investigators have no conflicts of interest to disclose.

Data availability

According to institutional and national rules, this data is not available to others than the members of the PC-ECMO study group.

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