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ORIGINAL RESEARCH

Patient and Management Variables Associated With Survival After Postcardiotomy Extracorporeal Membrane Oxygenation in Adults: The PELS-1 Multicenter Cohort Study

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BACKGROUND: Extracorporeal membrane oxygenation (ECMO) has been increasingly used for postcardiotomy cardiogenic shock, but without a concomitant reduction in observed in-hospital mortality. Long-term outcomes are unknown. This study describes patients' characteristics, in-hospital outcome, and 10-year survival after postcardiotomy ECMO. Variables associated with in-hospital and postdischarge mortality are investigated and reported.

METHODS AND RESULTS: The retrospective international multicenter observational PELS-1 (Postcardiotomy Extracorporeal Life Support) study includes data on adults requiring ECMO for postcardiotomy cardiogenic shock between 2000 and 2020 from 34 centers. Variables associated with mortality were estimated preoperatively, intraoperatively, during ECMO, and after the occurrence of any complications, and then analyzed at different time points during a patient's clinical course, through mixed Cox proportional hazards models containing fixed and random effects. Follow-up was established by institutional chart review or contacting patients. This analysis included 2058 patients (59% were men; median [interquartile range] age, 65.0 [55.0–72.0] years). In-hospital mortality was 60.5%. Independent variables associated with in-hospital mortality were age (hazard ratio [HR], 1.02 [95% CI, 1.01–1.02]) and preoperative cardiac arrest (HR, 1.41 [95% CI, 1.15–1.73]). In the subgroup of hospital survivors, the overall 1-, 2-, 5-, and 10-year survival rates were 89.5% (95% CI, 87.0%–92.0%), 85.4% (95% CI, 82.5%–88.3%), 76.4% (95% CI, 72.5%–80.5%), and 65.9% (95% CI, 60.3%–72.0%), respectively. Variables associated with postdischarge mortality included older age, atrial fibrillation, emergency surgery, type of surgery, postoperative acute kidney injury, and postoperative septic shock.

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CONCLUSIONS: In adults, in-hospital mortality after postcardiotomy ECMO remains high; however, two-thirds of those who are discharged from hospital survive up to 10 years. Patient selection, intraoperative decisions, and ECMO management remain key variables associated with survival in this cohort.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03857217.

Key Words: acute heart failure ■ cardiac surgery ■ extracorporeal membrane oxygenation ■ mechanical circulatory support ■ postcardiotomy cardiogenic shock

CLINICAL PERSPECTIVE

What Is New?

- In adults, in-hospital mortality after postcardiotomy extracorporeal membrane oxygenation (ECMO) is high, but postdischarge survival up to 10 years is favorable.
- Common variables, such as age and preoperative cardiac arrest, are associated with survival throughout each of the steps of the in-hospital patient stay, whereas specific variables affect the preoperative selection, intraoperative action, ECMO management, and weaning phases.

What Are the Clinical Implications?

- The in-hospital course remains the main limiting factor that needs to be addressed to improve the success of postcardiotomy ECMO.
- Action could be taken to address variables associated with mortality at different time points during the dynamic ECMO clinical course to possibly enhance outcomes and develop adequate predictive models.
- An adequate follow-up of patients undergoing postcardiotomy ECMO, especially in case of postoperative complications, is advised.

Nonstandard Abbreviations and Acronyms

PELS-1	Postcardiotomy Extracorporeal Life Support Study
RVF	right ventricular failure
V-A ECMO	veno-arterial extracorporeal membrane oxygenation

Over the past decades, veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has emerged as an essential modality of temporary mechanical circulatory support for refractory postcardiotomy cardiogenic shock.[1,2] The application of extracorporeal membrane oxygenation (ECMO) as bridge to recovery or more durable supportive care[3,4] after postcardiotomy shock has been reported between 0.4% and 3.7%,[5] with a significant and constant increase since 2007.[6,7] In conjunction with the growing complexity of cardiac surgical procedures, patient risk profiles, and their associated complication rates, V-A ECMO has taken on a progressively more important role in the perioperative care of these patients. Nonetheless, morbidity and mortality rates in such patients are consistently high,[8] although reported outcomes vary in literature.[7,9] Even less evidence is available on long-term outcomes and their determinants.[4,10,11] Although several studies investigated in-hospital outcomes, data on survival of patients who underwent postcardiotomy ECMO after discharge are lacking and urgently needed.[10,11] Besides the evidence-based support for the patient selection process, the intraoperative and postoperative optimization of ECMO management are required to address patient's needs and guide ECMO application. This may guarantee a more effective personalized and timely therapy, optimize use of resources, and improve in-hospital and postdischarge outcomes.

The PELS-1 (Postcardiotomy Extracorporeal Life Support) study includes data on adults experiencing postcardiotomy cardiogenic shock and requiring ECMO in an international group of participating hospitals. This study aimed at describing patients' characteristics, in-hospital outcomes, and 10-year survival of this specific cardiac surgery population. Moreover, we investigated variables associated with in-hospital and long-term mortality. We considered several clinically relevant determinants preoperatively, intraoperatively, and during ECMO management, then described their association with mortality. This may provide evidence on whether development of postcardiotomy support and subsequent patient follow-up should be tailored to these phases of ECMO support and postdischarge surveillance.

METHODS

Patient Population

The PELS-1 is an international, multicenter, retrospective observational study enrolling consecutive patients supported with ECMO in the postoperative phase (ClinicalTrials.gov: NCT03857217; registration date: February 27, 2019) in 34 centers from 16 countries (Figure S1 and Table S1).

Adult patients (aged ≥18 years) were included if they underwent postcardiotomy ECMO between January 2000 and December 2020. Inclusion criteria required cardiac surgery before ECMO (including V-A ECMO and veno-venous ECMO). Exclusion criteria comprised ECMO support after discharge or before surgery, ECMO support after noncardiac surgical procedures, and ECMO implantation not strictly related to cardiac surgery hospitalization. For the present analyses, characteristics and outcomes of patients who received V-A ECMO implantation were investigated (Figure S2).

PELS-1 was conducted in accordance with the Declaration of Helsinki. Institutional review board approval was required for all centers, of which the protocol was based on the institutional review board approval of the coordinating center (institutional review board approval number: METC-2018-0788; institutional review board approval date: December 19, 2018). Need for informed consent was waived on the basis of the retrospective nature of the study, the emergency of the performed procedure, and the pseudonymization of shared data. Data that support the findings of this study are available from the corresponding author on reasonable request and with the permission of all PELS-1 participating centers.

Data Collection and Outcomes

Demographics, preoperative clinical and laboratory variables, procedural characteristics, ECMO treatment modality, cannulation strategy, in-hospital morbidity and mortality, as well as postdischarge survival were collected from each participating hospital and included in a dedicated electronic case report form (data.castoredc.com), according to the predefined protocol and variable definitions (Data S1 and Table S2). The full data set was retained and centrally managed by the coordinating center, which had full access to all the data in the study and takes responsibility for their integrity and the data analysis. Long-term follow-up data were collected through the review of the most recent medical records or contact with patients at discretion of the treating center. The primary outcome of interest for the current study was all-cause in-hospital mortality. Secondary outcomes included in-hospital complications and postdischarge mortality in hospital survivors.

Statistical Analysis

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 SD for continuous variables after evaluation for normality. All descriptive statistics were performed on original data, and pairwise deletion was applied, as appropriate, after missing value analysis. Violin plots were applied to estimate the probability density function of continuous variables and represent their summary statistics. Stacked bar plots represent the distributions of levels within each categorical variable and compare them between study groups (in-hospital survivors versus nonsurvivors). Categorical data were compared with χ^2 test. Continuous variables were analyzed using Student *t* test or Mann-Whitney *U* test, as appropriate. Overall mortality was investigated with the Kaplan-Meier method. Patients' loss to follow-up was included in survival analyses and was considered censored at the time of their last control.

We described the population characteristics and preoperative variables, intraoperative variables, variables while on ECMO, and postoperative complications for the whole cohort and stratified for in-hospital survivors and nonsurvivors. To estimate the associations between determinants and in-hospital mortality, we conducted a mixed Cox proportional hazards model, containing both fixed and random effects. The random effect was used to consider differences among centers, or centers and years.[12] We considered sets of variables deemed important clinically for the association with mortality at patient selection, intraoperative decisions, and for ECMO management, based on clinical practice and literature.[2,10,11,13,14] For the association with in-hospital mortality, we used the following: (1) demographic data and preoperative variables; (2) demographic data and preoperative and intraoperative variables; (3) demographic data and preoperative, intraoperative, and ECMO variables; or (4) demographic data, preoperative, intraoperative, and ECMO variables, and postoperative complications. Finally, a subgroup survival analysis was performed including hospital survivors only. A multivariable model to identify variables associated with postdischarge mortality was performed using the mixed Cox proportional hazards model in the subgroup of in-hospital survivors. The proportional hazards assumption was checked using both statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Only variables having ≤20% missing data were considered to include in each Cox model after a multiple imputation process. Briefly, we used fully specified chained equations in the R package.[15] Mechanisms underlying missing data were investigated with sensitivity analyses. Ten imputed data sets were created and combined using between/within variance techniques to appropriately investigate uncertainty about the missing data.[15] Each model took intrinsic differences among centers using random effect into account. We report risk estimates as hazard ratios (HRs) with their 95% CIs and *P* values.

We considered $P<0.05$ as statistically significant, and hypothesis tests were 2-sided. All data were merged from deidentified files into SPSS 26.0 (IBM, Armonk, NY) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) for data management and statistical analysis.

RESULTS

Baseline, Surgical, and ECMO Characteristics

In total, data on 2163 patients were collected in the PELS-1 database. Of them, 72 patients lacked data on the primary outcome and 33 received veno-venous ECMO support. Thus, 2058 patients were included in the present analysis (Figures S2 and S3). Median age was 65.0 years (IQR, 55.0–72.0 years), with women accounting for 41% (n=843; Table 1). Hospital nonsurvivors (n=1244 [60.5%]) were older (P<0.001) and affected by a higher number of comorbidities compared with survivors (n=814 [39.5%]), as shown in Table 1. Preoperative serum creatinine (P=0.003) and EuroSCORE II values (P=0.002) were higher in nonsurvivors who presented more frequently in an unstable preoperative condition characterized by cardiogenic shock (P=0.002) or septic shock (P=0.005), or requiring mechanical ventilation (P=0.019). Preoperative cardiac arrest occurred in 189 (9.3%) of patients who were more frequently known for a history of myocardial infarction (n=68/189 [36%]; P=0.005), a recent myocardial infarction (n=34/189 [18%]; P=0.008), and peripheral vessel disease (n=39/189 [20.6%]; P=0.023) compared with those who did not experience a preoperative cardiac arrest. Moreover, 51.9% (n=97/189) of them underwent emergency surgery compared with the 23.5% (n=429/1847) of all other patients (P<0.001), and received a preoperative intra-aortic balloon pump at a rate that was almost double compared with other patients (preoperative cardiac arrest: n=29/188 [15.4%]; no preoperative cardiac arrest: n=161/1845 [8.7%]; P=0.005). Coronary artery bypass grafting was required in 114 (60.3%) postarrest cases, and surgery as an isolated coronary artery bypass grafting procedure was required in 55 (29.1%) of these patients.

Nonsurvivors were more often affected by valvular or aortic vessel diseases (Table 1), which was reflected by a higher percentage of concomitant procedures, aortic surgery, and valve surgery, but also by longer cardiopulmonary bypass and cross-clamp times (Table 2). Indications to start an ECMO support (Table 3) included failure to wean from cardiopulmonary bypass (n=788 [39.2%]), followed by cardiogenic shock (n=506 [25.2%]) and right ventricular failure (RVF; n=240 [11.9%]). Most patients received an intraoperative ECMO implantation (n=1287 [62.5%]), but nonsurvivors showed a higher percentage of cannulations in intensive care unit (n=462 [37.1%]; P<0.001). Peripheral cannulation was chosen in 965 (46.9%) patients, whereas 707 cases (34.4%) required a mixed cannulation, including both central and peripheral approaches or a dynamic approach where the cannulation setting was switched from central to peripheral or vice versa during the support time. This latter approach was particularly common in patients experiencing RVF (n=89/240 [37.1%]) compared with other indications (n=588/1770 [33.2%]; P=0.035). Use of intra-aortic balloon pump during any time of hospitalization was reported in 30.5% (n=620) patients with no differences between survivors and nonsurvivors (P=0.109). Impella (n=9 [0.4%]) and other mechanical circulatory support devices (n=22 [1.1%]) were reported in a minority of patients. Median ECMO duration was 118 hours (IQR, 60–192 hours) with no differences between survivors (median, 116 hours; IQR, 72–168 hours) and nonsurvivors (median, 120 hours; IQR, 48–210 hours; P=0.445; Table 3 and Figure S4).

