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Published version:

DOI:10.1016/j.athoracsur.2023.05.045

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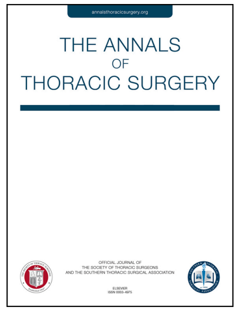
Journal Pre-proof



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PII: S0003-4975(23)00681-1

DOI: https://doi.org/10.1016/j.athoracsur.2023.05.045

Reference: ATS 36932

To appear in: *The Annals of Thoracic Surgery*

Received Date: 24 January 2023

Revised Date: 24 April 2023

Accepted Date: 30 May 2023

Please cite this article as: Mariani S, Schaefer AK, van Bussel BCT, Di Mauro M, Conci L, Szalkiewicz P, De Piero ME, Heuts S, Ravaux J, van der Horst ICC, Saeed D, Pozzi M, Loforte A, Boeken U, Samalavicius R, Bounader K, Hou X, Bunge JJH, Buscher H, Salazar L, Meyns B, Herr D, Matteucci S, Sponga S, MacLaren G, Russo C, Formica F, Sakiyalak P, Fiore A, Camboni D, Raffa GM, Diaz R, Wang Iw, Jung JS, Belohlavek J, Pellegrino V, Bianchi G, Pettinari M, Barbone A, Garcia JP, Whitman G, Shekar K, Wiedemann D, Lorusso R, PELS-1 Investigators, On-Support and Post-Weaning Mortality in Post-Cardiotomy Extracorporeal Membrane Oxygenation, *The Annals of Thoracic Surgery* (2023), doi: https://doi.org/10.1016/j.athoracsur.2023.05.045.

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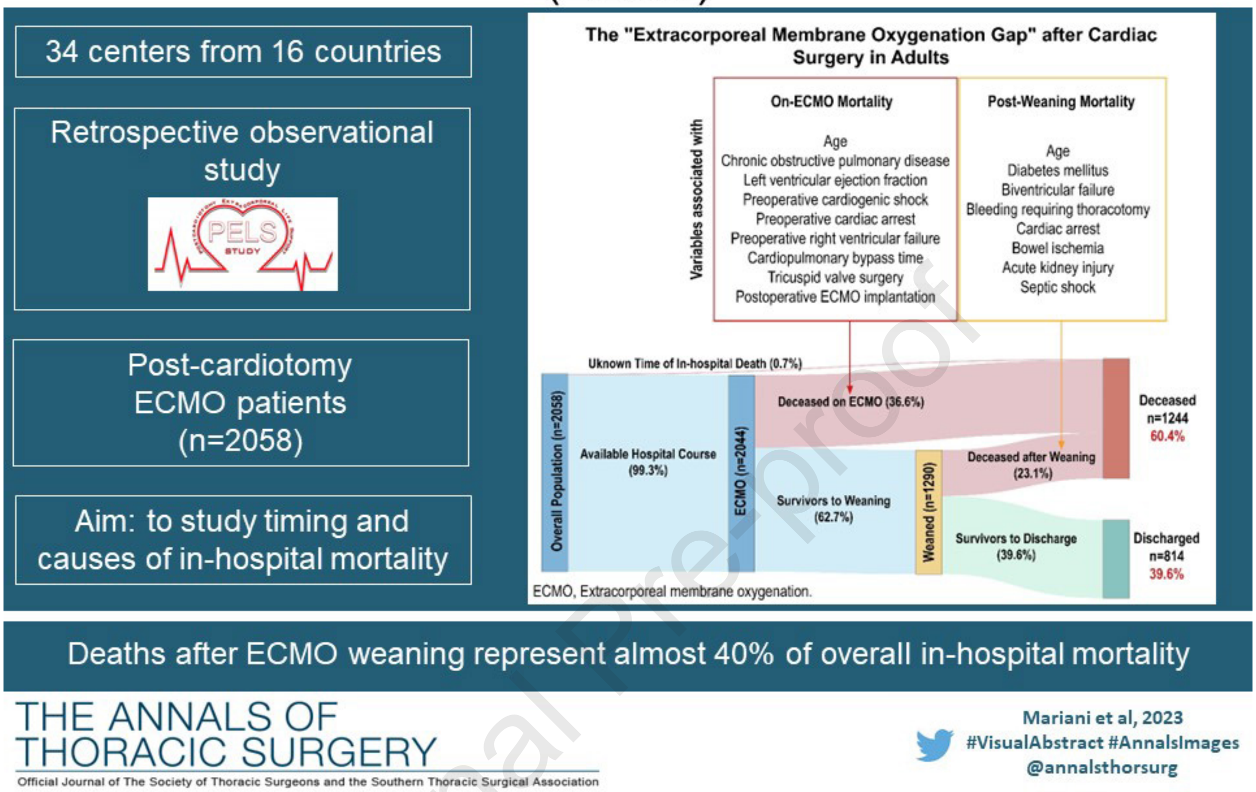

On-Support and Post-Weaning Mortality in Post-Cardiotomy Extracorporeal Membrane Oxygenation

Running Head: Post-cardiotomy ECMO gap

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Ethics approval and consent: Institutional Review Board approval number: METC-2018-0788, (December 19th, 2018). Need for informed consent was waived based on the retrospective nature of the study, the emergency of the procedure, and the pseudonymization of data.

Disclosures: RL: consultant for Medtronic, Getinge, Abiomed, LivaNova; Advisory Board Member of Eurosets, Hemocue, Xenios (honoraria paid as research funding). DW:Consultant/Proctor for Abbott;Scientific advisor for Xenios. KR:honorarium from Baxter and Fresenius for educational lectures not related to this topic.

Article word count: 4800

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ABSTRACT

BACKGROUND: Post-cardiotomy veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is characterized by discrepancies between weaning and survival-to-discharge rates. This study analyzes the differences between post-cardiotomy V-A ECMO patients who survived, died on ECMO, or died after ECMO weaning. Causes of death and variables associated with mortality at different time points are investigated.

