Original paper

Role of age in prognostication of hospital mortality in postcardiotomy patients supported with extracorporeal membrane oxygenation

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Abstract

Introduction: Despite the growing use of venoarterial extracorporeal membrane oxygenation (VA-ECMO), there are still no clearly defined criteria for VA-ECMO initiation in postcardiotomy (PC) patients.

Aim: To identify the pre-ECMO risk factors associated with increased hospital mortality, paying special attention to the patients' age.

Material and methods: Retrospective review of consecutive adult patients supported with PC ECMO for a 16-year period in a tertiary care center. The primary outcome was all-cause mortality. Logistic regression was performed to identify mortality predictors. To determine the optimal age cut-off that most accurately distinguishes between higher and lower probabilities of mortality, the Youden index was used.

Results: A total of 214 patients were enrolled in the final analysis and 55 (25.7%) survived until hospital discharge. Age was a significant mortality predictor with ROC-AUC of 0.596 (0.508–0.685), $p = 0.033$. Multivariable logistic regression showed that age over 60 years (OR = 2.119 (95% CI: 1.055, 4.255), $p = 0.035$), male gender (OR of 0.415, indicating a protective effect) (95% CI: 0.198, 0.869), $p = 0.020$), pre-ECMO vasoactive inotropic score (VIS) (OR = 1.015 (95% CI: 1.002, 1.027), $p = 0.019$), and mechanical ventilation duration before ECMO (OR = 1.053 (95% CI: 1.014, 1.092), $p = 0.007$) remained as independent prognostic factors.

Conclusions: Our study confirms that advanced age is a prognostic marker of mortality in PC ECMO patients and doubles the mortality risk above 60 years. However, age must be considered alongside other mortality predictors. These findings can significantly contribute to the decision-making process.

Key words: risk factors, elderly, postcardiotomy, venoarterial extracorporeal membrane oxygenation.

Summary

Despite the growing use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) in clinical practice, there are still no clearly defined selection criteria for which postcardiotomy patients VA-ECMO initiation would be the most effective. Our study found that age older than 60 years, female sex, the Vasoactive Inotropic Score, and the mechanical ventilation duration before postcardiotomy extracorporeal membrane oxygenation implantation were associated with an increased risk of in-hospital mortality. These findings can significantly contribute to the decision-making process regarding mechanical circulatory support initiation, providing a more comprehensive understanding of the risk factors involved.

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Introduction

The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) has increased significantly over the past decade. VA-ECMO has now become the most commonly used mechanical circulatory support (MCS) modality for the treatment of postcardiotomy shock (PCS) [1–3]. It is associated with rapidly developing technologies, greater availability, ease of use, and lower costs compared to other MCS types.

Despite the growing use of VA-ECMO in clinical practice, several debatable questions exist regarding its use in PCS settings. The risk factors for poor outcomes increase as the PCS patient population ages and become more complex. The main discussion topics among medical professionals are the benefit–risk ratio, ethical decision-making challenges (e.g., allocation of scarce resources and the potential for prolonging suffering), and indications and contraindications for initiating extracorporeal membrane oxygenation (ECMO), especially in older patients. Moreover, postcardiotomy extracorporeal membrane oxygenation (PC-ECMO) outcomes have remained worse than other VA-ECMO application areas, and overall mortality rates have not improved significantly over time [4–6].

One aspect that could improve PC-ECMO outcomes is the quality of patient selection. Typically, individuals receiving PC-ECMO are older patients with comorbidities, who have a higher mortality risk and, in most cases, are expected not to survive without ECMO support. To date, there are still no clearly defined criteria for which of these patients VA-ECMO initiation would be the most effective. The issue of age in selecting PC-ECMO candidates remains critical in the aging population setting.

Patient age is one of the most commonly used criteria in cardiac surgery and VA-ECMO risk scores. Although several studies have assessed the relationship between age and outcomes in patients undergoing VA-ECMO, the results are often contradictory. While some studies have shown that increasing age is not linked to increased mortality [2, 7], others have confirmed that advanced age is a significant risk factor for in-hospital mortality [1, 5]. According to the literature, the age cut-off associated with increased mortality is not definitively determined and typically varies from 60 to 85 years [1]. One recent multinational cohort study of 15,172 patients who underwent VA-ECMO found that advanced age was associated with increasing odds of death, with a significantly higher risk emerging even as early as 40 years of age [8]. However, some PC-ECMO studies have shown positive short-term and long-term outcomes for patients aged 70 years or older [9, 10].