In-Hospital Outcomes, Complications, and Variables Associated With In-Hospital Mortality

In-hospital mortality was 60.5%, with stable rates over the study period (P=0.322; Figure S5A). In-hospital survivors were discharged after a median of 38.0 (IQR, 26.0–60-0) days, whereas in-hospital death occurred at a median of 11.0 (IQR, 4–22) days after surgery (Table 4). On the basis of the different clinical profiles and hospitalization time, survivors and nonsurvivors experienced different kinds of complications (Table 4). Leg ischemia (P<0.001), cardiac arrest (P<0.001), bowel ischemia (P<0.001), RVF (P<0.001), acute kidney injury (P<0.001), septic shock (P<0.001), distributive shock (P<0.001), and multiorgan failure (P<0.001) were more frequent in nonsurvivors, whereas pneumonia (P<0.001) and pacemaker implantation (P<0.001) occurred more frequently in survivors. Acute kidney injury was more frequent in patients operated on before 2010 (n=284/452 [68.9%]) compared with those operated on since 2011 (n=785/1606 [53.3%]). In-hospital mortality significantly differed between centers (P<0.001), types of surgeries (P<0.001), and ECMO indications (P=0.013; Tables 2 and 3 and Figure S5). The mixed Cox proportional hazards analyses identified variables associated with in-hospital mortality at different time points of the in-hospital clinical course (full models presented in Tables S3–S6). Main variables associated with in-hospital mortality that remained statistically significant in each of the 4 prespecified models were age (HR, 1.02 [95% CI, 1.01–1.02]) and preoperative cardiac arrest (HR, 1.41 [95% CI, 1.15–1.73]; Table 5).

Long-Term Mortality and Its Determinants

For the overall survival probability, the Kaplan-Meier curves for 12-month survival and postdischarge survival are shown in the Figure. Overall, 1-, 2-, 5-, and 10-year survival probabilities were 32.4% (95% CI, 30.3%–34.6%), 30.9% (95% CI, 28.8%–33.1%),

Table 1. Preoperative Characteristics of the Overall Population

Characteristic	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
Age, y	65.00 (55–72)	61.75 (52.2–70)	67.00 (58–73)	<0.001
Sex				0.463
Women	843 (41)	325 (40)		
Men	1214 (59)	488 (60)	726 (58.4)	
Race or ethnicity				<0.001
Asian	141 (8.8)	36 (5.5)	105 (11.1)	
Black	12 (0.8)	5 (0.8)	7 (0.7)	
Hispanic	66 (4.1)	27 (4.1)	39 (4.1)	
White	1232 (77.1)	514 (78.4)	718 (76.2)	
Other*	50 (3.1)	30 (4.6)	20 (2.1)	
Unknown	97 (6.1)	44 (6.7)	53 (5.6)	
Body mass index, kg/m^2	26.45 (23.7–30)	26.29 (23.5–29.4)	26.56 (23.7–30.4)	0.141
Body surface area, m^2	1.89 (1.7–2)	1.91 (1.8–2.1)	1.88 (1.7–2)	0.010
Comorbidities				
Hypertension	1311 (66)	489 (62.4)	822 (68.4)	0.007
Dialysis	178 (8.9)	67 (8.5)	111 (9.2)	0.630
Impaired immunity	46 (2.9)	21 (3.6)	25 (2.5)	0.219
Previous myocardial infarction	554 (26.9)	240 (29.5)	314 (25.2)	0.037
Myocardial infarction (last 30 d)	233 (11.7)	95 (12.1)	138 (11.5)	0.670
Previous endocarditis	161 (7.8)	67 (8.2)	94 (7.6)	0.615
Smoking	470 (26.9)	202 (30.1)	268 (24.9)	0.020
Previous stroke	284 (13.8)	105 (12.9)	179 (14.4)	0.360
Atrial fibrillation	540 (26.3)	200 (24.6)	340 (27.4)	0.167
Previous pulmonary embolism	33 (1.8)	6 (0.8)	27 (2.4)	0.018
Diabetes	521 (25.3)	177 (21.7)	344 (27.7)	0.003
Previous transient ischemic attack	41 (2.2)	18 (2.5)	23 (2.1)	0.521
Implanted pacemaker	137 (7.3)	48 (6.6)	89 (7.7)	0.364
Implanted ICD	182 (9.6)	96 (13)	86 (7.5)	<0.001
Previous PCI	350 (17.1)	148 (18.3)	202 (16.4)	0.280
Chronic obstructive pulmonary disease	206 (10.4)	67 (8.7)	139 (11.5)	0.050
Peripheral artery disease	302 (14.7)	100 (12.3)	202 (16.2)	0.013
Previous transplant	75 (3.8)	24 (3.1)	51 (4.2)	0.187
Chronic pulmonary embolism	41 (2.1)	16 (2.1)	25 (2.1)	1.000
Asthma	23 (1.4)	11 (1.8)	12 (1.2)	0.386
Pulmonary hypertension (>50 mm Hg)	428 (20.9)	158 (19.6)	270 (21.8)	0.243
Previous cardiac surgery	541 (26.3)	213 (26.2)	328 (26.4)	0.959
Implanted LVAD	73 (3.7)	45 (5.7)	28 (2.3)	<0.001
Preoperative creatinine, μmol/L	101.7 (79.6–140.6)	98.1 (79.6–128)	105.60 (80–148.5)	0.003
LVEF, %	45.0 (30–60)	44.0 (25–60)	50.00 (31–60)	<0.001
EuroSCORE II	7.53 (3–18.5)	6.44 (2.6–16.8)	8.55 (3.2–20.7)	0.002
Preoperative condition				
NYHA class				0.115
I	144 (7.4)	69 (8.9)	75 (6.4)	
II	420 (21.5)	169 (21.9)	251 (21.3)	
III	769 (39.4)	287 (37.1)	482 (40.8)	
IV	621 (31.8)	248 (32.1)	373 (31.6)	
Preoperative cardiogenic shock	434 (21.4)	143 (17.9)	291 (23.6)	0.002
Preoperative intubation	232 (11.3)	75 (9.2)	157 (12.6)	0.019

(*Continued*)

Table 1. Continued

Characteristic	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
Preoperative cardiac arrest	189 (9.3)	67 (8.3)	122 (9.9)	0.242
Preoperative septic shock	50 (2.5)	10 (1.3)	40 (3.3)	0.005
Preoperative vasopressors	315 (15.4)	110 (13.6)	205 (16.6)	0.079
Preoperative acute pulmonary edema	140 (7.1)	51 (6.6)	89 (7.5)	0.474
Preoperative right ventricular failure	181 (10)	62 (8.9)	119 (10.8)	0.199
Preoperative biventricular failure	123 (7.6)	49 (8)	74 (7.3)	0.628
Emergency surgery	528 (25.9)	193 (24.1)	335 (27.1)	0.133
Urgent surgery	451 (22.1)	191 (23.8)	260 (21)	0.141
Diagnosis				
Coronary artery disease	992 (48.2)	390 (47.9)	602 (48.4)	0.857
Aortic vessel disease	336 (16.3)	109 (13.4)	227 (18.2)	0.003
Aortic valve disease	701 (34.1)	226 (27.8)	475 (38.2)	<0.001
Mitral valve disease	702 (34.1)	247 (30.3)	455 (36.6)	0.004
Tricuspid valve disease	330 (16)	113 (13.9)	217 (17.4)	0.032
Pulmonary valve disease	17 (0.8)	8 (1)	9 (0.7)	0.620
Post-AMI ventricular septal rupture	58 (2.8)	25 (3.1)	33 (2.7)	0.588
Free wall/papillary muscle rupture	38 (1.8)	13 (1.6)	25 (2)	0.616
Active endocarditis	148 (7.2)	55 (6.8)	93 (7.5)	0.479
Atrial septal defect	33 (1.6)	15 (1.8)	18 (1.4)	0.601
Post-LVAD right ventricular failure	19 (0.9)	11 (1.4)	8 (0.6)	0.155
Other diagnosis	260 (12.6)	117 (14.4)	143 (11.5)	0.058

Data are reported as number (percentage; as valid percentage excluding missing values) or median (interquartile range). *P* values determined by χ^2 test (for categorical data), Student *t* test (for parametric continuous data), and Mann-Whitney *U* test (for nonparametric continuous data) indicate statistically significant differences between survivors and nonsurvivors. AMI indicates acute myocardial infarction; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention. *Other indicates all races or ethnicities not included in the previous list.

27.8% (95% CI, 25.7%–30.1%), and 19.5% (95% CI, 16.7%–22.8%), respectively. In the subgroup of hospital survivors, the median follow-up was 2.5 years (IQR, 0.3–5.3 years). Data on survival at last follow-up contact were available in 93.1% of in-hospital survivors. In this subgroup, the overall 1-, 2-, 5-, and 10-year survival rates were 89.5% (95% CI, 87.0%–92.0%), 85.4% (95% CI, 82.5%–88.3%), 76.4% (95% CI, 72.5%–80.5%), and 65.9% (95% CI, 60.3%–72.0%), respectively. Older age (HR, 1.03 [95% CI, 1.02–1.05]), preoperative atrial fibrillation (HR, 1.52 [95% CI, 1.04–2.21]), emergency surgery (HR, 1.66 [95% CI, 1.07–2.55]), coronary artery bypass (HR, 1.51 [95% CI, 1.06–2.12]), aortic valve surgery (HR, 1.46 [95% CI, 1.01–2.12]), and septic shock (HR, 2.53 [95% CI, 1.42–4.53]) were associated with worse long-term postdischarge outcome (Table 6). Postoperative acute kidney injury (HR, 1.37 [95% CI, 1.01–1.95]) was significantly associated with worse long-term postdischarge outcome in the mixed Cox model adjusted for center only. The effect estimate remained similar (HR, 1.37 [95% CI, 0.95–1.95]) in the mixed Cox model adjusted for center and year of operation but lost statistical significance (*P*=0.09; Table 6).

DISCUSSION

The PELS-1 has 5 main findings. First, in-hospital mortality was 60.5%, with stable rates over the study years. Second, duration of ECMO support was a median of 5 days in both survivors and nonsurvivors. Third, age and preoperative cardiac arrest are the main variables associated with in-hospital mortality. However, different phases of the postcardiotomy ECMO support are characterized by specific variables associated with in-hospital mortality and, thus, prediction models for patient selection, intraoperative decisions, and ECMO management should be developed separately, to aid in the decision-making about such a temporary support. Fourth, hospital survivors appear to have a good postdischarge outcome, with 89.5% (95% CI, 87.0%–92.0%), 85.4% (95% CI, 82.5%–88.3%), 76.4% (95% CI, 72.5%–80.5%), and 65.9% (95% CI, 60.3%–72.0%) survival at 1, 2, 5, and 10 years, respectively. Finally, the overall postdischarge survival is mainly determined by patient's age, with an HR of 1.03 (95% CI, 1.02–1.05) for each additional year of age, and preexistent comorbidities, such as atrial fibrillation, emergency and type of surgery, and postoperative complications, like acute