METHODS: The retrospective, multicenter, observational Post-cardiotomy Extracorporeal Life Support Study includes adults requiring post-cardiotomy V-A ECMO between 2000 and 2020. Variables associated with on-ECMO mortality and post-weaning mortality were modeled using mixed-Cox proportional hazards including random effects for center.

RESULTS: In 2058 patients [males:59%; median age:65 (IQR:55-72 years)], weaning rate was 62.7%, while survival-to-discharge was 39.6%. Deceased patients (n=1244) included 754 on-ECMO deaths [(36.6%; median support time:79 (IQR:24-192 hours)], and 476 post-weaning deaths [(23.1%; median support time:146 (IQR:96-235.5 hours)]. Multi-organ (n=431/1158, 37.2%) and persistent heart failure (n=423/1158, 36.5%) were the main causes of death, followed by bleeding (n=56/754, 7.4%) for on-ECMO mortality and sepsis (n=61/401, 15.4%) for post-weaning mortality. On-ECMO death was associated with emergency surgery, preoperative cardiac arrest, cardiogenic shock, right ventricular failure, cardiopulmonary bypass time, ECMO implantation timing. Diabetes, post-operative bleeding, cardiac arrest, bowel ischemia, acute kidney injury, and septic shock were associated with post-weaning mortality.

CONCLUSIONS: A discrepancy exists between weaning and discharge rate in post-cardiotomy ECMO. Deaths occurred during ECMO support in 36.6% of patients, mostly associated with unstable pre-operative hemodynamics. Another 23.1% of patients died after weaning in association with severe complications. This underscores the importance of post-weaning care for post-cardiotomy V-A ECMO patients.

Abbreviations:

CI = Confidence interval

HR = Hazard ratio

ICU = Intensive care unit

IABP = Intra-aortic balloon pump

IQR = Interquartile range

IRB = Institutional review board

V-A ECMO = Veno-arterial extra-corporeal membrane oxygenation

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has been utilized in cardiac surgery since the 1970s(1). Despite the expansion of indications for V-A ECMO(2), post-cardiotomy cardiogenic shock remains among the most common ones and has been reported in 0.4-3.7% of all cardiac ECMO cases(3). Successful ECMO weaning after post-cardiotomy shock varies greatly, ranging from 31% to 76%, with most published experiences showing a weaning rate of 50%(3). Nevertheless, survival to hospital discharge is much lower, ranging from 16% to 52%(3-7), with few published studies reporting survival-to-discharge above 40%(3). Such a discrepancy has been defined as the “V-A ECMO-gap”(8). There are scarce data on the time of death (i.e., during ECMO support or after weaning) as well as on the main causes of death related to each setting(8). Such a knowledge gap further complicates the efforts to properly understand and potentially reduce the high mortality rates after post-cardiotomy V-A ECMO. A better understanding of the “ECMO gap” is thus necessary to recognize patients with high risk of early mortality on ECMO, avoid futility, identify the right weaning time, prevent the precipitating factors and complications, which may lead to post-weaning mortality despite successful ECMO withdrawal, and optimize resources.

This study describes the characteristics and outcomes of adult patients supported with post-cardiotomy V-A ECMO, focusing on the differences between those who survived, those who died while on ECMO support, and those who died after ECMO weaning. Furthermore, it investigates variables that are either associated with on-ECMO or post-weaning in-hospital mortality.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

The Post-cardiotomy Extracorporeal Life Support study is a retrospective, multi-center observational study which enrolled adults (≥18 years old) who underwent cardiac surgery prior to ECMO and during the same hospitalization between January 2000 and December 2020 in 34 centers from 16 countries (ClinicalTrials.gov:NCT03857217).

For the current study, exclusion criteria comprised unknown mortality status, extracorporeal life support other than V-A ECMO, ECMO after discharge or before surgery, and ECMO support after non-cardiac surgery or other hospitalizations.

This study is conducted in accordance with the declaration of Helsinki. Primary institutional review board (IRB) approval was obtained at the leading center (Maastricht University Medical Centre+, Maastricht, the Netherlands:METC-2018-0788). Need for informed consent was waived based on the retrospective nature of the study, the emergency of the performed procedure, and the de-identification of shared data. IRB approval was obtained in all centers based on the leading center's protocol.

DATA COLLECTION AND OUTCOMES

Data were collected using an electronic case report form, according to a pre-defined protocol and variable definitions (Supplementary Methods and Supplementary Table 1). The dataset was retained and centrally managed by the coordinating center. The primary outcome of interest was in-hospital mortality defined as: on-ECMO mortality if the patient died while on ECMO support; post-weaning mortality if the patient died after decannulation but during the same hospitalization.

STATISTICAL ANALYSIS

First, we described the preoperative and intraoperative characteristics, ECMO details and post-operative complications for survivors, patients who died on ECMO and patients who died after weaning. Demographic and clinical variables are expressed as numbers (valid percentage on available data, excluding missing values) for categorical variables and median (interquartile range: IQR) or mean and standard deviation for continuous variables. All descriptive statistics were performed on available original data and pairwise deletion was applied. No imputations were performed for descriptive analyses. Categorical data were compared with Chi-squared test. Continuous variables were analyzed using the Kruskal-Wallis test.

Second, we estimated associations between variables and on-ECMO or post-weaning mortality using a mixed-Cox proportional hazards model, containing both fixed and random effects. The random effects were used to consider differences among centers and years(9). We considered sets of variables deemed clinically important for the association with mortality, based on clinical practice and literature(4,10-13). The association with on-ECMO mortality was investigated on the whole population and including variables known at the moment of ECMO initiation (demographic, preoperative, intraoperative variables, ECMO indication, cannulation strategy). The association with post-weaning mortality was tested only on patients who underwent ECMO weaning, excluding those deceased on ECMO support, and we used variables likely known at ECMO weaning (demographic, preoperative, intraoperative, ECMO variables, post-operative complications). Only variables having ≤20% missing data were included in mixed-Cox models after a multiple imputation process. We used fully specified chained equations in the R package(14). Mechanisms underlying missing data were investigated. Missing data patterns were found to be random, so multiple imputation was chosen with five imputed datasets created and combined using between/within variance techniques to appropriately investigate uncertainty about missing data(14). We report risk estimates as hazard ratios (HRs) with their 95% confidence intervals (CIs) and p-values.