Aim

Our study aimed to identify the pre-ECMO risk factors associated with increased in-hospital mortality, focusing on patient age.

Material and methods

Study population

This epidemiological retrospective study was conducted among all adult postcardiotomy VA-ECMO cases at Vilnius University Hospital Santaros Clinics from June 2007 to December 2023. This specific population was selected as it represents a significant proportion of patients who could benefit from our findings. The Vilnius Regional Bioethics Committee (Lithuania) approved the study (reference number 158200-16-850-359), further validating the relevance of our research.

Mortality predictors

The primary outcome investigated was in-hospital mortality, defined as all-cause mortality during VA-ECMO cases. Conventional predictors of VA-ECMO outcomes were evaluated. Data on patients' demographic characteristics, comorbidities, initial laboratory test results, pre-existing medical conditions, risk score evaluations (Survival After Veno-Arterial ECMO (SAVE) score, European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) score, Clinical Frailty Score, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment Score, prediction of early mortality associated with VA-ECMO using preimplantation characteristics (IMPACT) score), and perioperative outcomes were collected from medical records retrospectively. Information on age on the day of VA-ECMO initiation was collected and evaluated.

Clinical management

VA-ECMO (Medos Deltastream MDC, manufactured by Medos Medizintechnik AG) was initiated following the diagnosis of refractory PCS in the operating room or the intensive care unit (ICU). All patients underwent a cardiac surgical procedure through a median sternotomy. Minimally diluted tepid blood or crystalloid cardioplegia was used for myocardial protection during cardiopulmonary bypass (CPB) (Stockert S5, Sorin Group Deutschland GmbH, München, Germany).

In the operating room, ECMO was considered when patients could not be successfully weaned from CPB. After the first failed weaning attempt, 45–60 min of reperfusion was usually applied. In the absence of contraindications, an intra-aortic balloon pump (IABP) (Datascope CS300, Datascope Corporation, Mahwah, NJ, USA) was additionally inserted. After the second failed CPB weaning attempt, when the Vasoactive Inotropic Score (VIS; dopamine dose at µg/kg/min + dobutamine dose at µg/kg/min + 100 × epinephrine dose at µg/kg/min + 10 × milrinone dose at µg/kg/min + 10,000 × vasopressin dose at U/kg/min + 100 × norepinephrine dose at µg/kg/min) exceeded 50 points despite optimizing the preload, ECMO was initiated based on the team decision.

The most commonly used vasoactive agents were norepinephrine, dobutamine, and milrinone.

In cases of refractory PCS during surgery without CPB and in the postoperative ICU, the decision to initiate MCS was made based on the same hemodynamic parameters. Depending on the team decision, VA-ECMO was initiated via central or peripheral cannulation. The size of the cannulas was selected considering patients' body surface area and the expected ECMO blood flow rate required to meet metabolic needs. A drain was additionally inserted into the left ventricle to unload it if necessary.

Near-infrared spectroscopy monitoring (INVOS5100 cerebral/somatic oximeter, Medtronic Inc., Minneapolis, MN, USA) was used in all cases of peripheral cannulation to assess the distal-extremity perfusion. When signs of limb ischemia were noted, an 8-Fr catheter was inserted distal to the arterial cannula for antegrade or a 4–5-Fr catheter was inserted into the posterior tibial artery for retrograde perfusion of the limb. Blood gas samples were taken through a catheter inserted into the right radial artery. Heparin infusion was used as a standard to maintain the activated clotting time within 180–220 s or increase the activated partial thromboplastin time by 1.5 times.

Anticoagulation was started the next day after ECMO initiation if there were no signs of increased bleeding. In cases of postoperative coagulopathy and excessive bleeding, blood products and coagulation factors were transfused to maintain the hemoglobin level at 80–100 g/l, platelet count above 100 × 10^9/l, INR below 1.5, and fibrinogen concentration above 2 g/l. Despite adequately corrected coagulopathy with persistently increased drainage or sudden deterioration of hemodynamics, a sternotomy was performed.