Table 2. Procedural Characteristics

Characteristic	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
Weight of surgery				<0.001
Unknown	13 (0.6)	6 (0.7)	7 (0.6)	
Isolated CABG	370 (18)	166 (20.4)	204 (16.4)	
Isolated non-CABG	1152 (56)	470 (57.7)	682 (54.8)	
2 Procedures	148 (7.2)	61 (7.5)	87 (7)	
≥3 Procedures	375 (18.2)	111 (13.6)	264 (21.2)	
CABG	912 (44.3)	351 (43.1)	561 (45.1)	0.389
Aortic valve surgery	714 (34.7)	229 (28.1)	485 (39)	<0.001
Mitral valve surgery	647 (31.5)	224 (27.6)	423 (34)	0.002
Tricuspid valve surgery	275 (13.4)	83 (10.2)	192 (15.4)	<0.001
Aortic surgery	382 (18.6)	124 (15.2)	258 (20.7)	0.002
Pulmonary valve surgery	12 (0.6)	6 (0.7)	6 (0.5)	0.557
LVAD	23 (1.1)	8 (1)	15 (1.2)	0.831
RVAD	6 (0.3)	2 (0.2)	4 (0.3)	1
Atrial septal defect repair	38 (1.8)	15 (1.8)	23 (1.8)	1
Ventricular septal defect repair	68 (3.3)	28 (3.4)	40 (3.2)	0.802
Ventricular surgery	75 (3.6)	20 (2.5)	55 (4.4)	0.022
Rhythm surgery	67 (3.3)	26 (3.2)	41 (3.3)	1
Pulmonary embolectomy	23 (1.1)	10 (1.2)	13 (1)	0.676
Pulmonary endarterectomy	48 (2.3)	15 (1.8)	33 (2.7)	0.296
Heart transplantation	209 (10.2)	130 (16)	79 (6.4)	<0.001
Off-pump surgery	83 (4.1)	34 (4.3)	49 (4)	0.732
Conversion to cardiopulmonary bypass	25 (29.1)	7 (19.4)	18 (36)	0.148
Cardioplegia type				0.178
Blood	706 (51.2)	290 (54.7)	416 (48.9)	
Crystalloid	392 (28.4)	139 (26.2)	253 (29.8)	
Custodiol	281 (20.4)	101 (19.1)	180 (21.2)	
Other	1 (0.1)	0 (0)	1 (0.1)	
Cardioplegia route				0.616
Antegrade	927 (71.5)	355 (73)	572 (70.5)	
Retrograde	58 (4.5)	20 (4.1)	38 (4.7)	
Antegrade+retrograde	312 (24.1)	111 (22.8)	201 (24.8)	
Cardiopulmonary bypass time, min	204 (139–288)	198 (137–272)	210 (142–300)	0.015
Cross-clamp time, min	99 (64–148)	94 (62–132)	104 (65–155)	0.003
Intraoperative transfusions	776 (92.4)	279 (90.9)	497 (93.2)	0.226

Data are reported as number (percentage; as valid percentage excluding missing values) or median (interquartile range). *P* values determined by χ^2 test (for categorical data), Student *t* test (for parametric continuous data), and Mann-Whitney *U* test (for nonparametric continuous data) indicate statistically significant differences between survivors and nonsurvivors. CABG indicates coronary artery bypass grafting; LVAD, left ventricular assist device; and RVAD, right ventricular assist device.

kidney injury (HR, 1.37 [95% CI, 1.01–1.95]) and septic shock (HR, 2.53 [95% CI, 1.42–4.53]).

On the basis of the increased complexity of patients undergoing cardiac surgery and the growing popularity of ECMO, its use has increased over time, but with persistently high in-hospital mortality.[3,7,8,11,16–20] Resource demands for postcardiotomy V-A ECMO are high.[2] This has led to a debate about proper patient selection to optimize resources and provide best treatments to patients who might benefit from it. Although several attempts have been made to identify best practices for postcardiotomy V-A ECMO, robust evidence on this topic is still lacking and expert consensus recommendations have been only recently released.[2] Thus, the real-world clinical application of postcardiotomy V-A ECMO remains highly variable and based on individual or center-based expertise, surgeon's choices, and inhomogeneous management strategies.

The PELS-1 included elderly patients (median age, 65 years; 30.5% of patients aged >70 years), a high

Table 3. Details on ECMO

Variable	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
ECMO indication				0.013
Failure to wean	788 (39.2)	318 (40.4)	470 (38.5)	
Acute pulmonary embolism	3 (0.1)	1 (0.1)	2 (0.2)	
Arrhythmia	43 (2.1)	25 (3.2)	18 (1.5)	
Cardiac arrest	170 (8.5)	61 (7.7)	109 (8.9)	
Cardiogenic shock	506 (25.2)	177 (22.5)	329 (26.9)	
Pulmonary hemorrhage	9 (0.4)	6 (0.8)	3 (0.2)	
Right ventricular failure	240 (11.9)	99 (12.6)	141 (11.5)	
Respiratory failure	72 (3.6)	29 (3.7)	43 (3.5)	
Biventricular failure	149 (7.4)	54 (6.9)	95 (7.8)	
Other	30 (1.5)	18 (2.3)	12 (1)	
ECMO implantation timing				<0.001
Intraoperative	1287 (62.5)	547 (62.7)	740 (59.5)	
Intensive care unit	716 (34.8)	254 (31.2)	462 (37.1)	
Ward	39 (1.9)	6 (0.7)	33 (2.7)	
Catheterization laboratory	16 (0.8)	7 (0.9)	9 (0.7)	
Chest status				0.002
Chest closed	858 (57.5)	364 (62.7)	494 (54.2)	
Chest open	634 (42.5)	217 (37.3)	417 (45.8)	
Cannulation approach				0.006
Only central cannulation	341 (16.6)	106 (13)	235 (18.9)	
Only peripheral cannulation	965 (46.9)	400 (49.1)	565 (45.4)	
Mixed/switch cannulation	707 (34.4)	289 (35.5)	418 (33.6)	
Unknown	45 (2.2)	19 (2.3)	26 (2.1)	
LV venting	519 (30.8)	190 (27.5)	329 (33.1)	0.014
LV venting site				0.108
Right superior pulmonary vein	41 (7.9)	14 (7.4)	27 (8.2)	
LV apex	30 (5.8)	6 (3.2)	24 (7.3)	
Pulmonary artery	15 (2.9)	3 (1.6)	12 (3.7)	
Septostomy	2 (0.4)	1 (0.5)	1 (0.3)	
Left atrium	38 (7.4)	9 (4.8)	29 (8.8)	
Transaortic device	1 (0.2)	1 (0.5)	0 (0)	
Additional venous cannula	3 (0.6)	1 (0.5)	2 (0.6)	
IABP	387 (74.9)	154 (81.5)	233 (71)	
IABP during any time of hospitalization	620 (30.5)	226 (27.8)	394 (32.2)	0.035
IABP implantation timing				0.928
Preoperative	192 (31)	69 (30.5)	123 (31.2)	
Intraoperative	428 (69)	157 (69.5)	271 (68.8)	
Distal femoral perfusion	778 (65.8)	332 (69)	446 (63.5)	0.053
Anticoagulation				0.039
None	187 (9.4)	55 (7.1)	132 (10.9)	
Heparin	1785 (89.9)	716 (92)	1069 (88.5)	
Bivalirudin	3 (0.2)	1 (0.1)	2 (0.2)	
Argatroban	5 (0.3)	2 (0.3)	3 (0.2)	
Protamine only	6 (0.3)	4 (0.5)	2 (0.2)	
ECMO duration, h	118 (60–192)	116 (72–168)	120.00 (48–210)	0.445

Data are reported as number (percentage; as valid percentage excluding missing values) or median (interquartile range). *P* values determined by χ^2 test (for categorical data), Student *t* test (for parametric continuous data), and Mann-Whitney *U* test (for nonparametric continuous data) indicate statistically significant differences between survivors and nonsurvivors. ECMO indicates extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; and LV, left ventricular.

Table 4. Details on Postoperative Outcomes

Variable	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
Intensive care unit stay, d	13 (6–26)	21 (13–36.5)	9.00 (3–18)	<0.001
Hospital stay, d	20 (8–40)	38 (26–60)	11.00 (4–22)	<0.001
Postoperative bleeding	1156 (57.2)	382 (48.2)	774 (63)	<0.001
Requiring rethoracotomy	765 (39.7)	253 (34.2)	512 (43.2)	<0.001
Cannulation site bleeding	246 (12.2)	73 (9.2)	173 (14.1)	<0.001
Diffuse no surgical-related bleeding	472 (25.4)	139 (18.9)	333 (29.7)	<0.001
Neurological complications				
Brain edema	84 (4.3)	15 (1.9)	69 (5.8)	<0.001
Cerebral hemorrhage	66 (3.4)	22 (2.9)	44 (3.7)	0.37
Severity				0.276
Minor	21 (43.8)	7 (58.3)	14 (38.9)	
Disabling	15 (31.3)	4 (33.3)	11 (30.6)	
Fatal	12 (25)	1 (8.3)	11 (30.6)	
Seizure	41 (2.1)	16 (2.1)	25 (2.1)	1
Stroke	217 (10.6)	95 (11.7)	122 (9.9)	0.213
Severity				<0.001
Minor	83 (46.9)	47 (60.3)	36 (36.4)	
Disabling	57 (32.2)	31 (39.7)	26 (26.3)	
Fatal	37 (20.9)	0 (0)	37 (37.4)	
Vasospasm	3 (0.2)	1 (0.2)	2 (0.2)	1
Arrhythmia	624 (33)	276 (37.3)	348 (30.2)	0.001
Leg ischemia	200 (10.3)	57 (7.4)	143 (12.2)	<0.001
Cardiac arrest	304 (16.1)	69 (9.3)	235 (20.4)	<0.001
Pacemaker implantation	56 (3)	40 (5.4)	16 (1.4)	<0.001
Bowel ischemia	107 (5.7)	13 (1.8)	94 (8.1)	<0.001
Right ventricular failure	389 (21)	87 (12.1)	302 (26.7)	<0.001
Heart transplant	111 (7.2)	54 (9.4)	57 (5.9)	0.011
Acute kidney injury	1069 (56.7)	366 (50)	703 (61)	<0.001
Pneumonia	411 (22.2)	196 (27.3)	215 (19)	<0.001
Septic shock	310 (16.8)	73 (10.2)	237 (20.9)	<0.001
Vasoplegic syndrome	176 (9.5)	32 (4.5)	144 (12.7)	<0.001
Acute respiratory distress syndrome	104 (5.5)	31 (4.2)	73 (6.3)	0.05
Multiorgan failure	697 (34.3)	46 (5.7)	651 (52.9)	<0.001
Embolism	113 (6.1)	39 (5.4)	74 (6.5)	0.371
Postoperative procedures				
Percutaneous coronary intervention	48 (2.6)	24 (3.4)	24 (2.2)	0.1
Cardiac surgery	413 (21.8)	144 (19.5)	269 (23.4)	0.046
Abdominal surgery	85 (4.7)	29 (4.2)	56 (5)	0.426
Vascular surgery	209 (11.5)	95 (13.6)	114 (10.2)	0.029
In-hospital mortality				NA
Deceased on ECMO			754 (60.6)	
Deceased after weaning			476 (38.3)	
Death time unknown			14 (1.1)	
Main cause of death				NA
Multiorgan failure			431 (37.2)	
Sepsis			85 (7.3)	
Persistent heart failure			423 (36.5)	
Distributive shock syndrome			22 (1.9)	

(*Continued*)

Table 4. Continued

Variable	Overall population (n=2058)	Survivors (n=814)	Nonsurvivors (n=1244)	*P* value
Bleeding			64 (5.5)	
Neurological injury			58 (5.0)	
Bowel ischemia			22 (1.9)	
Other			53 (4.6)	

Data are reported as number (percentage; as valid percentage excluding missing values) or median (interquartile range). *P* values determined by χ^2 test (for categorical data), Student *t*-test (for parametric continuous data), and Mann-Whitney *U* test (for nonparametric continuous data) indicate statistically significant differences between survivors and nonsurvivors. ECMO, extracorporeal membrane oxygenation; NA, not applicable.

percentage of women (41%), patients on preoperative dialysis (8.9%), and patients with a history of cardiac surgery (26.3%). Despite the high preoperative risk profile of the PELS-1 population, the current study confirmed that in-hospital mortality of patients undergoing postcardiotomy V-A ECMO is around 60%, as previously reported.[3,7–9,21] Moreover, this study demonstrates that 9.3% of included patients experienced a preoperative cardiac arrest, a variable rarely reported in this kind of population. Interestingly, these patients with a preoperative cardiac arrest are frequently known for vasculopathy and ischemic myocardial disease. They often require a preoperative intra-aortic balloon pump and emergency coronary artery bypass grafting. Nevertheless, cardiac arrest is not the most common indication for postcardiotomy V-A ECMO implantation. Failure to wean from cardiopulmonary bypass remains the primary indication (39.7%), followed by cardiogenic shock (25.2%) and RVF (11.9%). The latter indicates the significant impact of RVF in patients undergoing cardiac surgery. Indeed, literature reports that 2.9% of them develop clinically relevant postoperative RVF, which is associated with death, stroke, reintubation, and prolonged intensive care unit stay.[22] The current study highlights the need of further investigations to better understand the role, indication, timing, and cannulation setting for any mechanical circulatory support in postcardiotomy RVF.