Finally, we performed two sensitivity analyses(15): one excluding centers with in-hospital mortality ≥80% and one excluding patients who received post-cardiotomy ECMO between 2000 and 2010.

We considered a two-sided p-value <0.05 statistically significant. All data were merged from de-identified files into SPSS 26.0 (IBM,New York,USA), and R 4.1.2 (R Foundation for Statistical Computing,Vienna,Austria) for statistical analysis.

RESULTS

PELS includes 2163 patients of whom 2058 patients were studied (Supplemental Figure 1, Supplemental Table 2). Of them, 754 patients died on ECMO support (36.6%), 476 died after ECMO weaning during the same hospitalization (23.1%), 814 patients survived to hospital discharge (39.6%), and for 14 patients the time of in-hospital death was unknown (0.7%;Figure 1). Most differences were observed between survivors and the other two groups in terms of preoperative characteristics, and type of surgery (Table 1-3). Survivors were younger, with less co-morbidities (less hypertension, ischemic cardiomyopathy, previous pulmonary embolism, diabetes mellitus, peripheral artery disease, pulmonary hypertension, and lower creatinine values) and a more stable pre-operative condition (lower Euroscore II, less frequent pre-operative cardiogenic shock, intubation, emergency surgery, vasopressors use and acute pulmonary oedema (Supplemental

Table 3: post-hoc analyses for between-group differences). Isolated procedures were more frequent in survivors, while surgeries with 2 or more procedures occurred more frequently in deceased patients (p<0.001), with consequently longer cardiopulmonary and cross-clamp time in non-survivors. Patients deceased on ECMO remained more often without anticoagulation (n=103, 14%; Table 3, Supplemental Figure 2). Left ventricular venting site and use of intra-aortic balloon pump (IABP) during the whole hospital stay differed between groups (p=0.037 and p=0.021, respectively; Table 3, Supplemental Table 3). Patients who deceased on ECMO had the shortest support time (79 hours; IQR: 43.4-205.2; Supplemental Figure 3), while the longest time was observed in patients deceased after weaning (146 hours; IQR: 96.4-235.5), both compared to survivors (116 hours; IQR: 72-168).

IN-HOSPITAL OUTCOMES

Patients who deceased on ECMO had the shortest intensive care unit (ICU) length of stay (5 days, IQR:2-10, p<0.001) and hospital length of stay (6 days, IQR:2-12, p<0.001; Supplemental Figure 2). ICU length of stay was comparable between survivors (21 days, IQR:13-36.5) and post-weaning deaths (20 days, IQR:11-35). Complications occurred with a different distribution between groups (Table 4, Supplemental Table 3). Compared to patients deceased on ECMO, patients who died after weaning experienced more bowel ischemia (p=0.006), right ventricular failure (p=0.026), acute kidney injury (p=0.001), pneumonia (p<0.001), septic shock (p<0.001), distributive shock (p=0.001), and required more abdominal (p=0.002) and vascular surgery (p=0.007). Number of units of post-operatively transfused erythrocyte concentrates was lower in survivors (median: 8, IQR:3-16) compared to post-weaning deaths (median: 13, IQR:5-26, p<0.001) and on-ECMO deaths (median: 11, IQR:5-22, p<0.001, Supplemental Table 4).

CAUSES OF DEATH AND VARIABLES ASSOCIATED WITH MORTALITY

The most common cause of death was multi-organ failure (n=291/758, 38.4%) for on-ECMO mortality and persistent heart failure for post-weaning mortality (n=141/401, 35.2%). In patients who died having multi-organ failure, the most frequently damaged organ in the post-operative period was the kidney (acute kidney injury: n=288/431, 68.6%), followed by the lungs (pneumonia: n=76/431, 18.5%; acute respiratory distress syndrome: n=40/431, 9.6%; Supplemental Table 5). Age was the only variables associated with both types of mortality (Figure 2). Chronic obstructive pulmonary disease, preoperative cardiogenic shock, preoperative cardiac arrest, left ventricular ejection fraction, preoperative right ventricular failure, cardiopulmonary bypass time, tricuspid valve surgery and post-operative ECMO implantation were associated with on-ECMO mortality (Figure 2, Supplemental Table 6). Variables associated with post-weaning mortality included diabetes mellitus, biventricular failure, bleeding requiring thoracotomy, cardiac arrest, bowel ischemia, acute kidney injury and septic shock (Figure 2, Supplemental Table 7).

SENSITIVITY ANALYSES

The sensitivity analyses after exclusion of patients operated between 2000 and 2010 (n=452) showed minor discrepancies compared to the main analyses (Supplemental tables 8-11). Overall mortality remained 59.2% (on-ECMO deaths: n=591/1592, 37.1%; post-weaning deaths: n=352/1592, 22.1%) and survival 40.8% (n=649/1592). In detail, some differences between groups lost statistical significance: hypertension (p=0.053), previous pulmonary embolism (p=0.116), peripheral artery disease (p=0.083), preoperative intubation (p=0.109), emergency surgery (p=0.096), mitral valve disease (p=0.071), cardiopulmonary bypass time (p=0.173), use of IABP (p=0.138), cannulation site bleeding (p=0.056) and acute respiratory distress syndrome (p=0.331). In the sensitivity analyses after exclusion of patients(n=67) from centers with high mortality (n=5), mortality remained 59.3% (on-ECMO deaths: n=713/1985, 35.9%; post-weaning deaths: n=464/1985, 23.4%) and survival was 40.7% (n=808/1985). Similarly, some differences between groups lost statistical significance (Supplemental tables 12-15, Supplemental Figure 4): previous myocardial infarction (p=0.088), and cardiopulmonary bypass time (p=0.115). Post-operative cardiac surgery (p=0.025) was less frequently observed in survivors (p=0.025) compared to other groups. Mortality remained 59.2% (on-ECMO deaths: n=591/1592, 37.1%; post-weaning deaths: n=352/1592, 22.1%) and survival was 40.8% (n=649/1592).