VA-ECMO blood and gas flow rates were adjusted individually for each patient to maintain the SvO_2 above 60%. Lung-protective mechanical ventilation was applied to all patients. If their conditions allowed, patients were extubated with the continuation of MCS. Clinical and echocardiographic hemodynamic parameters were evaluated 48 h after ECMO support. Following the positive dynamics of cardiac function recovery, the ECMO weaning protocol was initiated. A velocity time integral of ≥ 12 cm, a left ventricular ejection fraction of 20–25%, and minimal doses of vasoactive agents at a reduced ECMO blood flow rate (up to 2 l/min) usually led to the decision to discontinue VA-ECMO. Patients were decannulated in the operating room under general anesthesia.

Statistical analysis

Descriptive statistics such as mean with standard deviation (SD) and median with quartiles (Q1, Q3) were calculated for continuous variables. Categorical variables were presented as frequencies with percentages. The normality of quantitative variables was assessed using the Shapiro-Wilk test. A *t*-test and the Mann-Whitney U (Wilcoxon) test were used to compare the means and medians for normally and non-normally distributed variables, respectively. Frequency distributions between groups were compared using Fisher's exact test. Univariate logistic regression models were used to evaluate the possible predictive factors for survival status (dependent variable) regardless of surviving time. Only factors that remained statistically significant in the univariate logistic regression analysis were selected and entered into the multivariable binary logistic regression model. Confidence intervals (CIs) of odds ratios were calculated using likelihood ratio statistics. The DeLong test was used to compare area under the curve (AUC) values in receiver operating characteristic (ROC) analysis. Youden's J statistic with ROC analysis was utilized for age cut-off values. A two-tailed *p*-value less than 0.05 was considered a significant level for rejecting the null hypothesis. Statistical analysis was performed using RStudio version 2024.09.1.

Results

Patient characteristics

Between June 2007 and December 2023, 293 adult VA-ECMO procedures were performed at our center. The study sample for this analysis included only VA-ECMO cases due to PCS that occurred during or after cardiac surgery. A total of 214 patients (> 18 years of age) were included in the final analysis (Figure 1).

One hundred fifteen (53.7%) patients were successfully weaned from ECMO, and 55 (25.7%) survived until hospital discharge (in-hospital mortality rate: 74.3%). Among the 55 discharged patients, 47 (85.5%) were alive after 1 year, and 35 (63.6%) were alive after 5 years. Of these 35 patients, 15 (42.9%) were older than 60 years at the time of ECMO initiation.

The majority of the patients were men (*n* = 130, 60.7%). The median (Q1, Q3) age at the time of PC-ECMO was 61.0 (53.0, 69.0) years for the survivors and 66.0 (58.0, 72.0) years for the non-survivors, with a sig-

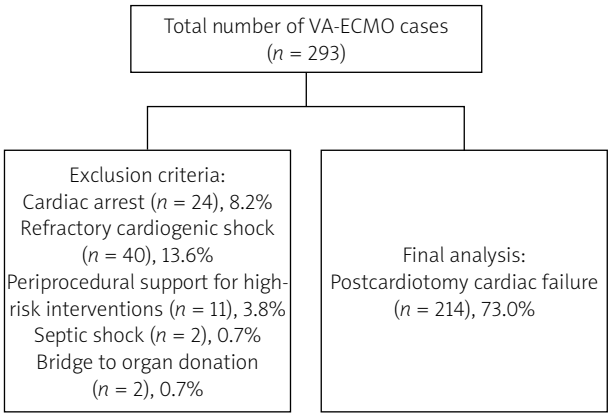

Figure 1. Flowchart of patients included in the study

ECMO – extracorporeal membrane oxygenation.