Significant variability was observed within the PELS-1 population for the cannulation approach. Indeed, the debate about the best strategy between peripheral or central cannulation is still controversial. Interestingly, 34.4% of included patients received a change in cannulation approach or underwent a mixed cannulation strategy with one central cannula combined with one peripheral cannula. This was particularly true for patients diagnosed with RVF. This finding might indicate the uncertainty about the best cannulation strategy or the dynamism of these patients undergoing V-A ECMO whose circulatory and respiratory situation can change rapidly along the disease course. This aspect might also explain why several previous studies that investigated outcomes after central or peripheral cannulation were not able to identify a definitive answer.[16,23]

The PELS-1 shows that both survivors and nonsurvivors were supported with V-A ECMO for a median of 5 days. Conflicting results have been reported on this topic, with some studies showing longer ECMO support in survivors[8] and some others showing longer support time in nonsurvivors,[7,11] suggesting a selection bias and the heterogeneity among ECMO policies. Whether the poor in-hospital survival after ECMO is mainly attributable to suboptimal patient selection, an intrinsically complex disease, suboptimal weaning time, or the futility of this support remains an open question. Indeed, in many centers, 3 to 5 days of inadequate cardiac function in a patient who is not a candidate for transplant or ventricular assist device (such as elderly patients) is considered futile.[2] This common practice might reflect the effects of previous studies, which demonstrated that V-A ECMO support >7 days is associated with increased risks of complications and higher mortality.[24] However, tools to identify potential survivors or to prevent futile treatments are still limited.

To date, published studies have focused attention on the identification of mortality prediction models mainly developed using statistical methods.[8,20,25–30] Nevertheless, scores and prediction models are rarely applied in the clinical practice. In fact, most of them lack external validation, are static, and do not consider the dynamism of the ECMO process and underlying disease course. Studies have reported on single tools, such as arterial lactates,[8,31,32] which become a negative prognostic factor when >6[8,26] or 10[31] mmol/L at ECMO initiation. Lactates are useful in unexpected emergencies, such as periarrest situations, when clinicians must decide whether to initiate rescue ECMO. However, for most patients undergoing postcardiotomy ECMO, their management does not always begin with an unexpected sudden event requiring ECMO, but it starts earlier when they are accepted for cardiac surgery. Furthermore, the concept of "prophylactic" or "early" postcardiotomy ECMO is changing the clinical scenario and increasing the use of elective ECMO in situations where lactates are still low.[2] In these cases, clinicians lack tools to identify those patients with low chances of survival, to develop preventive ECMO strategies, and to target variables associated with mortality. The current analysis proposes a stepwise approach to

Table 5. Mixed Cox Proportional Hazards for Significant Variables Associated With In-Hospital Mortality

Variable	By center				By center and year			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
		Lower limit	Upper limit			Lower limit	Upper limit	
Model 1: demographic data and preoperative variables								
Age, y	1.02	1.01	1.02	<0.0001	1.02	1.01	1.02	<0.0001
Sex (reference: men)	1.15	1.02	1.29	0.0280	1.15	1.01	1.29	0.0290
COPD	1.28	1.06	1.53	0.0086	1.28	1.06	1.53	0.0090
Preoperative cardiogenic shock	1.23	1.04	1.45	0.0150	1.23	1.04	1.45	0.0140
Emergency surgery (vs elective)	1.15	1.02	1.36	0.0430	1.15	0.97	1.36	0.1000
Preoperative cardiac arrest	1.41	1.15	1.73	0.0008	1.41	1.15	1.73	0.0009
Preoperative right ventricular failure	1.29	1.06	1.58	0.0110	1.29	1.06	1.58	0.0120
Preoperative creatinine, µmol/L	1.01	1.01	1.02	0.0410	1.01	1.01	1.02	0.0450
Aortic vessel disease	1.40	1.20	1.64	<0.0001	1.40	1.20	1.65	0.0000
Aortic valve disease	1.16	1.02	1.32	0.0240	1.16	1.02	1.31	0.0260
Model 2: demographic data and preoperative and intraoperative variables								
Age, y	1.02	1.01	1.03	<0.0001	1.02	1.01	1.03	0.0000
Sex (reference: men)	1.15	1.01	1.29	0.0330	1.14	1.01	1.29	0.0300
COPD	1.23	1.02	1.48	0.0310	1.23	1.02	1.48	0.0300
Preoperative cardiogenic shock	1.25	1.06	1.48	0.0073	1.25	1.06	1.48	0.0077
Emergency surgery (vs elective)	1.16	1.03	1.37	0.0460	1.16	0.98	1.37	0.0850
Preoperative cardiac arrest	1.45	1.18	1.77	0.0004	1.45	1.18	1.77	0.0004
Preoperative right ventricular failure	1.30	1.07	1.59	0.0090	1.30	1.07	1.59	0.0093
Tricuspid valve disease	0.74	0.57	0.97	0.0280	0.74	0.57	0.97	0.0280
Cardiopulmonary bypass time, min	1.01	1.01	1.02	0.0035	1.01	1.01	1.02	0.0004
Tricuspid valve surgery	1.49	1.12	1.99	0.0066	1.49	1.12	1.99	0.0066
Model 3: demographic data and preoperative, intraoperative, and ECMO variables								
Age, y	1.02	1.01	1.03	<0.0001	1.02	1.01	1.03	0.0000
Sex (reference: men)	1.14	1.01	1.28	0.0410	1.14	1.01	1.28	0.0410
COPD	1.23	1.02	1.48	0.0280	1.23	1.02	1.48	0.0280
Preoperative cardiogenic shock	1.27	1.07	1.50	0.0055	1.27	1.07	1.50	0.0054
Preoperative cardiac arrest	1.41	1.14	1.74	0.0016	1.41	1.14	1.74	0.0016
Preoperative right ventricular failure	1.36	1.11	1.66	0.0032	1.36	1.11	1.66	0.0032
Tricuspid valve disease	0.73	0.56	0.96	0.0220	0.73	0.56	0.96	0.0220
Cardiopulmonary bypass time, min	1.01	1.01	1.02	<0.0001	1.01	1.01	1.02	0.0001
Tricuspid valve surgery	1.53	1.15	2.04	0.0038	1.53	1.15	2.04	0.0038
ECMO implanting time: postoperative (reference: intraoperative)	1.25	1.06	1.46	0.0063	1.25	1.06	1.46	0.0068
ECMO indication: right ventricular failure	0.74	0.60	0.93	0.0093	0.74	0.60	0.93	0.0083
ECMO indication: other	0.70	0.54	0.91	0.0080	0.70	0.54	0.91	0.0079
ECMO central cannulation	2.86	1.17	6.98	0.0210	2.86	1.17	6.99	0.0210
ECMO cannulation change/mixed	2.46	1.01	5.98	0.0470	2.46	1.01	5.99	0.0470
Model 4: demographic data, preoperative, intraoperative, and ECMO variables, and complications								
Age, y	1.02	1.01	1.02	<0.0001	1.02	1.01	1.02	0.0000
Preoperative cardiac arrest	1.34	1.08	1.66	0.0073	1.34	1.08	1.66	0.0078
Tricuspid valve surgery	1.53	1.14	2.05	0.0043	1.53	1.14	2.05	0.0044
Aortic surgery	1.32	1.00	1.75	0.0470	1.32	1.00	1.75	0.0470
ECMO indication: right ventricular failure	0.75	0.60	0.93	0.0100	0.75	0.60	0.93	0.0100

(*Continued*)

Table 5. Continued

Variable	By center				By center and year			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
		Lower limit	Upper limit			Lower limit	Upper limit	
ECMO indication: other	0.68	0.52	0.88	0.0038	0.68	0.52	0.88	0.0038
ECMO central cannulation complications	2.71	1.08	6.79	0.0330	2.72	1.09	6.80	0.0330
LV failure	1.70	1.48	1.96	<0.0001	1.70	1.48	1.96	0.0000
RV failure	1.25	1.08	1.46	0.0033	1.25	1.08	1.46	0.0033
Cardiac arrest	1.53	1.31	1.79	<0.0001	1.53	1.31	1.79	0.0000
Bowel ischemia	1.28	1.03	1.60	0.0270	1.28	1.03	1.60	0.0270
Septic shock	0.85	0.72	0.99	0.0480	0.85	0.72	0.99	0.0420
Pneumonia	0.48	0.41	0.56	<0.0001	0.48	0.41	0.56	0.0000
Multiorgan failure	3.74	3.27	4.29	<0.0001	3.75	3.27	4.29	0.0000

COPD indicates chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; LV, left ventricular; and RV, right ventricular.

identify variables associated with in-hospital mortality during different phases of the postcardiotomy ECMO clinical course: preoperative (model 1), intraoperative (model 2), during ECMO support (model 3), and when complications occur (model 4). Each of these phases is characterized by different variables to answer questions about patient's candidacy, ECMO management, and futility. Variables that remain always associated with in-hospital mortality are age and cardiac arrest, in accordance with previous studies.[7,11,30,33] On top of these constant determinants, several variables with potential influence on mortality should be considered in the decision-making process at specific time points on the in-hospital course. Finally, in all models developed in this study, we considered the influence of the treating center and year. Indeed, center experience, local policies, differences in health care systems, changes over time, and resource allocations[34] might also impact the postcardiotomy ECMO decision-making process.

Acknowledging that patient selection and in-hospital mortality are the major limiting factors in the clinical success of postcardiotomy ECMO, patients who survive to discharge demonstrate a good long-term survival. However, older age, atrial fibrillation, emergency surgery, coronary artery bypass and aortic surgery, postoperative acute kidney injury, and septic shock are associated with worse long-term mortality. Interestingly, about 10% of discharged patients die during the first year after surgery. Chen et al previously demonstrated that patients undergoing postcardiotomy ECMO are at increased risk for all-cause mortality and hospital readmission during the first year of follow-up.[19,35] However, mortality, readmission rates, and medical expenditures are similar from the second year of follow-up onwards. This might be explained by the influence of postoperative complications on the early postdischarge mortality, as shown by our data. Therefore, a comprehensive follow-up program should be advised after postcardiotomy ECMO, especially during the early postdischarge time, whereas our data show that longer-term follow-up is characterized by reduced rate of unfavorable events. Furthermore, additional studies are required to investigate quality of life and functional status of patients who underwent postcardiotomy ECMO after discharge.

Strengths and Limitations

The structured data collection performed in the PELS-1, the participation of 34 centers from 16 countries, and the large sample size support data robustness and statistical power. Nevertheless, PELS-1 is observational by nature, preventing causal inferences. Data on how many adult patients received cardiac surgery at each center during the study period were not available because the analysis of ECMO implantation rates in cardiac surgery was beyond the aim of this study. Furthermore, specific data on ECMO selection criteria, protocols, weaning strategies, serial arterial lactate concentrations, longitudinal/serial data, vasopressor, and inotrope use are not captured by the database and could therefore not be included in this study. Furthermore, an in-depth analysis of intraoperative and postoperative hemodynamic parameters, as well as coagulation parameters, anesthesia management protocols, quality of life, and rehospitalization events after discharge, was not possible. Septic shock was reported by each investigator according to the study definition.[36] However, codes for surgical site infection, bloodstream infections, antibiotics, and infectious agents are not present in the data set, and we cannot exclude a misdiagnosis of some patients who experienced persistent distributive shock or other kinds of shock accounting for persistent