COMMENT

This study demonstrates that the “ECMO gap” (the proportion of patient who are successfully weaned but die during the same hospitalization) significantly impacts the outcomes of post-cardiotomy ECMO patients. The study has four main findings. First, deaths during ECMO support contribute to 60% of all in-hospital deaths while deaths after ECMO weaning represent almost 40% of overall in-hospital mortality. Second, death on ECMO generally occurs after 3 days of support while survivors are weaned after 4.8 days, and patients deceased after weaning usually requires a longer ECMO run of about 6 days. Third, multi-organ failure and persistent heart failure are the main causes of death overall. However, bleeding leads to death more often during ECMO support (7.4%), despite a higher percentage of patients without anticoagulation (14%), while sepsis has a more important role in post-weaning mortality (15.2%). Fourth, variables associated with death are different when considering the two types of mortality. Variables indicating an unstable pre-operative situation (preoperative cardiac arrest, cardiogenic shock, and right ventricular failure) as well as cardiopulmonary bypass time, and ECMO implantation after the end of the operation, are associated with on-ECMO mortality. Post-operative complications (bleeding requiring thoracotomy, cardiac arrest, bowel ischemia, acute kidney injury and septic shock) are associated with post-weaning mortality.

Post-cardiotomy V-A ECMO is required in 0.3-3.6% of cardiac surgery patients(3,4,7) and40–60% of post-cardiotomy patients are successfully weaned from ECMO(3,7,13,16-18). However, reported survival-to-hospital-discharge ranges ~20-50%(2,4,13,18,19). This “ECMO gap” was confirmed by the current analysis which observed an in-hospital mortality of 60.4%, but with post-weaning mortality accounting for almost 40% of all deaths. Most studies analyze in-hospital mortality as a single entity without considering that on-ECMO and post-ECMO mortality might be associated with different factors and, thus, might require different approaches to prevent them.

Death on ECMO occurs early, at a median time of 72 hours of support due to multi-organ failure or persistent heart failure. When analyzing the variables associated with on-ECMO mortality, most of them indicate a pre-operative hemodynamic instability in terms of cardiac arrest, cardiogenic shock, and right ventricular failure. Moreover, another under-investigated variable that negatively influences on-ECMO mortality is the initiation of an extracorporeal support after surgery compared to an intra-operative ECMO implantation(20). Interestingly, patients with a pre-operative good left ventricular function who experience an acute event have a higher risk of on-ECMO mortality. Finally, prolonged cardiopulmonary bypass or cross-clamp times are known to be associated to early on-ECMO mortality(13). Their impact might be explained with the systemic inflammatory reaction syndrome or their effects on coagulation dysfunction and hemodilution(8). Indeed, major bleeding is a mortality trigger on ECMO support(8,21) and it was the death cause in 7.4% of patients deceased on ECMO, even though 14% of them did not receive anticoagulation(22). Both survivors and patients deceased after weaning were characterized by a longer median ECMO support (4.8 and 6.1 days, respectively). ICU stay was also similar between these 2 groups, indicating that the weaning-to-death and the weaning-to-ICU discharge times might be comparable. Differently from patients who died on ECMO within 3 days, these patients were characterized by a more favorable situation before cannulation. Nevertheless, most differences between survivors and post-weaning deaths were related to post-operative complications. Indeed, bleeding requiring thoracotomy, post-operative cardiac arrest, bowel ischemia, acute kidney injury, and septic shock were the associated to post-weaning mortality. Previous studies observed that most common causes of death after weaning are multi-organ failure, cardiac failure, neurological causes, and respiratory causes(8). Moreover, acute kidney injury and lower estimated glomerular filtration rate are independent predictors for multi-organ failure and post-weaning mortality(8,13). Consequently, patients with more favorable pre-ECMO characteristics and who survive the first days of support need special attention in terms of complication prevention(7,22). Furthermore, prevention of acute kidney injury and infective events might not only reduce post-weaning mortality but also post-discharge mortality and improve patients' quality of life(23).

The structured data collection, multicenter design and large patient population provided adequate statistical power to the study. However, the observational design prevents causal inferences(24). Data on patient selection criteria, intraoperative failure to correct any residual lesions or occurrence of surgical complications, ECMO management strategies, weaning protocols, and longitudinal/serial data (including lactates or echocardiographic parameters) were not collected and included in this analysis, representing potential confounding factors. Analyses of detailed hemodynamic parameters and anesthesia protocols were not possible. The database did not capture the exact time of complications occurrence to discriminate between on-ECMO or post-weaning events. Several variables were collected but showed a significant amount of missing data (>20%) and were not included in the mixed-Cox models. Caution should be applied in the interpretation of data regarding post-operative transfusions due to a high percentage of missing data (n=1029/2058, 50%). Multiple scoring systems (such as STS, MELD, APACHE II or VIS score) to stratify patients for disease severity were not included in the study database. The study by design did not include data on single organ dysfunction at death time. Thus, it is not possible to identify which types of organ failure were responsible for the diagnosis of “multi-organ failure”. Nevertheless, we performed a subgroup analysis on patients whose death reason was marked as “multi-organ failure” and we identified the reported complications that can provide some information on which organs suffered more post-operatively. The heterogeneity in practice and outcomes among centers and over time might have impacted the observed results. For this reason, the random effect was used to consider differences among centers and over time in the mixed-Cox proportional hazards models and sensitivity analyses excluding centers with a mortality rate ≥80% or patients operated before 2010 were performed. The local policies for left ventricular venting differed widely among participating centers, preventing any speculation on relationships between cardiac venting and enhanced myocardial recovery or survival. Finally, a partial overlap with previously reported series cannot be excluded. We calculated an overlap of 478 patients between this study and the study by Schaefer et al.(25).