Table I. Descriptive statistics and comparison among survivors and non-survivors

Parameter	Total (*N* = 214)	Survivors (*N* = 55)	Non-survivors (*N* = 159)	*P*-value
Demographic parameters				
Female patients, *n* (%)	84 (39.3)	14 (25.5)	70 (44.0)	0.016
Age [years] median (IQR)	65.0 (57.0, 71.0)	61.0 (53.0, 69.0)	66.0 (58.0, 72.0)	0.034
Age > 60 years, *n* (%)	137 (64.0)	28 (50.9)	109 (68.6)	0.023
BMI [kg/m^2] mean ± SD	28.8 ±5.52	28.6 ±5.10	28.8 ±5.68	0.80
Comorbidities, *n* (%)				
Diabetes	44 (20.6)	13 (23.6)	31 (19.5)	0.56
Diabetes on insulin	16 (7.5)	5 (9.1)	11 (6.9)	0.60
Chronic kidney disease	44 (20.6)	8 (14.5)	36 (22.6)	0.25
Hypertension	139 (65.0)	33 (60.0)	106 (66.7)	0.41
COPD	22 (10.3)	6 (10.9)	16 (10.1)	0.80
PVD	29 (13.6)	7 (12.7)	22 (13.8)	1.00
Congenital heart disease	24 (11.2)	9 (16.4)	15 (9.4)	0.21
Endocarditis	12 (5.6)	1 (1.8)	11 (6.9)	0.31
Pulmonary hypertension	131 (61.2)	35 (63.6)	96 (60.4)	0.75
CrCl [ml/min] median (IQR)	72.0 (51.0, 93.0)	87.0 (57.0, 96.0)	68.0 (50.0, 89.0)	0.009
NYHA, class, median (IQR)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	0.80
Clinical Frailty Score [units] median (IQR)	5.0 (4.0, 5.0)	4.0 (4.0, 5.0)	5.0 (4.0, 5.0)	0.003
Laboratory and instrumental investigations				
Preoperative LVEF, %, median (IQR)	50.0 (38.0, 55.0)	40.0 (35.0, 54.0)	50.0 (40.0, 55.0)	0.001
Estimated pressure in PA [mm Hg] median (IQR)	51.0 (41.0, 65.0)	49.5 (43.0, 64.0)	54.0 (40.0, 66.0)	0.93
Lactate pre-ECMO [mmol/l] median (IQR)	7.9 (4.4, 11.8)	6.3 (3.5, 9.4)	8.4 (4.8, 13.1)	0.005
pH pre-ECMO [units] mean ± SD	7.3 ±0.15	7.3 ±0.13	7.3 ±0.15	0.86
Bilirubin pre-ECMO [µmol/l] median (IQR)	26.6 (18.0, 44.7)	23.2 (15.0, 38.2)	27.0 (18.1, 47.0)	0.047
Clinical evaluation before ECMO				
Mechanical ventilation duration [h] median (IQR)	11.0 (7.0, 26.0)	8.0 (6.0, 11.0)	15.0 (8.0, 29.0)	< 0.001
MAP [mm Hg] median (IQR)	42.0 (33.0, 49.0)	42.0 (34.0, 50.0)	42.0 (31.0, 49.0)	0.51
HR [bpm] median (IQR)	80.0 (62.0, 90.0)	80.0 (70.0, 100.0)	80.0 (60.0, 90.0)	0.45
Pulse pressure [mm Hg] median (IQR)	26.0 (20.0, 35.0)	26.0 (20.0, 38.0)	26.0 (20.0, 35.0)	0.43
VIS score [points] median (IQR)	60.0 (40.0, 82.0)	40.0 (27.0, 70.0)	60.0 (50.0, 84.0)	< 0.001
Cardiac arrest, *n* (%)	51 (23.8)	15 (27.3)	36 (22.6)	0.58
Operative risk, *n* (%)				
Previous cardiac surgery	53 (24.8)	8 (14.5)	45 (28.3)	0.047
Urgent surgery	66 (31.0)	16 (29.1)	50 (31.6)	0.87
Critical preoperative state	54 (25.2)	13 (23.6)	41 (25.8)	0.86
EuroSCORE II, %, median (IQR)	5.8 (2.9, 14.1)	5.2 (2.7, 10.4)	6.1 (3.0, 15.8)	0.32
Type of surgical procedure, *n* (%)				
CABG	33 (15.4)	13 (23.6)	20 (12.6)	0.08
Valve surgery on 1 valve	40 (18.7)	11 (20.0)	29 (18.2)	0.84
Valve surgery on > 1 valve	50 (23.4)	10 (18.2)	40 (25.2)	0.36
Combined	40 (18.7)	11 (20.0)	29 (18.2)	0.84
Heart transplantation	11 (5.1)	2 (3.6)	9 (5.7)	0.73
PA endarterectomy	9 (4.2)	1 (1.8)	8 (5.0)	0.45
Other	31 (14.5)	7 (12.7)	24 (15.1)	0.83
Operative course				
Use of CPB, *n* (%)	198 (92.5)	49 (89.1)	149 (93.7)	0.25
CPB time [min] median (IQR)	214.0 (151.0, 300.0)	243.0 (152.0, 343.0)	208.0 (151.0, 290.0)	0.344
Aortic cross clamp time [min] median (IQR)	113.5 (84.5, 151.0)	122.0 (84.0, 156.0)	111.0 (86.0, 146.0)	0.83
Duration of surgery [min] median (IQR)	382.5 (300.0, 540.0)	440.0 (295.0, 570.0)	375.0 (300.0, 520.0)	0.44