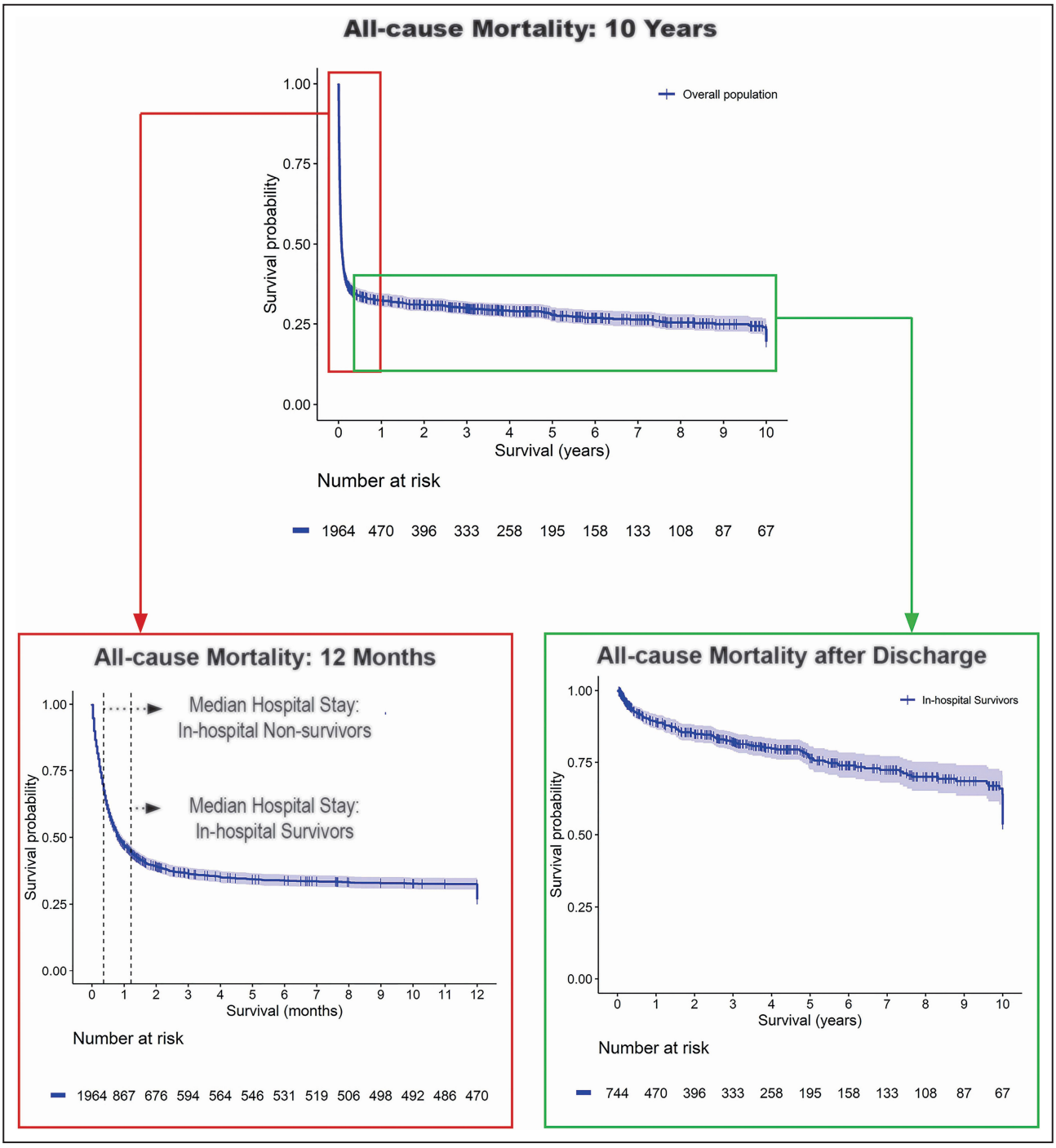

Figure. **Kaplan-Meier survival curves with 95% CIs.**

hemodynamic failure. The local policies for left ventricular venting differed widely among participating centers, preventing any speculation on relationships between cardiac venting and enhanced myocardial recovery/ability to wean off ECMO support. Finally, several clinical variables were collected but showed a significant amount of missing data (>20%) and were not included in the mixed Cox models.

CONCLUSIONS

The PELS-1 shows that postcardiotomy V-A ECMO, during an observation time of 20 years, is associated with 60% in-hospital mortality with no improvement over time. However, 66% postdischarge survival probability up to 10 years indicates that the in-hospital course remains the main limiting factor that needs to

Table 6. Mixed Cox Proportional Hazards for Postdischarge Mortality Based on Model 4

Variable	By center				By center and year			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
		Lower limit	Upper limit			Lower limit	Upper limit	
Age, y	1.03	1.02	1.05	<0.0001	1.03	1.02	1.05	0.0001
Sex (reference: men)	0.98	0.69	1.40	0.9100	0.99	0.69	1.41	0.9400
Dialysis	1.16	0.64	2.09	0.6300	1.22	0.67	2.23	0.5100
Preoperative atrial fibrillation	1.45	1.01	2.11	0.0420	1.52	1.04	2.21	0.0310
COPD	1.32	0.78	2.24	0.3000	1.19	0.68	2.07	0.5400
LVEF, %	1.00	0.99	1.01	0.5300	1.00	0.99	1.01	0.9100
Urgent vs elective	1.45	0.96	2.20	0.0800	1.39	0.92	2.11	0.1200
Emergency vs elective	1.68	1.04	2.70	0.0330	1.66	1.07	2.55	0.0220
CABG	1.49	1.05	2.12	0.0270	1.51	1.06	2.16	0.0230
Aortic valve surgery	1.41	1.07	2.24	0.0230	1.46	1.01	2.12	0.0450
Mitral valve surgery	1.12	0.76	1.64	0.5700	1.13	0.77	1.65	0.5300
Complications: cerebral hemorrhage	0.92	0.36	2.33	0.8600	0.94	0.37	2.38	0.8900
Complications: cardiac arrest	1.06	0.56	2.01	0.8500	1.06	0.56	2.01	0.8600
Complications: AKI	1.37	1.01	1.95	0.0480	1.36	0.95	1.95	0.0900
Complications: septic shock	2.59	1.45	4.63	0.0013	2.53	1.42	4.53	0.0010

Model 4 includes demographic data; preoperative, intraoperative, and extracorporeal membrane oxygenation variables; and complications. AKI indicates acute kidney disease; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; and LVEF, left ventricular ejection fraction.

be addressed to improve the success of this therapeutic approach. PELS-1 adds that common variables, such as age and preoperative cardiac arrest, affect survival throughout each of the steps of the in-hospital patient stay, whereas specific variables affect the preoperative selection, intraoperative action, ECMO management, and ECMO weaning phases. This has implications for prediction model development in postcardiotomy ECMO. Moreover, PELS-1 highlights the importance of preventing complications, such acute kidney injury and septic shock, based on their impact on long-term mortality. Finally, an adequate follow-up of patients undergoing postcardiotomy V-A ECMO, especially in case of postoperative complications, is advised and critical for the first postdischarge year. Further studies are warranted to verify the feasibility and efficacy of these proposed interventions, particularly in the long-term.

APPENDIX

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Disclosures

Roberto Lorusso is a consultant for Medtronic, Getinge, Abiomed, and LivaNova; and advisory board member of Eurosets, Hemocue, and Xenios (honoraria are paid as research funding). Dominik Wiedemann is a consultant/proctor for Abbott and scientific advisor for Xenios. Kollengode Ramanathan has received honorarium from Baxter and Fresenius for educational lectures not related to this topic. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Tables S1–S6
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Data collection

The following predefined groups of data were collected:

- Demographic data: age, sex, race
- Patients characteristics: EuroSCORE, length, weight, serum creatinine level, left ventricular ejection fraction, comorbidities (hypertension, chronic kidney disease requiring dialysis, previous myocardial infarction, previous endocarditis, smoking, previous stroke, atrial fibrillation, previous pulmonary embolism, diabetes mellitus, previous transient ischemic attack (TIA), implanted pacemaker (PM), implanted implantable cardioverter defibrillator (ICD), previous percutaneous coronary intervention (PCI), chronic obstructive pulmonary disease (COPD), peripheral artery disease, chronic pulmonary embolism, asthma, pulmonary hypertension, previous cardiac surgery, implanted left ventricular assist device (LVAD), NYHA class,
- Preoperative status: urgency of the procedure, weight of intervention, planned intervention, preoperative cardiogenic shock, preoperative intubation, preoperative cardiac arrest, preoperative septic shock, preoperative vasopressors, preoperative acute pulmonary oedema, preoperative intra-aortic balloon pump (IABP), preoperative right ventricular failure, preoperative biventricular failure
- Diagnosis: coronary artery disease, aortic vessel disease, aortic valve disease, mitral valve disease, tricuspid valve disease, pulmonary valve disease, post-acute myocardial infarction (AMI) ventricular septal rupture, free wall/Papillary muscle rupture, graft failure, active endocarditis, atrial septal defect, post-LVAD right ventricular failure, other diagnosis

- Coronary surgery: arterial graft, number of distal arterial anastomoses, left internal mammary artery (LIMA), right internal mammary artery (RIMA), radial artery, gastro-epiploic artery (GEA), other arterial graft, venous graft, number of distal venous anastomoses, other coronary surgery
- Valve surgery: valve surgery, aortic valve surgery, aortic valve procedure, mitral valve surgery, mitral valve procedure, pulmonary valve surgery, pulmonary valve procedure, pulmonary valve implant, tricuspid valve surgery, tricuspid valve procedure.
- Aortic surgery: approach to aortic surgery, aortic ascending surgery, aortic arch surgery, descending aortic procedure
- Other cardiac surgeries: cardiac assist device, heart transplantation, rhythm surgery, additional PM-/ICD procedure, ventricular septal defect (VSD) closure, atrial septal defect (ASD) closure, ventricular surgery, pericardiectomy, pulmonary embolectomy/endoarterectomy, other cardiac surgery, other cardiac surgery description.
- Preoperative, intraoperative and postoperative measures: lactates, hemoglobin, hematocrit, platelets, pO2, pCO2, bilirubin, aspartato aminotransferase (AST), alanina aminotransferase (ALT), creatinine, urea, CK, CK-MB, fluid balance, bleeding in the first 24 hours after surgery, transfusions.
- Extracorporeal circulation (ECC): ECC duration, cross-clamp duration, circulation arrest, cardioplegia characteristics, off-pump conversion.
- Extracorporeal membrane oxygenation (ECMO) variables: ECMO indication, chest status, cannulation approach, use of left ventricular vent, ECMO duration (hours), configuration change, ECMO monitoring.
- In-hospital outcomes: deceased in hospital, deceased timing, intensive care unit (ICU) stay (days), hospital stay (days), in-hospital mortality, death timing, postoperative bleeding (requiring rethoracotomy, cannulation site bleeding, diffuse no-surgical related bleeding), neurological complications (brain edema, cerebral hemorrhage, seizure, stroke, vasospasm), arrhythmia, leg ischemia, cardiac arrest, pacemaker implant, bowel ischemia, right ventricular failure, acute kidney

injury, pneumonia, septic shock, vasoplegic syndrome, acute respiratory distress syndrome (ARDS), multi-organ failure, embolism

- Postoperative procedures: PCI, new cardiac surgery, abdominal surgery, vascular surgery
- Outcomes at follow-up: mortality status, follow-up time

Table S1. Centre characteristics.

	Overall population (n=2058)		Survivors (n=814)		Non-Survivors (n=1244)		P-value
Centre type. n (%)							< 0.001
VAD centre	100	4.9%	17	0.8%	14	0.7%	
HTx/VAD centre	1788	86.9%	737	36.1%	426	20.8%	
non-HTx/non-VAD centre	170	8.3%	60	2.9%	36	1.8%	
Country. n (%)							< 0.001
Australia	73	3.5%	47	5.8%	13	2.7%	
Austria	489	23.8%	242	29.7%	120	25.2%	
Belgium	40	1.9%	16	2.0%	13	2.7%	
Chile	15	0.7%	8	1.0%	4	0.8%	
China	66	3.2%	22	2.7%	20	4.2%	
Colombia	41	2.0%	14	1.7%	14	2.9%	
Czech Republic	9	0.4%	3	0.4%	0	0.0%	
France	214	10.4%	86	10.6%	29	6.1%	
Germany	496	24.1%	169	20.8%	122	25.6%	
Italy	236	11.5%	74	9.1%	55	11.6%	
Lithuania	78	3.8%	23	2.8%	21	4.4%	
Netherlands	192	9.3%	75	9.2%	45	9.5%	
Singapore	28	1.4%	8	1.0%	5	1.1%	
South Korea	11	0.5%	1	0.1%	2	0.4%	
Thailand	24	1.2%	0	0.0%	0	0.0%	
USA	46	2.2%	26	3.2%	13	2.7%	

HTx. Heart Transplant. USA. United States of America. VAD. Ventricular Assist Device. P values by chi squared (for categorical data) indicate statistically significant differences between survivors and non survivors.

Table S2. Variable and outcomes definitions.