In conclusion, the “ECMO gap” in adult postcardiotomy V-A ECMO is substantial and represents almost 40% of in-hospital mortality. Patients who die on ECMO are characterized by a more unstable pre-operative situation. Bleeding plays an important role as cause of death together with multi-organ failure and persistent heart failure leading to an early death. Conversely, post-weaning mortality is associated with a higher occurrence of complications such as re-thoracotomy, post-operative cardiac arrest, bowel ischemia, acute kidney injury and septic shock. This underlies the importance of post-weaning care for post-cardiotomy V-A ECMO patients. Further prospective and/or interventional studies are required to test the hypotheses generated by this observational study. Prospective and randomized designs are needed to investigate the role of favorable patient selection, ECMO timing and clinical management to reduce on-ECMO mortality and the role of complication prevention or prompt treatment to decrease post-weaning deaths.

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Table 1 – Pre-operative characteristics.

	Survivors (n=814,39.6%)	Deceased after weaning (n=476,23.1%)	Deceased on ECMO (n=754,36.6%)	P-value
Age (years)	61.75(52.2-70)	67.00(58.1-73)	66.18(57-73)	<0.001
Sex				0.767
Female	325(40%)	200(42%)	309(41%)	
Male	488(60%)	276(58%)	445(59%)	
Race				0.001
Asian	36(5.5%)	28(7.7%)	69(12.3%)	
Black	5(0.8%)	2(0.5%)	5(0.9%)	
Hispanic	27(4.1%)	22(6%)	17(3%)	
White	514(78.4%)	279(76.4%)	433(76.9%)	
Other	30(4.6%)	10(2.7%)	10(1.8%)	
Unknown	44(6.7%)	24(6.6%)	29(5.2%)	
Body mass index (kg/m2)	26.29(23.5-29.4)	26.45(23.7-30.2)	26.64(23.7-30.5)	0.230
Body surface area (m2)	1.91(1.8-2.1)	1.88(1.7-2)	1.89(1.7-2)	0.038
Comorbidities				
Hypertension	489(62.4%)	320(67.7%)	492(68.8%)	0.021
Dialysis	67(8.5%)	46(10.1%)	63(8.6%)	0.607
Previous myocardial infarction	240(29.5%)	133(27.9%)	179(23.7%)	0.033
Smoking	202(30.1%)	105(25%)	159(24.8%)	0.056
Atrial fibrillation	200(24.6%)	133(28%)	205(27.2%)	0.322
Previous pulmonary embolism	6(0.8%)	9(2%)	18(2.6%)	0.035
Diabetes mellitus	177(21.7%)	158(33.2%)	183(24.3%)	<0.001
Implantable cardioverter defibrillator	96(13%)	47(10.5%)	39(5.6%)	<0.001
Chronic obstructive pulmonary disease	67(8.7%)	50(11%)	89(12.1%)	0.093
Peripheral artery disease	100(12.3%)	79(16.6%)	123(16.3%)	0.035
Pulmonary hypertension (>50 mmHg)	158(19.6%)	123(26.1%)	146(19.4%)	0.009
Previous cardiac surgery	213(26.2%)	116(24.4%)	204(27.1%)	0.578
Creatinine (umol/L)	98.1(79.6-128)	104.5(80.5-149.6)	105.6(80-146.8)	0.013
Left ventricular ejection fraction (%)	44.0(25-60)	45.0(30-58)	50.0(35-60)	<0.001
Euroscore II	6.44(2.6-16.8)	8.47(3.1-20.9)	8.80(3.2-20.3)	0.007
Preoperative condition				
NYHA class				0.079
Class I	69(8.9%)	22(4.8%)	53(7.4%)	
Class II	169(21.9%)	101(22.1%)	142(19.9%)	
Class III	287(37.1%)	198(43.3%)	280(39.3%)	
Class IV	248(32.1%)	136(29.8%)	237(33.3%)	
Cardiogenic shock	143(17.9%)	100(21.2%)	188(25.2%)	0.003
Intubation	75(9.2%)	51(10.7%)	105(13.9%)	0.012
Cardiac arrest	67(8.3%)	46(9.7%)	76(10.2%)	0.422
Septic shock	10(1.3%)	15(3.2%)	25(3.5%)	0.015
Vasopressors	110(13.6%)	66(14%)	139(18.6%)	0.015
Acute pulmonary edema	51(6.6%)	24(5.1%)	65(9.2%)	0.022
Right ventricular failure	62(8.9%)	46(11%)	73(10.9%)	0.366
Biventricular failure	49(8%)	27(7.1%)	47(7.5%)	0.871
Emergency surgery	193(24.1%)	114(24.2%)	221(29.5%)	0.029
Urgent surgery	191(23.8%)	106(22.5%)	153(20.4%)	0.261

Data are reported as n (% as valid percentage excluding missing values) or median (interquartile range). NYHA,New York Heart Association.