BMI – body mass index, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, CPB – cardiopulmonary bypass, CrCl – Creatinine Clearance, EuroSCORE II-European System for Cardiac Operative Risk Evaluation, HR – heart rate, IQR – interquartile range, LVEF – left ventricular ejection fraction, MAP – mean arterial pressure, NYHA – New York Heart Association, PA – pulmonary artery, PVD – peripheral vascular disease, VIS – vasoactive inotropic score.

Table II. Outcome prognostication scores evaluated before VA-ECMO

Parameter	Total (*N* = 214)	Survivors (*N* = 55)	Non-survivors (*N* = 159)	*P*-value
SAVE [units] median (IQR)	–11.0 (–14.0, –6.0)	–7.0 (–11.0, –5.0)	–11.0 (–15.0, –8.0)	< 0.001
SAPS II [units] median (IQR)	42.0 (34.0, 48.0)	38.0 (31.0, 43.0)	44.0 (36.0, 50.0)	< 0.001
SOFA [units] median (IQR)	9.0 (7.0, 11.0)	7.0 (6.0, 9.0)	9.0 (8.0, 11.0)	< 0.001
IMPACT [units] median (IQR)	3.0 (0.0, 6.0)	2.0 (0.0, 5.0)	4.0 (0.0, 7.0)	0.002

IMPACT – prediction of early mortality associated with veno-arterial ECMO using preimplantation characteristics score, SAPS II – Simplified Acute Physiology Score, SAVE – Survival After Veno-Arterial ECMO Score, SOFA – Sequential Organ Failure Assessment Score.

nificant difference (p = 0.034). The most frequent underlying disease was hypertension (n = 139, 65.0%), followed by pulmonary hypertension (n = 131, 61.2%), diabetes (n = 44, 20.6%), and chronic kidney disease (n = 44, 20.6%). A quarter of the patients were in a critical preoperative state.

Most patients had a valve or combined procedure, with an estimated median (Q1, Q3) EuroSCORE II score of 5.8 (2.9, 14.1). Table I presents further descriptives.

ECMO was started in the operating room in 97 (45.3%) patients and in the ICU in 117 (54.7%) patients. Central cannulation was performed in 179 (83.6%) patients. An IABP was used in 143 (66.8%) patients before VA-ECMO implantation. There was no significant difference in the cannulation site (central: n = 134 (74.9%) vs. peripheral: n = 25 (71.4%), p = 0.69), IABP use (n = 104 (72.7%) vs. n = 55 (77.5%), p = 0.51), or ECMO cannulation location (ICU: n = 93 (79.5%) vs. operating room: n = 66 (68.0%), p = 0.06) between the survivors and non-survivors. The median (Q1, Q3) ECMO duration was 120.0 (92.0, 213.0) and 164.0 (92.0, 303.0) h in the survivors and non-survivors, respectively (p = 0.22).

All evaluated mortality scores, except for the EuroSCORE II score, showed significant differences between the groups. The risk scores evaluated before ECMO implantation are presented in Table II. Furthermore, age was a significant mortality predictor, with an ROC-AUC value of 0.596 (0.508–0.685, p = 0.033). The ROC-AUC for prognosticating mortality is presented in Figure 2.