Variable	Definition
Baseline characteristics	
Hypertension	Systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg[37], or use of antihypertensive agents to maintain normal blood pressure
Impaired immunity	Use of immunosuppressant drugs or history of immunosuppressive disorders including HIV and hematological malignancies.
Smoking	Active (smoking during the past 30 days) and more than 100 cigarettes during lifetime[38]
COPD	Diagnosis of chronic obstructive pulmonary disease, any Gold classification[39]
Peripheral arterial disease	Claudication, carotid occlusion or >50% stenosis, amputation for arterial disease or previous or planned intervention on the abdominal aorta, limb arteries or carotids[40]
Asthma	Reversible obstructive airway disease for which bronchodilators are currently or intermittently used with or without exacerbations or reduction in FEV1. [41]
Pulmonary hypertension	Systolic pulmonary artery pressure >50mmHg
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II proposing a risk assessment of cardiac surgical procedures which incorporates patient age, sex, diabetic status, pulmonary disease, neurological function, renal function, presence of active endocarditis, pre-operative state, procedural urgency and procedure type[40]
NYHA class	Functional class of dyspnea according to the classification as proposed by the New York Heart Association
Preoperative cardiogenic shock	Preoperative state with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, with worsening acidosis and/or lactate levels[42]
Preoperative cardiac arrest	Preoperative cardiopulmonary resuscitation in the 24 hours prior to surgery
Preoperative septic shock	Septic patients with vasopressor requirement to maintain MAP >65mmHg and serum lactate levels greater than 2mmol/L in the absence of hypovolemia[36]
Preoperative right ventricular failure	Evidence of right-sided structural and/or functional abnormalities in combination with clinical symptoms and signs of RV failure[43]
Preoperative biventricular failure	Biventricular dysfunction accompanied by both signs and symptoms of right-sided and left-sided heart failure[44]
Emergency surgery	Surgery before the beginning of the next working day after the decision to operate is made[40]
Urgent surgery	Patients not electively admitted for operation but requiring surgery during the current admission without a possibility to be discharged before undergoing the definite procedure[40]
Aortic vessel disease	And disease of the ascending aorta, aortic arch or proximal descending aorta warranting surgical correction during the current procedure
Aortic valve disease	Any aortic valve disease, including (prosthetic) aortic valve stenosis, regurgitation and endocarditis
Mitral valve disease	Any mitral valve disease, including (prosthetic) mitral valve stenosis, regurgitation and endocarditis
Tricuspid valve disease	Any tricuspid valve disease, including (prosthetic) tricuspid valve stenosis, regurgitation and endocarditis
Pulmonary valve disease	Any pulmonary valve disease, including (prosthetic) pulmonary valve stenosis, regurgitation and endocarditis

Graft failure	Severe ventricular dysfunction of the donor graft which fails to meet the circulatory requirements of the recipient in the immediate post-transplant period[45]
Active endocarditis	Patients still on antibiotic treatment for endocarditis at the time of surgery[40]
Post LVAD right ventricular failure	RV failure as described previously in presence of LVAD
Procedural characteristics	
Ventricular surgery	Surgery performed to restore structural ventricular function, especially in case of ventricular aneurysm formation or rupture
Rhythm surgery	Surgical (either epicardial or endo-epicardial) ablation performed for atrial or ventricular arrhythmia
Details on ECMO	
Failure to wean	Failure to wean from CPB despite preload optimization and completeness of surgery
Arrhythmia	Refractory ventricular arrhythmia with uncontrollable hemodynamic consequences
Cardiac arrest	Abrupt loss of heart function despite acute and simple interventions such as pacing and defibrillation
Cardiogenic shock	State of life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, with worsening acidosis and/or lactate levels[42]
Right ventricular failure	Evidence of right-sided structural and/or functional abnormalities in combination with clinical symptoms and signs of RV failure[43]
Respiratory failure	Reversible pulmonary disease which cannot anymore be managed by conventional mechanical ventilation, despite optimization of pharmacological interventions with or without prone positioning
Biventricular failure	Biventricular dysfunction accompanied by both signs and symptoms of right-sided and left-sided heart failure[44]
Chest closed	Any cannulation condition in which the sternum is closed irrespective location of cannulas
Chest open	Any cannulation condition in which the sternum is left open irrespective of skin closure
Postoperative outcomes	
Stroke	Neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms lasting less more than 24 hours, with or without permanent disability
TIA	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms lasting less than one hour, without evidence of acute brain infarction[46]
Arrhythmia	Any atrial or ventricular arrhythmia lasting more than 30 seconds
Leg ischemia	Clinical signs of lower extremity ischemia requiring intervention (either by vascular surgery or cannula removal)
Bowel ischemia	Intestinal ischemia with elevated lactate levels requiring abdominal surgical intervention
Acute kidney injury	Postoperative requirement for dialysis while not on dialysis before or duplication of preoperative creatinine levels (and absolute creatinine level >177μmol/L)
Pneumonia	Any (suspected) pulmonary infection treated with antibiotics
Septic shock	Sepsis with vasopressor requirement to maintain MAP >65mmHg and serum lactate levels greater than 2mmol/L in the absence of hypovolemia[36]
Distributive shock syndrome	MAP <50mmHg with cardiac index >2.5L/min/m^2, right atrial pressure <5mmHg, left atrial pressure <10mmHg an low systemic vascular resistance

	(<800 dyne/s/cm^{-5}) during intranvenous norepinephrine infusion (>0.5μg/kg/min) [47]
ARDS	Acute diffuse inflammatory lung injury requiring invasive mechanical ventilation of extracorporeal membrane oxygenation
Multi-organ failure	Hypometabolic state with involvement of more than one organ as established by biochemical and/or radiological analysis

ARDS: acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease, ECMO: extracorporeal membrane oxygenation, FEV1: forced expiratory volume during one second, HIV: human immunodeficiency virus, LVAD: left ventricular assist device, MAP: mean arterial pressure, RV: right ventricle/ventricular, TIA: transient ischemic attack.

Table S3. Mixed Cox proportional hazards for in-hospital mortality based on model 1 (demographic data and preoperative variables).

	By Center				By Center and year			
	Hazard Ratio	95% Confidence Interval		P-value	Hazard Ratio	95% Confidence Interval		P-value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age (years)	**1.02**	**1.01**	**1.02**	**<0.0001**	**1.02**	**1.01**	**1.02**	**<0.0001**
Sex (Reference: Males)	**1.15**	**1.02**	**1.29**	**0.0280**	**1.15**	**1.01**	**1.29**	**0.0290**
Body mass index (Kg/m2)	1.00	0.99	1.02	0.5100	1.00	0.99	1.02	0.5000
Dialysis	1.03	0.82	1.29	0.8100	1.03	0.82	1.29	0.7800
Previous myocardial infarction	0.90	0.77	1.05	0.1900	0.90	0.78	1.05	0.2000
Previous stroke	1.16	0.97	1.40	0.1100	1.17	0.97	1.40	0.1100
Atrial fibrillation	0.99	0.87	1.14	0.9300	0.99	0.87	1.14	0.9300
Diabetes mellitus	1.07	0.93	1.23	0.3200	1.07	0.93	1.23	0.3300
COPD	**1.28**	**1.06**	**1.53**	**0.0086**	**1.28**	**1.06**	**1.53**	**0.0090**
Peripheral artery disease	1.06	0.90	1.25	0.4700	1.06	0.90	1.25	0.4800
Pulmonary hypertension (>50 mmHg)	1.05	0.90	1.22	0.5100	1.05	0.91	1.23	0.4900
Previous cardiac surgery	1.05	0.92	1.21	0.4800	1.05	0.92	1.21	0.4700
LVEF (%)	1.01	1.00	1.01	0.0560	1.01	1.00	1.01	0.0750
Preoperative cardiogenic shock	**1.23**	**1.04**	**1.45**	**0.0150**	**1.23**	**1.04**	**1.45**	**0.0140**
Emergency surgery (vs Elective)	**1.15**	**1.02**	**1.36**	**0.0430**	1.15	0.97	1.36	0.1000
Urgent surgery (vs Elective)	1.10	0.94	1.30	0.2300	1.11	0.94	1.30	0.2200
Preoperative cardiac arrest	**1.41**	**1.15**	**1.73**	**0.0008**	**1.41**	**1.15**	**1.73**	**0.0009**
Preoperative septic shock	1.35	0.96	1.89	0.0840	1.35	0.96	1.90	0.0820
Preoperative acute pulmonary edema	0.98	0.77	1.25	0.8900	0.98	0.77	1.25	0.8700
Preoperative IABP	0.98	0.79	1.22	0.6500	0.98	0.78	1.22	0.8300
Preoperative right ventricular failure	**1.29**	**1.06**	**1.58**	**0.0110**	**1.29**	**1.06**	**1.58**	**0.0120**
Preoperative creatinine (umol/L)	**1.01**	**1.01**	**1.02**	**0.0410**	**1.00**	**1.01**	**1.02**	**0.0450**
Coronary artery disease	0.95	0.83	1.10	0.5100	0.96	0.83	1.10	0.5300
Aortic vessel disease	**1.40**	**1.20**	**1.64**	**0.0000**	**1.40**	**1.20**	**1.65**	**0.0000**
Aortic valve disease	**1.16**	**1.02**	**1.32**	**0.0240**	**1.16**	**1.02**	**1.31**	**0.0260**
Mitral valve disease	1.08	0.95	1.24	0.2500	1.08	0.94	1.24	0.2500
Tricuspid valve disease	0.94	0.79	1.12	0.5100	0.94	0.79	1.12	0.5100
Post-myocardial infarction complication	1.09	0.81	1.47	0.5600	1.09	0.81	1.47	0.5600

COPD. Chronic Obstructive Pulmonary Disease. IABP. Intra-Aortic Balloon Pump. LVEF. Left Ventricular Ejection Fraction.

Table S4. Mixed Cox proportional hazards for in-hospital mortality based on model 2 (demographic data. preoperative. and intraoperative variables).

	By Center				By Center and year			
	Hazard Ratio	95% Confidence Interval		P-value	Hazard Ratio	95% Confidence Interval		P-value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age (years)	**1.02**	**1.01**	**1.03**	**<0.0001**	**1.02**	**1.01**	**1.03**	**0.0000**
Sex (Reference: Males)	**1.15**	**1.01**	**1.29**	**0.0330**	**1.14**	**1.01**	**1.29**	**0.0300**
Body mass index (Kg/m2)	1.00	0.99	1.02	0.5600	1.00	0.99	1.02	0.5500
Dialysis	1.09	0.87	1.37	0.4400	1.09	0.87	1.37	0.4300
Previous myocardial infarction	0.95	0.81	1.11	0.5100	0.95	0.81	1.11	0.5200
Previous stroke	1.16	0.97	1.40	0.1100	1.16	0.97	1.40	0.1100
Atrial fibrillation	0.98	0.85	1.12	0.7300	0.98	0.85	1.12	0.7400
Diabetes mellitus	1.08	0.94	1.24	0.2700	1.08	0.94	1.24	0.2800
COPD	**1.23**	**1.02**	**1.48**	**0.0310**	**1.23**	**1.02**	**1.48**	**0.0300**
Peripheral artery disease	1.09	0.92	1.29	0.3100	1.09	0.92	1.29	0.3100
Pulmonary hypertension (>50 mmHg)	1.03	0.89	1.20	0.6800	1.03	0.89	1.20	0.6800
Previous cardiac surgery	1.01	0.87	1.15	0.6800	1.00	0.87	1.15	0.9700
LVEF (%)	1.00	1.00	1.01	0.1710	1.00	1.00	1.01	0.3900
Preoperative cardiogenic shock	**1.25**	**1.06**	**1.48**	**0.0073**	**1.25**	**1.06**	**1.48**	**0.0077**
Emergency surgery (vs Elective)	**1.16**	**1.03**	**1.37**	**0.0460**	1.16	0.98	1.37	0.0850
Urgent surgery (vs Elective)	1.09	0.93	1.28	0.2900	1.09	0.93	1.28	0.2900
Preoperative cardiac arrest	**1.45**	**1.18**	**1.77**	**0.0004**	**1.45**	**1.18**	**1.77**	**0.0004**
Preoperative septic shock	1.40	0.99	1.97	0.0550	1.40	0.99	1.97	0.0550
Preoperative acute pulmonary edema	0.96	0.75	1.23	0.7600	0.96	0.75	1.23	0.7600
Preoperative IABP	1.01	0.80	1.26	0.9300	1.00	0.80	1.25	0.9700
Preoperative right ventricular failure	**1.30**	**1.07**	**1.59**	**0.0090**	**1.30**	**1.07**	**1.59**	**0.0093**
Preoperative creatinine (umol/L)	1.00	1.00	1.00	0.1010	1.00	1.00	1.00	0.1000
Coronary artery disease	0.93	0.77	1.13	0.4500	0.93	0.77	1.13	0.4500
Aortic vessel disease	1.16	0.89	1.51	0.2600	1.16	0.89	1.51	0.2600
Aortic valve disease	1.14	0.92	1.42	0.2300	1.14	0.92	1.42	0.2300
Mitral valve disease	0.88	0.69	1.12	0.3000	0.88	0.69	1.12	0.3000
Tricuspid valve disease	**0.74**	**0.57**	**0.97**	**0.0280**	**0.74**	**0.57**	**0.97**	**0.0280**
Post-myocardial infarction complication	0.99	0.72	1.37	0.9700	0.99	0.72	1.37	0.9700
Cardiopulmonary bypass time (min)	**1.01**	**1.01**	**1.02**	**0.0035**	**1.01**	**1.01**	**1.02**	**0.0004**
Isolated CABG	0.81	0.36	1.79	0.5900	0.81	0.36	1.79	0.6000
Isolated non-CABG	0.91	0.42	1.98	0.8200	0.91	0.42	1.98	0.8200
Two procedures	0.99	0.43	2.26	0.9800	0.99	0.43	2.26	0.9800
Three or more procedures	0.89	0.39	2.02	0.7800	0.89	0.39	2.02	0.7800
CABG	1.08	0.88	1.33	0.4700	1.08	0.88	1.33	0.4700
Aortic valve surgery	0.99	0.79	1.25	0.9500	0.99	0.79	1.25	0.9500
Mitral valve surgery	1.22	0.94	1.57	0.1300	1.22	0.94	1.57	0.1300
Tricuspid valve surgery	**1.49**	**1.12**	**1.99**	**0.0066**	**1.49**	**1.12**	**1.99**	**0.0066**
Aortic surgery	1.17	0.89	1.54	0.2600	1.17	0.89	1.54	0.2700
Other kind of surgery	1.12	0.88	1.42	0.3700	1.12	0.88	1.42	0.3700

CABG. Coronary Artery Bypass Surgery. COPD. Chronic Obstructive Pulmonary Disease. IABP. Intra-Aortic Balloon Pump. LVEF. Left Ventricular Ejection Fraction.