Table 2 - Procedural characteristics

	Survivors (n=814,39.6%)	Deceased after weaning (n=476,23.1%)	Deceased on ECMO (n=754,36.6%)	p-value
Weight of surgery				<0,001
Unknown	6(0.7%)	1(0.2%)	6(0.8%)	
Isolated CABG	166(20.4%)	90(18.9%)	110(14.6%)	
Isolated non-CABG	470(57.7%)	251(52.7%)	423(56.1%)	
2 procedures	61(7.5%)	42(8.8%)	45(6%)	
3 or more procedures	111(13.6%)	92(19.3%)	170(22.5%)	
CABG	351(43.1%)	220(46.2%)	333(44.2%)	0.557
Aortic valve surgery	229(28.1%)	170(35.7%)	310(41.1%)	<0.001
Mitral valve surgery	224(27.6%)	168(35.3%)	253(33.6%)	0.005
Tricuspid valve surgery	83(10.2%)	70(14.7%)	119(15.8%)	0.003
Aortic surgery	124(15.2%)	66(13.9%)	189(25.1%)	<0.001
Pulmonary valve surgery	6(0.7%)	1(0.2%)	5(0.7%)	0.461
Left ventricular assist device	8(1%)	7(1.5%)	8(1.1%)	0.709
Right ventricular assist device	2(0.2%)	3(0.6%)	1(0.1%)	0.276
Atrial septal defect repair	15(1.8%)	6(1.3%)	17(2.3%)	0.453
Ventricular septal defect repair	28(3.4%)	17(3.6%)	23(3.1%)	0.861
Ventricular surgery	20(2.5%)	23(4.8%)	32(4.2%)	0.052
Rhythm surgery	26(3.2%)	14(2.9%)	27(3.6%)	0.816
Pulmonary embolectomy	10(1.2%)	4(0.8%)	9(1.2%)	0.796
Pulmonary endarterectomy	15(1.8%)	12(2.5%)	21 (2.8%)	0.450
Heart transplantation	130(16%)	47(9.9%)	31(4.1%)	<0.001
Off-pump surgery	34(4.3%)	21(4.5%)	28(3.7%)	0.784
Conversion to cardiopulmonary bypass	7(19.4%)	3(13.6%)	15(53.6%)	0.002
Cardiopulmonary bypass time (min)	198(137-272)	206(137-295)	213.0(143-300)	0.028
Crossclamp time (min)	94(62-132)	100(64-148)	106.0(66-160)	0.007
Intraoperative transfusions	279(90.9%)	173(93.0%)	310(93.1%)	0.525

Data are reported as n (% as valid percentage excluding missing values) or median (interquartile range).
CABG,Coronary Artery Bypass Graft. ECMO,Extracorporeal Membrane Oxygenation.

Table 3 - Details on Extracorporeal Membrane Oxygenation.

	Survivors (n=814,39.6%)	Deceased after weaning (n=476,23.1%)	Deceased on ECMO (n=754,36.6%)	P-value
ECMO indication				0.052
Failure to wean	318(40.4%)	173(37.2%)	293(39.4%)	
Acute pulmonary embolism	1(0.1%)	1(0.2%)	1(0.1%)	
Arrhythmia	25(3.2%)	8(1.7%)	10(1.3%)	
Cardiac arrest	61(7.7%)	35(7.5%)	72(9.7%)	
Cardiogenic shock	177(22.5%)	120(25.8%)	205(27.6%)	
Pulmonary hemorrhage	6(0.8%)	2(0.4%)	1(0.1%)	
Right ventricular failure	99(12.6%)	61(13.1%)	78(10.5%)	
Respiratory failure	29(3.7%)	15(3.2%)	26(3.5%)	
Biventricular failure	54(6.9%)	45(9.7%)	50(6.7%)	
Other	18(2.3%)	5(1.1%)	7(0.9%)	
Cannulation approach				0.022
Only central cannulation	106(13%)	85(17.9%)	142(18.8%)	
Only peripheral cannulation	400(49.1%)	214(45%)	348(46.2%)	
Mixed/switch cannulation	289(35.5%)	162(34%)	253(33.6%)	
Unknown	19(2.3%)	15(3.2%)	11(1.5%)	
LV venting	190(27.5%)	124(32.2%)	200(33.2%)	0.060
LV venting site				0.037
Right superior pulmonary vein	14(7,4%)	3(2,4%)	24(12,1%)	
LV apex	6(3,2%)	7(5,6%)	17(8,5%)	
Pulmonary artery	3(1,6%)	4(3,2%)	8(4%)	
Septostomy	1(0,5%)	0(0%)	1(0,5%)	
Left atrium	9(4,8%)	12(9,7%)	17(8,5%)	
Transaortic device	1(0,5%)	0(0%)	0(0%)	
Additional venous cannula	1(0,5%)	1(0,8%)	1(0,5%)	
IABP	154(81,5%)	97(78,2%)	131(65,8%)	
IABP during any time of hospitalization	226(27.8%)	167(35.2%)	222(30.0%)	0.021
IABP implantation timing				0.928
Pre-operative	69(30.5%)	54(32.3%)	69(31.1%)	
Intra-operative	157(69.5%)	113(67.7%)	153(68.9%)	
Anticoagulation				<0.001
None	55(7.1%)	25(5.4%)	103(14%)	
Heparin	716(92%)	431(93.7%)	628(85.6%)	
Bivalirudin	1(0.1%)	1(0.2%)	1(0.1%)	
Argatroban	2(0.3%)	2(0.4%)	1(0.1%)	
Protamine only	4(0.5%)	1(0.2%)	1(0.1%)	
ECMO duration (hours)	116(72-168)	146(96-235.5)	79(24-192)	<0.001

Data are reported as n (% as valid percentage excluding missing values) or median (interquartile range). ECMO,Extracorporeal Membrane Oxygenation. IABP, Intra-aortic Balloon Pump. LV,Left Ventricular

Table 4 – Post-operative outcomes.

	Survivors (n=814,39.6%)	Deceased after weaning (n=476,23.1%)	Deceased on ECMO (n=754,36.6%)	P-value
Intensive care unit stay (days)	21(13-36.5)	20(11-35)	5(2-10)	<0.001
Hospital stay (days)	38(26-60)	23(13-40)	6(2-12)	<0.001
Bleeding	382(48.2%)	299(63.3%)	470(62.9%)	<0.001
Requiring rethoracotomy	253(34.2%)	192(42.8%)	316(43.5%)	<0.001
Cannulation site	73(9.2%)	68(14.5%)	105(14.1%)	0.003
Diffuse non-surgical	139(18.9%)	142(32.2%)	191(28.4%)	<0.001
Neurological complications				
Brain edema	15(1.9%)	23(4.9%)	46(6.6%)	<0.001
Cerebral hemorrhage	22(2.9%)	23(4.9%)	21(3%)	0.113
Seizure	16(2.1%)	14(3%)	11(1.6%)	0.251
Stroke	95(11.7%)	58(12.2%)	64(8.6%)	0.069
Arrhythmia	276(37.3%)	163(36.4%)	183(26.5%)	<0.001
Leg ischemia	57(7.4%)	61(13.2%)	82(11.7%)	0.002
Cardiac arrest	69(9.3%)	99(22.2%)	131(19%)	<0.001
Pacemaker implant	40(5.4%)	11(2.5%)	5(0.7%)	<0.001
Bowel ischemia	13(1.8%)	51(11.4%)	43(6.2%)	<0.001
Right ventricular failure	87(12.1%)	137(31.4%)	165(24.2%)	<0.001
Acute kidney injury	366(50%)	306(68.5%)	397(57.4%)	<0.001
Pneumonia	196(27.3%)	141(32.3%)	71(10.4%)	<0.001
Septic shock	73(10.2%)	150(34.4%)	83(12.2%)	<0.001
Distributive shock syndrome	32(4.5%)	37(8.5%)	107(15.7%)	<0.001
Acute respiratory distress syndrome	31(4.2%)	35(7.8%)	38(5.5%)	0.031
Multi-organ failure	46(5.7%)	227(48.2%)	421(56.5%)	<0.001
Embolism	39(5.4%)	30(6.8%)	44(6.5%)	0.571
Post-operative procedures				
Percutaneous Coronary Intervention	24(3.4%)	9(2.1%)	15(2.2%)	0.268
Cardiac surgery	144(19.5%)	101(22.6%)	167(24.2%)	0.092
Abdominal surgery	29(4.2%)	34(7.9%)	22(3.3%)	0.002
Vascular surgery	95(13.6%)	60(13.8%)	54(8.1%)	0.002