Prognostic factors for in-hospital mortality

The univariate and multivariable logistic regression analyses were performed to identify the in-hospital mortality predictors. Age was found to be a significant predictor of in-hospital mortality, indicating the importance of assessing the optimal age cut-off that most accurately distinguishes between higher and lower probabilities of in-hospital mortality. For this purpose, the optimal age cut-off based on Youden's index was estimated to be 61.4 years. Based on this estimate, an age cut-off of 60 years was further used without reducing statistical significance.

All baseline, comorbidity, and other pre-ECMO parameters were evaluated in the univariate logistic regression analysis to determine the odds ratio for in-hospital mortality. The age cut-off (60 years), sex, pre-ECMO creatinine clearance, previous cardiac surgery, the pre-ECMO VIS, the mechanical ventilation duration, the pre-ECMO lactate level, and the pre-ECMO bilirubin level were found to be significant parameters in the univariate logistic regression analysis (Table III). The multivariable logistic regression analysis showed that the age cut-off (60 years), sex, the pre-ECMO VIS, and the mechanical ventilation duration remained independent prognostic parameters for in-hospital mortality (Table III).

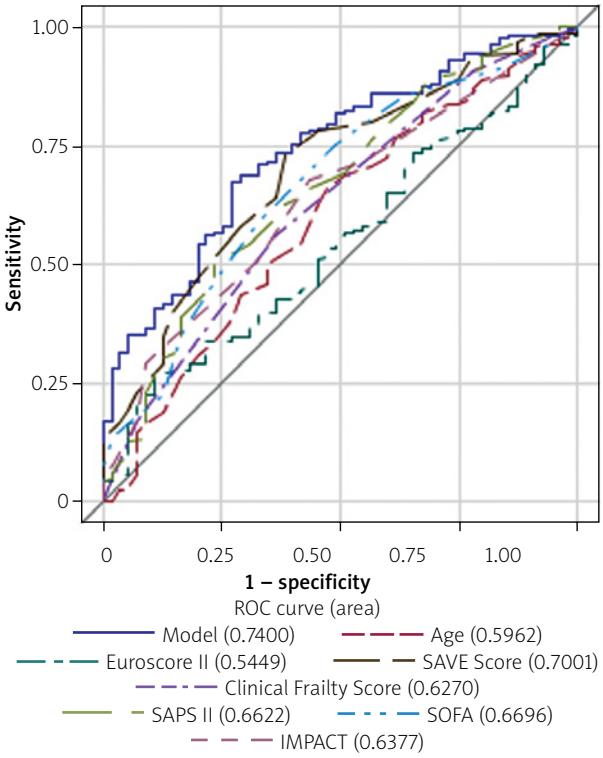

Figure 2. ROC-AUC curves for prognostication of mortality. Age 0.596 (0.508–0.685), p = 0.033; EuroSCORE II 0.545 (0.460–0.630), p = 0.30; SAVE score 0.700 (0.622–0.779), p < 0.001; Clinical frailty score 0.627 (0.546–0.708), p = 0.002; SAPS II 0.662 (0.578–0.746), p < 0.001; SOFA 0.670 (0.588–0.751), p < 0.001; IMPACT 0.638 (0.558–0.717), p = 0.001.

EuroSCORE II – European System for Cardiac Operative Risk Evaluation, IMPACT – prediction of early mortality associated with veno-arterial ECMO using preimplantation characteristics score, SAPS II – Simplified Acute Physiology Score, SAVE – Survival After Veno-Arterial ECMO Score, SOFA – Sequential Organ Failure Assessment Score.

Table III. Logistic regression analysis for hospital mortality

Parameter	Univariable model		Multivariable model	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Older than 60 years	2.102 (1.124–3.930)	0.020	2.119 (1.055, 4.255)	0.035
Male	0.434 (0.219–0.859)	0.017	0.415 (0.198, 0.869)	0.020
Pre-ECMO creatinine clearance	0.987 (0.976–0.997)	0.011		n.s.s.
Pre-ECMO VIS score,	1.018 (1.006–1.029)	0.002	1.015 (1.002, 1.027)	0.019
Mechanical ventilation duration pre-ECMO	1.076 (1.036–1.118)	< 0.001	1.053 (1.014, 1.092)	0.007
Pre-ECMO lactate	1.108 (1.034–1.187)	0.004		n.s.s.
Pre-ECMO bilirubin	1.015 (1.000–1.030)	0.049		n.s.s.