Table S5. MixedCox proportional hazards for in-hospital mortality based on model 3 (demographic data. preoperative. intraoperative and ECMO variables).

	By Center				By Center and year			
	Hazard Ratio	95% Confidence Interval		P-value	Hazard Ratio	95% Confidence Interval		P-value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age (years)	**1.02**	**1.01**	**1.03**	**<0.0001**	**1.02**	**1.01**	**1.03**	**0.0000**
Sex (Reference: Males)	**1.14**	**1.01**	**1.28**	**0.0410**	**1.14**	**1.01**	**1.28**	**0.0410**
Body mass index (Kg/m2)	1.00	0.99	1.01	0.6300	1.00	0.99	1.01	0.6300
Dialysis	1.07	0.86	1.35	0.5300	1.08	0.86	1.35	0.5300
Previous myocardial infarction	0.96	0.82	1.12	0.5800	0.96	0.82	1.12	0.5800
Previous stroke	1.16	0.96	1.39	0.1100	1.16	0.96	1.39	0.1200
Atrial fibrillation	0.96	0.83	1.10	0.5400	0.96	0.83	1.10	0.5400
Diabetes mellitus	1.08	0.94	1.24	0.3100	1.08	0.93	1.24	0.3100
COPD	**1.23**	**1.02**	**1.48**	**0.0280**	**1.23**	**1.02**	**1.48**	**0.0280**
Peripheral artery disease	1.08	0.91	1.28	0.3900	1.08	0.91	1.28	0.3900
Pulmonary hypertension (>50 mmHg)	1.04	0.89	1.21	0.6300	1.04	0.89	1.21	0.6200
Previous cardiac surgery	0.99	0.86	1.14	0.8500	0.99	0.86	1.14	0.8600
LVEF (%)	1.00	0.99	1.01	0.0660	1.01	1.00	1.01	0.1200
Preoperative cardiogenic shock	**1.27**	**1.07**	**1.50**	**0.0055**	**1.27**	**1.07**	**1.50**	**0.0054**
Emergency surgery (vs Elective)	1.15	0.97	1.36	0.1200	1.15	0.97	1.36	0.1200
Urgent surgery (vs Elective)	1.09	0.93	1.28	0.2900	1.09	0.93	1.28	0.2900
Preoperative cardiac arrest	**1.41**	**1.14**	**1.74**	**0.0016**	**1.41**	**1.14**	**1.74**	**0.0016**
Preoperative septic shock	1.41	1.00	1.98	0.0600	1.41	1.00	1.98	0.0500
Preoperative acute pulmonary edema	0.96	0.75	1.22	0.7500	0.96	0.75	1.22	0.7400
Preoperative IABP	1.02	0.81	1.27	0.8900	1.02	0.81	1.27	0.9000
Preoperative right ventricular failure	**1.36**	**1.11**	**1.66**	**0.0032**	**1.36**	**1.11**	**1.66**	**0.0032**
Preoperative creatinine (umol/L)	1.00	1.00	1.00	0.0990	1.00	1.00	1.00	0.0990
Coronary artery disease	0.92	0.76	1.12	0.4100	0.92	0.76	1.12	0.4200
Aortic vessel disease	1.12	0.86	1.45	0.4100	1.12	0.86	1.46	0.4100
Aortic valve disease	1.17	0.94	1.46	0.1600	1.17	0.94	1.45	0.1600
Mitral valve disease	0.92	0.72	1.17	0.4800	0.92	0.72	1.17	0.4800
Tricuspid valve disease	**0.73**	**0.56**	**0.96**	**0.0220**	**0.73**	**0.56**	**0.96**	**0.0220**
Post-myocardial infarction complication	1.00	0.72	1.38	0.9800	1.00	0.72	1.38	0.9800
Cardiopulmonary bypass time (min)	**1.01**	**1.01**	**1.02**	**<0.0001**	**1.01**	**1.01**	**1.02**	**0.0001**
Isolated CABG	0.74	0.33	1.64	0.4500	0.74	0.33	1.64	0.4600
Isolated non-CABG	0.85	0.39	1.84	0.6800	0.85	0.39	1.85	0.6800
Two procedures	0.90	0.39	2.07	0.8100	0.90	0.39	2.07	0.8100
Three or more procedures	0.83	0.36	1.88	0.6500	0.83	0.36	1.89	0.6500
CABG	1.08	0.88	1.32	0.4700	1.08	0.88	1.32	0.4700
Aortic valve surgery	0.97	0.76	1.22	0.7700	0.97	0.76	1.22	0.7700
Mitral valve surgery	1.13	0.87	1.46	0.3500	1.13	0.87	1.46	0.3500
Tricuspid valve surgery	**1.53**	**1.15**	**2.04**	**0.0038**	**1.53**	**1.15**	**2.04**	**0.0038**
Aortic surgery	1.20	0.91	1.59	0.1900	1.20	0.91	1.59	0.1900
Other kind of surgery	1.13	0.89	1.43	0.3300	1.13	0.89	1.43	0.3200
ECMO implanting time (Reference: intraoperative)	**1.25**	**1.06**	**1.46**	**0.0063**	**1.25**	**1.06**	**1.46**	**0.0068**
ECMO indication (Reference CPB weaining failure):								
Cardiac arrest	0.93	0.73	1.19	0.5800	0.93	0.73	1.19	0.5900
Cardiogenic shock	0.92	0.77	1.11	0.4100	0.92	0.77	1.11	0.4100
Right ventricular failure	**0.74**	**0.60**	**0.93**	**0.0083**	**0.74**	**0.60**	**0.93**	**0.0083**
Biventricular failure	0.98	0.76	1.25	0.8600	0.98	0.76	1.25	0.8600
Other	**0.70**	**0.54**	**0.91**	**0.0080**	**0.70**	**0.54**	**0.91**	**0.0079**

ECMO central cannulation	**2.86**	**1.17**	**6.98**	**0.0210**	**2.86**	**1.17**	**6.99**	**0.0210**
ECMO peripheral cannulation	2.36	0.98	5.72	0.0570	2.36	0.98	5.73	0.0570
ECMO cannulation change	**2.46**	**1.01**	**5.98**	**0.0470**	**2.46**	**1.01**	**5.99**	**0.0470**

CABG. Coronary Artery Bypass Surgery. COPD. Chronic Obstructive Pulmonary Disease. ECMO. extracorporeal membrane oxygenation. IABP. Intra-Aortic Balloon Pump. LVEF. Left Ventricular Ejection Fraction.

Table S6. Mixed Cox proportional hazards for in-hospital mortality based on model 4 (demographic data. preoperative. intraoperative. ECMO variables and postoperative complications).

	By Center				By Center and year			
	Hazard Ratio	95% Confidence Interval		P-value	Hazard Ratio	95% Confidence Interval		P-value
		Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Age (years)	**1.02**	**1.01**	**1.02**	**<0.0001**	**1.02**	**1.01**	**1.02**	**0.0000**
Sex (Reference: Males)	1.11	0.98	1.26	0.0930	1.11	0.98	1.26	0.0940
Body mass index (Kg/m2)	1.00	0.99	1.01	0.6700	1.00	0.99	1.01	0.6700
Dialysis	1.15	0.92	1.45	0.2100	1.15	0.92	1.45	0.2100
Previous myocardial infarction	0.94	0.81	1.10	0.4600	0.94	0.81	1.10	0.4600
Previous stroke	1.12	0.93	1.35	0.2200	1.12	0.93	1.35	0.2200
Atrial fibrillation	0.95	0.83	1.09	0.4800	0.95	0.83	1.09	0.4800
Diabetes mellitus	0.94	0.82	1.09	0.4000	0.94	0.82	1.09	0.4100
COPD	1.16	0.96	1.40	0.1300	1.16	0.96	1.40	0.1300
Peripheral artery disease	1.11	0.93	1.31	0.2400	1.11	0.94	1.31	0.2400
Pulmonary hypertension (>50 mmHg)	1.00	0.85	1.16	0.9600	1.00	0.85	1.16	0.9700
Previous cardiac surgery	1.00	0.87	1.15	0.6000	1.00	0.87	1.15	1.0000
LVEF (%)	1.00	1.00	1.01	0.1330	1.00	1.00	1.01	0.3400
Preoperative cardiogenic shock	1.24	1.04	1.46	0.1400	1.24	1.04	1.46	0.0140
Emergency surgery (vs Elective)	1.15	0.97	1.36	0.1010	1.15	0.97	1.36	0.1000
Urgent surgery (vs Elective)	1.06	0.90	1.25	0.4700	1.06	0.90	1.25	0.4700
Preoperative cardiac arrest	**1.34**	**1.08**	**1.66**	**0.0073**	**1.34**	**1.08**	**1.66**	**0.0078**
Preoperative septic shock	1.33	0.94	1.88	0.1100	1.33	0.94	1.89	0.1100
Preoperative acute pulmonary edema	0.99	0.77	1.26	0.9200	0.99	0.77	1.26	0.9200
Preoperative IABP	0.95	0.76	1.19	0.6500	0.95	0.76	1.19	0.6500
Preoperative right ventricular failure	1.19	0.97	1.47	0.9700	1.19	0.97	1.47	0.0970
Preoperative creatinine (umol/L)	1.00	1.00	1.00	0.3400	1.00	1.00	1.00	0.3400
Coronary artery disease	0.89	0.74	1.08	0.2500	0.89	0.74	1.08	0.2500
Aortic vessel disease	1.04	0.79	1.35	0.7900	1.04	0.79	1.35	0.7900
Aortic valve disease	1.12	0.90	1.39	0.3100	1.12	0.90	1.39	0.3200
Mitral valve disease	0.84	0.66	1.07	0.1600	0.84	0.66	1.07	0.1600
Tricuspid valve disease	0.76	0.58	1.00	0.0540	0.77	0.58	1.00	0.0540
Post-myocardial infarction complication	0.91	0.66	1.26	0.5800	0.91	0.66	1.26	0.5800
Cardiopulmonary bypass time (min)	1.00	1.00	1.00	0.0670	1.00	1.00	1.00	0.0670
Isolated CABG	0.97	0.43	2.19	0.9500	0.97	0.43	2.19	0.9500
Isolated non-CABG	1.01	0.46	2.22	0.9800	1.01	0.46	2.22	0.9800
Two procedures	1.16	0.50	2.69	0.7300	1.16	0.50	2.69	0.7300
Three or more procedures	0.95	0.42	2.19	0.9100	0.95	0.42	2.19	0.9100
CABG	1.13	0.92	1.38	0.2600	1.13	0.92	1.39	0.2600
Aortic valve surgery	0.95	0.75	1.19	0.6300	0.95	0.75	1.19	0.6400
Mitral valve surgery	1.20	0.93	1.55	0.1500	1.20	0.93	1.55	0.1500
Tricuspid valve surgery	**1.53**	**1.14**	**2.05**	**0.0043**	**1.53**	**1.14**	**2.05**	**0.0044**
Aortic surgery	**1.32**	**1.00**	**1.75**	**0.0470**	**1.32**	**1.00**	**1.75**	**0.0470**
Other kind of surgery	1.21	0.96	1.54	0.1100	1.21	0.96	1.54	0.1100
ECMO implanting time (Reference: intraoperative)	1.11	0.94	1.31	0.2200	1.11	0.94	1.31	0.2200
ECMO indication (Reference CPB weaning failure):								
Cardiac arrest	0.79	0.62	1.02	0.7200	0.79	0.62	1.02	0.0740
Cardiogenic shock	0.90	0.74	1.09	0.2800	0.90	0.74	1.09	0.2800
Right ventricular failure	**0.75**	**0.60**	**0.93**	**0.0100**	**0.75**	**0.60**	**0.93**	**0.0100**
Biventricular failure	0.93	0.72	1.20	0.5900	0.93	0.72	1.20	0.5900
Other	**0.68**	**0.52**	**0.88**	**0.0038**	**0.68**	**0.52**	**0.88**	**0.0039**