Data are reported as n (% as valid percentage excluding missing values) or median (interquartile range). ECMO, Extracorporeal Membrane Oxygenation.

FIGURE LEGENDS

Figure 1. A: Sankey diagram indicating the number of patients deceased while supported with extracorporeal membrane oxygenation (ECMO), after ECMO weaning or survived. B: Bar chart indicating the reported causes of on-ECMO mortality. C: Bar chart indicating the reported causes of in-hospital post-weaning mortality.

Figure 2. Cox proportional hazard ratios (HR) and 95% confidence intervals (95% CI) for variables associated with on-ECMO (A) and post- weaning (B) mortality.

ACKNOWLEDGMENT:

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Jawad Khalil[1], PhD, Sven Lehmann[1], PhD, Jean-Francois Obadia[2], PhD, Nikolaos Kalampokas[3], MD, Erwan Flecher[4], PhD, Dinis Dos Reis Miranda[5], PhD, Kogulan Sriranjan[6], MD; Michael A Mazzeffi[7], MD, MPH, Nazli Vedadi[7], MD; Marco Di Eusanio[8], PhD, Vitaly Sorokin[9], PhD, Kollengode Ramanathan[9], MD, Alessandro Costetti[10], MD, Chistof Schmid[11], PhD, Roberto Castillo[12], MD, Vladimir Mikulenka[13], MD, MBA, Marco Solinas[14], MD.

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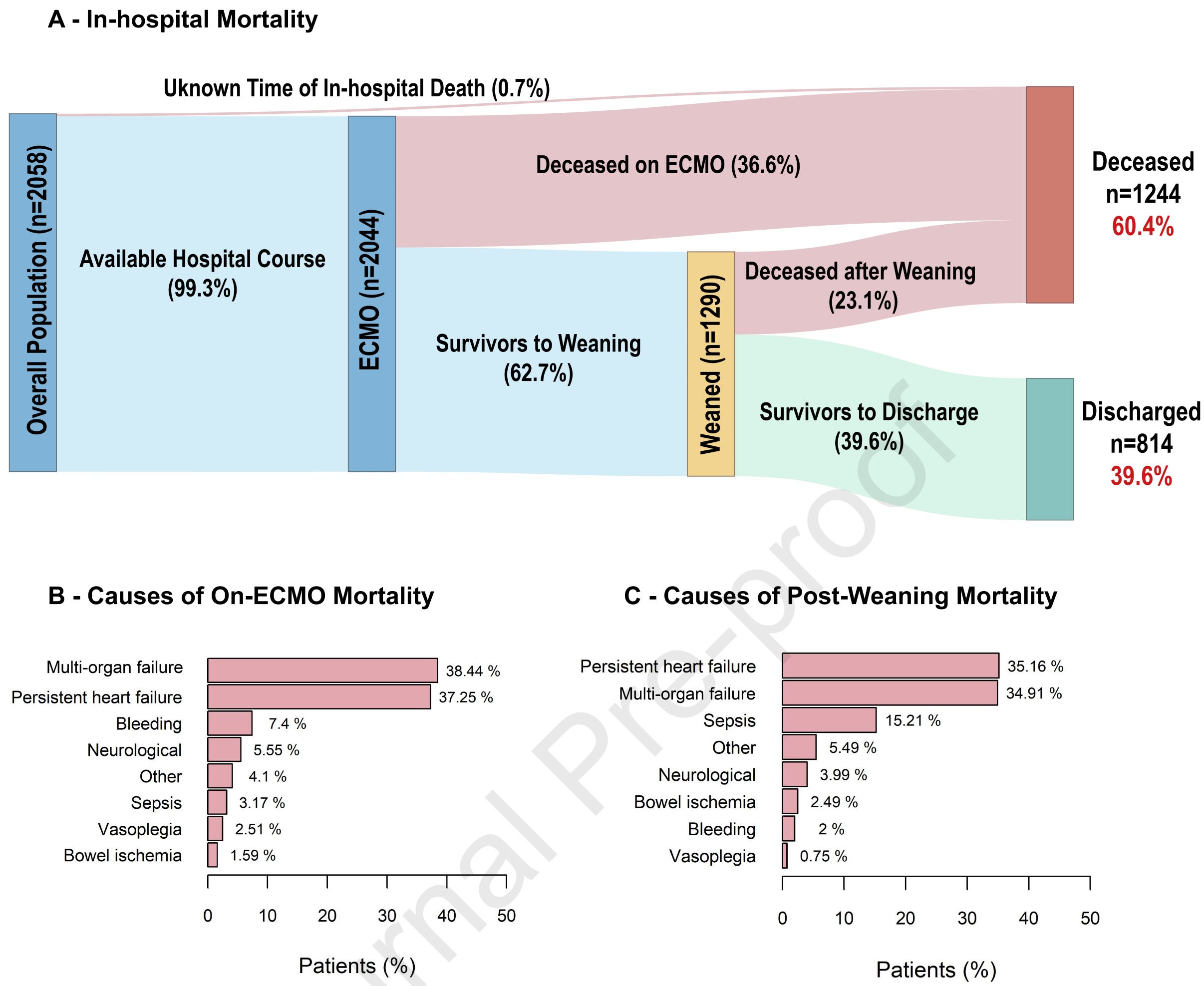
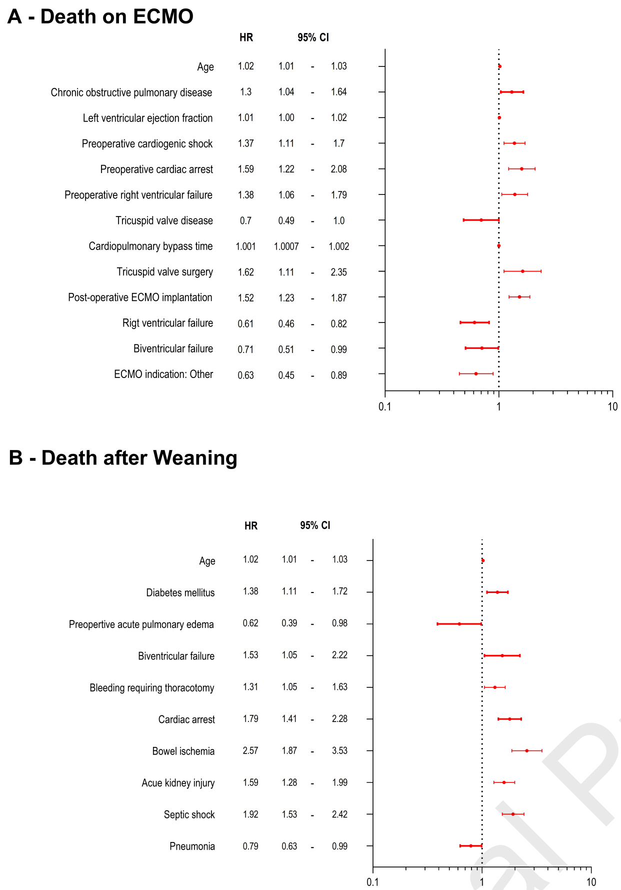