ECMO – extracorporeal membrane oxygenation, n.s.s. – not statistically significant, VIS – vasoactive inotropic score.

In the final analysis, the VIS remained a significant predictor of mortality, with an odds ratio of 1.015 (95% CI: 1.002, 1.027). Furthermore, a longer intubation length before ECMO increased the mortality risk by 1.053 times per hour, that is 3.454 times higher mortality risk for every 24 h. The male patients were less likely to experience lethal outcomes by 0.415 times, while the female patients had a 2.410-fold higher risk. Conversely, the older patients had a 2.119-fold higher mortality risk than the patients younger than 60 years.

Discussion

In our study, we did not evaluate the impact of either ECMO parameters or complications that developed during hospitalization on the patients' early outcomes. We examined the variables present before PC-ECMO implantation only to assess the role of age and to identify other risk factors that could help in making a decision regarding the initiation of MCS. Additionally, we did not evaluate long-term outcomes either. According to the literature, despite higher in-hospital mortality rates, patients receiving VA-ECMO achieve good long-term outcomes with a satisfactory quality of life after discharge [3, 5]. Some data show that most patients undergoing PC-ECMO die during hospitalization, showing a fall in the mortality rate after being discharged [4]. This emphasizes the importance of focusing on improving early outcomes.

The present study showed that age was significantly associated with in-hospital mortality among the patients who received PC-ECMO. Higher mortality rates were noted in the patients above 60 years old. These patients constituted two-thirds of the study cohort and were exposed to a twofold higher mortality risk. Without any statistical justification, most studies set an age cut-off of 65 or 70 years as a risk factor and include different etiologies of cardiogenic shock when evaluating the outcomes of VA-ECMO. The advantages of our study are the statistically justified age limit and the inclusion of only PC-ECMO patients. Our study results are consistent with those published by many leading ECMO centers. For example, in a cohort of 781 patients who underwent PC-ECMO, Biancari *et al.* reported advanced age (> 60 years) as an independent pre-ECMO predictor of in-hospital mortality [1]. In the multicenter cohort Postcardiotomy Extracorporeal Life Support (PELS-1) study of 2058 patients, age was also identified as an independent variable associated with in-hospital mortality [5]. A recent large-sample cohort study, which prospectively collected data from the ELSO Registry, found that increasing age in patients receiving VA-ECMO was strongly associated with increasing odds of death and complications [8].

The final prediction model in our study revealed the VIS, female sex, and the mechanical ventilation duration before ECMO implantation as independent predictors of in-hospital mortality as well. These risk factors are also concordant with those reported in the literature [1, 11].

An ROC-AUC analysis was also performed to determine the accuracy of mortality prediction with age. In this analysis, despite only moderate discrimination, age was as accurate as the mortality prediction scores, with an ROC-AUC value of 0.596. The most accurate score was the SAVE score, with an ROC-AUC value of 0.700. Age is included in the SAVE score, which means that additional criteria for age in the SAVE score did not substantially increase the accuracy of mortality prediction. These results partly explain our final regression model and leave us with only two non-modifiable mortality predictors: age above 60 years and female sex. Female sex has also been considered in the literature as a risk factor for patients receiving VA-ECMO. In a multicenter retrospective propensity score-matched analysis of 358 postcardiotomy VA-ECMO cases, female patients exhibited higher in-hospital mortality rates than male patients [11]. Since age did not differ between the men and women in our study, the observed outcomes may be attributed to sex differences in anatomy, physiology, and vascular pathophysiology, particularly those related to sex hormones. These differences are well known to be associated with a negative prognostic impact on in-hospital mortality for women after cardiac surgery [12].

Further comments must be made about our study cohort's mortality rate and conventional mortality predictors. According to the literature, including single-center

experiences, the in-hospital mortality rate among patients receiving PC-ECMO ranges from 58% to 75% [1, 5, 6, 13, 14]. In our study, the overall in-hospital mortality rate reached 74.3% (64.9% for the patients aged < 60 years, 79.6% for those aged ≥ 60 years, and 80.6% for those aged ≥ 70 years). Our center does not have age or other strict contraindication criteria for ECMO implantation. Hence, a significant proportion of the patients were in more complex conditions before being placed on PC-ECMO compared to patients in other centers. A quarter of the patients were already in a critical condition or resuscitated before the operation, with a history of previous heart surgery, while a third were undergoing emergency procedures. As previously published, cardiopulmonary resuscitation before ECMO and previous cardiac surgery are independent variables associated with in-hospital mortality in patients undergoing PC-ECMO [1, 5]. Secondly, a prolonged low perfusion state before ECMO may have also increased the mortality rate in our patients. At the time of MCS initiation, the median lactate level was 7.9 (4.4, 11.8) mmol/l, and the mean arterial pressure was only 42.0 (33.0, 49.0) mm Hg despite administering high doses of vasopressors and inotropes; the median VIS value at the time of ECMO initiation was 60.0 (40.0, 82.0) points. In the study, which included patients with refractory cardiogenic shock, Fux *et al.* identified the arterial lactate level and several inotropes and vasopressors as independent pre-VA-ECMO predictors of 90-day mortality. They suggested that VA-ECMO should be considered before profound hyperlactatemia occurs and that the number of vasoactive agents increases [15]. In other previous studies, the cut-off value of the lactate level associated with greater PC-ECMO-related in-hospital mortality was 6 mmol/l, while levels greater than 15 mmol/l were associated with negligible survival rates [1, 3, 5, 7, 14]. In our study, the pre-ECMO lactate level was significantly higher in the non-survivors than in the survivors as well (8.4 (4.8, 13.1) vs. 6.3 (3.5, 9.4) mmol/l, respectively, $p = 0.005$). A recent study of 109 patients receiving PC-ECMO, which analyzed the utility of risk scores, revealed that the VIS significantly predicted 30-day mortality and had a satisfactory discriminatory ability, with an AUC value of 0.844 [16]. In our study, we did not enter the VIS into the ROC-AUC analysis. The VIS served more as a hemodynamic parameter than a risk stratification score. Similar to the lactate level, the VIS in our study was significantly higher in the non-survivors than in the survivors (60.0 (50.0, 84.0) vs. 40.0 (27.0, 70.0), respectively, $p < 0.001$). Thirdly, patients had already been mechanically ventilated for an average of 24 h before being placed on ECMO in our center. We did not find any appropriate data on the impact of the duration of mechanical ventilation on the outcomes of the patients who received VA-ECMO. A duration of mechanical ventilation of only 24 h should not affect or be associated with the severity of lung injury; therefore, in our study it reflects the patients' more complex condition and time to ECMO implantation and indicates a delayed initiation of circulatory support. A recent retrospective multicenter observational PELS-1 study of 2003 patients showed that those who received postoperative ECMO in the ICU had more complications and more significant in-hospital mortality than those who received intraoperative VA-ECMO application [13]. Another source suggests that ECMO initiation in the early phase of refractory cardiogenic shock leads to better clinical outcomes [17]. Our center has no strict criteria for when to initiate ECMO, and each PC-ECMO case depends on the individual decision of the surgeons and anesthesiology team. Therefore, a standardized protocol for initiating PC-ECMO could improve the outcomes. Finally, many elderly patients were included in our sample; 30% of the patients were older than 70 years. The literature indicates that the mortality rate of patients receiving PC-ECMO over the age of 70 years increases threefold compared to that of younger patients [1]. There is no consensus on the age limit at which PC-ECMO is not recommended; however, several centers do not initiate MCS in patients of that age.

This study was a retrospective analysis of single-center experience. Thus, all results should be regarded as associations rather than as causal.

Conclusions

Although advanced age is no longer an absolute contraindication for VA-ECMO, this study reports age as a prognostic marker of mortality in patients receiving PC-ECMO, showing an association between increasing age and increasing mortality rates. The mortality risk doubles in patients aged over 60 years. However, age should be evaluated in the context of other mortality predictors. Female sex, the VIS, and the mechanical ventilation duration before PC-ECMO implantation are also associated with an increased risk of in-hospital mortality. They may help in the decision-making process regarding the initiation of MCS.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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