A - In-hospital Mortality
Uknown Time of In-hospital Death (0.7%)
Overall Population (n=2058)
Available Hospital Course (99.3%)
ECMO (n=2044)
Deceased on ECMO (36.6%)
Survivors to Weaning (62.7%)
Weaned (n=1290)
Deceased after Weaning (23.1%)
Survivors to Discharge (39.6%)
Deceased n=1244 60.4%
Discharged n=814 39.6%
B - Causes of On-ECMO Mortality
Multi-organ failure 38.44 %
Persistent heart failure 37.25 %
Bleeding 7.4 %
Neurological 5.55 %
Other 4.1 %
Sepsis 3.17 %
Vasoplegia 2.51 %
Bowel ischemia 1.59 %
0 10 20 30 40 50
Patients (%)
C - Causes of Post-Weaning Mortality
Persistent heart failure 35.16 %
Multi-organ failure 34.91 %
Sepsis 15.21 %
Other 5.49 %
Neurological 3.99 %
Bowel ischemia 2.49 %
Bleeding 2 %
Vasoplegia 0.75 %
0 10 20 30 40 50
Patients (%)


A - Death on ECMO
HR
95% CI
Age 1.02 1.01 - 1.03
Chronic obstructive pulmonary disease 1.3 1.04 - 1.64
Left ventricular ejection fraction 1.01 1.00 - 1.02
Preoperative cardiogenic shock 1.37 1.11 - 1.7
Preoperative cardiac arrest 1.59 1.22 - 2.08
Preoperative right ventricular failure 1.38 1.06 - 1.79
Tricuspid valve disease 0.7 0.49 - 1.0
Cardiopulmonary bypass time 1.001 1.0007 - 1.002
Tricuspid valve surgery 1.62 1.11 - 2.35
Post-operative ECMO implantation 1.52 1.23 - 1.87
Rigt ventricular failure 0.61 0.46 - 0.82
Biventricular failure 0.71 0.51 - 0.99
ECMO indication: Other 0.63 0.45 - 0.89
0.1
1
10
B - Death after Weaning
HR
95% CI
Age 1.02 1.01 - 1.03
Diabetes mellitus 1.38 1.11 - 1.72
Preopertive acute pulmonary edema 0.62 0.39 - 0.98
Biventricular failure 1.53 1.05 - 2.22
Bleeding requiring thoracotomy 1.31 1.05 - 1.63
Cardiac arrest 1.79 1.41 - 2.28
Bowel ischemia 2.57 1.87 - 3.53
Acue kidney injury 1.59 1.28 - 1.99
Septic shock 1.92 1.53 - 2.42
Pneumonia 0.79 0.63 - 0.99
0.1
1
10

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Silvia Mariani reports was provided by Maastricht University. Roberto Lorusso reports a relationship with Medtronic that includes: consulting or advisory. Roberto Lorusso reports a relationship with Getinge AB that includes: consulting or advisory. Roberto Lorusso reports a relationship with AbioMed Inc that includes: consulting or advisory. Roberto Lorusso reports a relationship with LivaNova that includes: consulting or advisory. Roberto Lorusso reports a relationship with Eurosets that includes: board membership. Roberto Lorusso reports a relationship with HemoCue AB that includes: board membership. Roberto Lorusso reports a relationship with Xenios AG that includes: board membership. Dominik Wiedemann reports a relationship with Abbott that includes: consulting or advisory. Dominik Wiedemann reports a relationship with Xenios AG that includes: consulting or advisory. Kogulan Ramanathan reports a relationship with Baxter that includes: consulting or advisory. Kogulan Ramanathan reports a relationship with Fresenius Kabi AG that includes: consulting or advisory.