ECMO central cannulation	**2.71**	**1.08**	**6.79**	**0.0330**	**2.72**	**1.09**	**6.80**	**0.0330**
ECMO peripheral cannulation	2.18	0.88	5.41	0.0920	2.19	0.88	5.42	0.0920
ECMO cannulation change	2.31	0.93	5.74	0.0720	2.31	0.93	5.76	0.0710
Complications								
Bleeding requiring thoracotomy	1.00	0.88	1.14	0.9700	1.00	0.88	1.14	0.9700
Cerebral Hemorrhage	0.88	0.64	1.20	0.4100	0.88	0.64	1.20	0.4100
Stroke	0.83	0.68	1.02	0.7100	0.83	0.68	1.02	0.0710
Leg Ischemia	1.07	0.88	1.29	0.5100	1.07	0.88	1.29	0.5100
LV failure	**1.70**	**1.48**	**1.96**	**<0.0001**	**1.70**	**1.48**	**1.96**	**0.0000**
RV failure	**1.25**	**1.08**	**1.46**	**0.0033**	**1.25**	**1.08**	**1.46**	**0.0033**
Cardiac Arrest	**1.53**	**1.31**	**1.79**	**<0.0001**	**1.53**	**1.31**	**1.79**	**0.0000**
Bowel ischemia	**1.28**	**1.03**	**1.60**	**0.0270**	**1.28**	**1.03**	**1.60**	**0.0270**
Acute kidney injury	1.06	0.93	1.21	0.4100	1.06	0.93	1.21	0.4100
Pneumonia	**0.48**	**0.41**	**0.56**	**<0.0001**	**0.48**	**0.41**	**0.56**	**0.0000**
Septic Shock	**0.85**	**0.72**	**0.99**	**0.0480**	**0.85**	**0.72**	**0.99**	**0.0420**
Multiorgan failure	**3.74**	**3.27**	**4.29**	**<0.0001**	**3.75**	**3.27**	**4.29**	**0.0000**

CABG. Coronary Artery Bypass Surgery. COPD. Chronic Obstructive Pulmonary Disease. CPB. Cardiopulmonary Bypass. ECMO. Extracorporeal Membrane Oxygenation. IABP. Intra-Aortic Balloon Pump. LV. Left Ventricular. LVEF. Left Ventricular Ejection Fraction. RV. Right Ventricular.

Figure S1. Distribution of PELS-1-1 contributing centres.

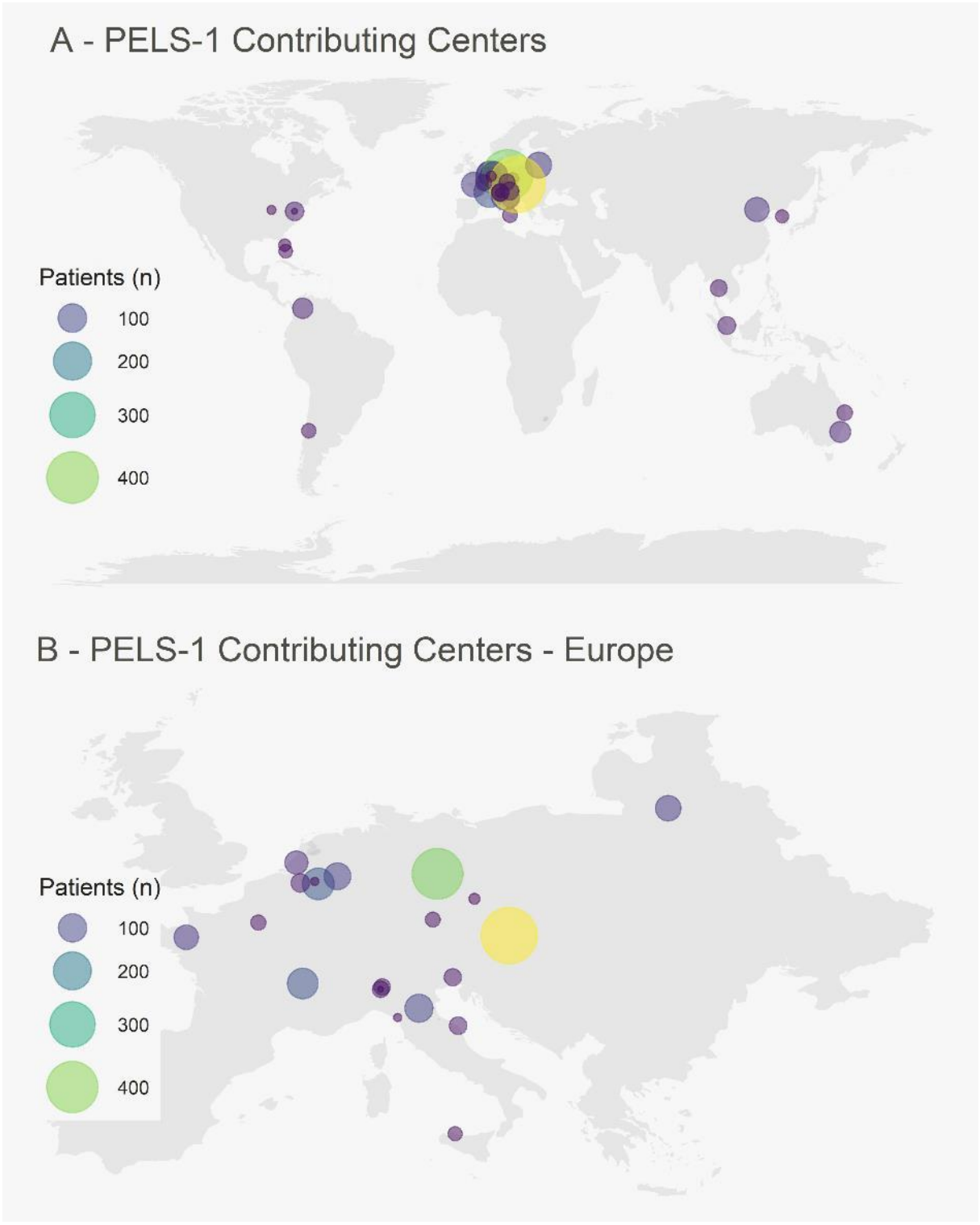


Figure S2. Flow-chart describing the patients included in the current study.

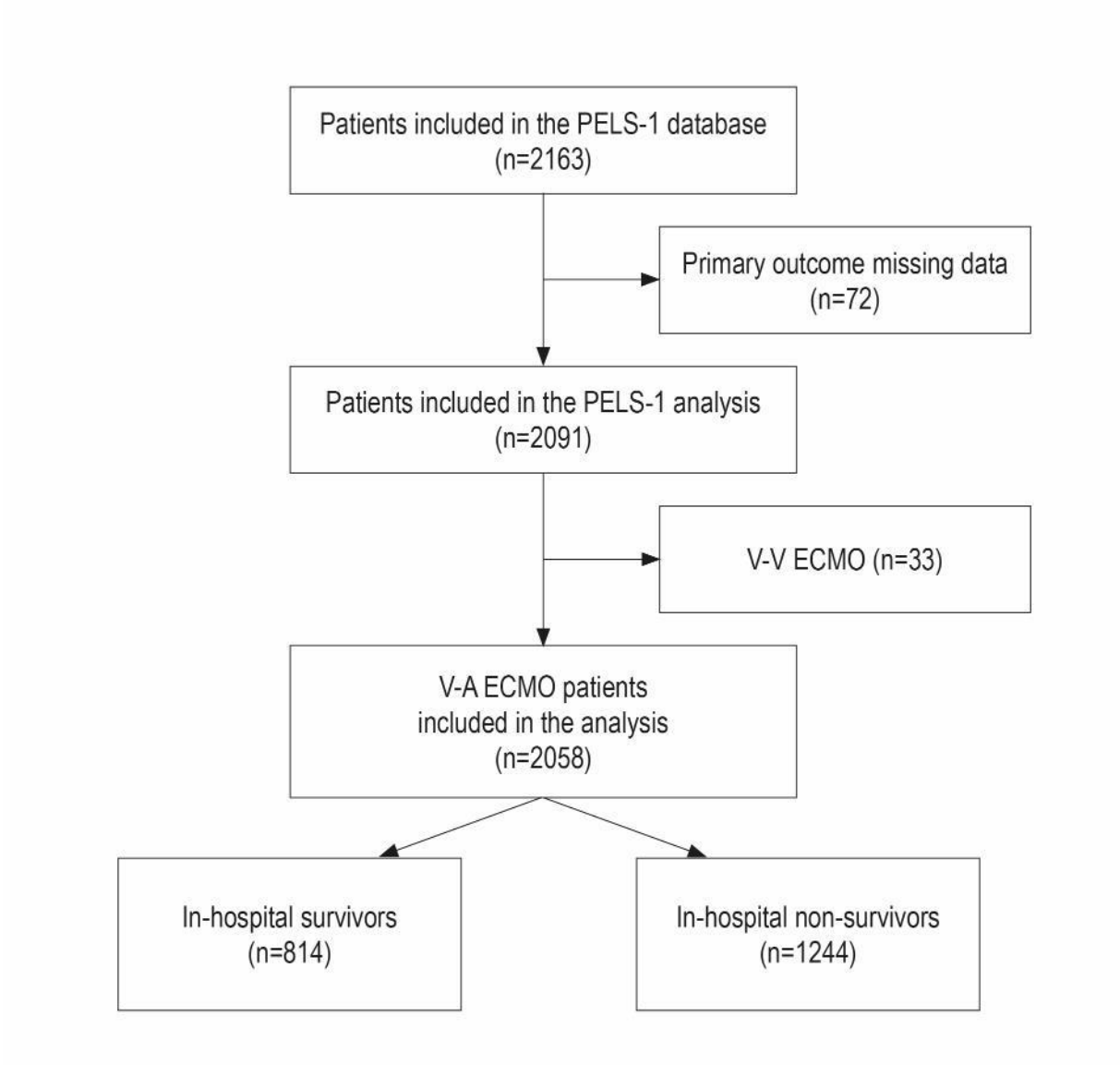


Figure S3. Patients included in the PELS-1 Study over time.

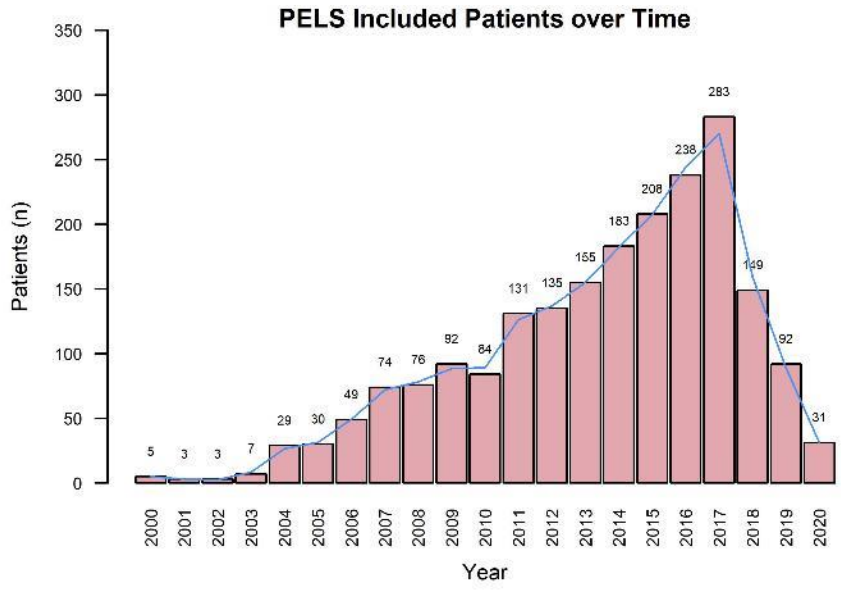
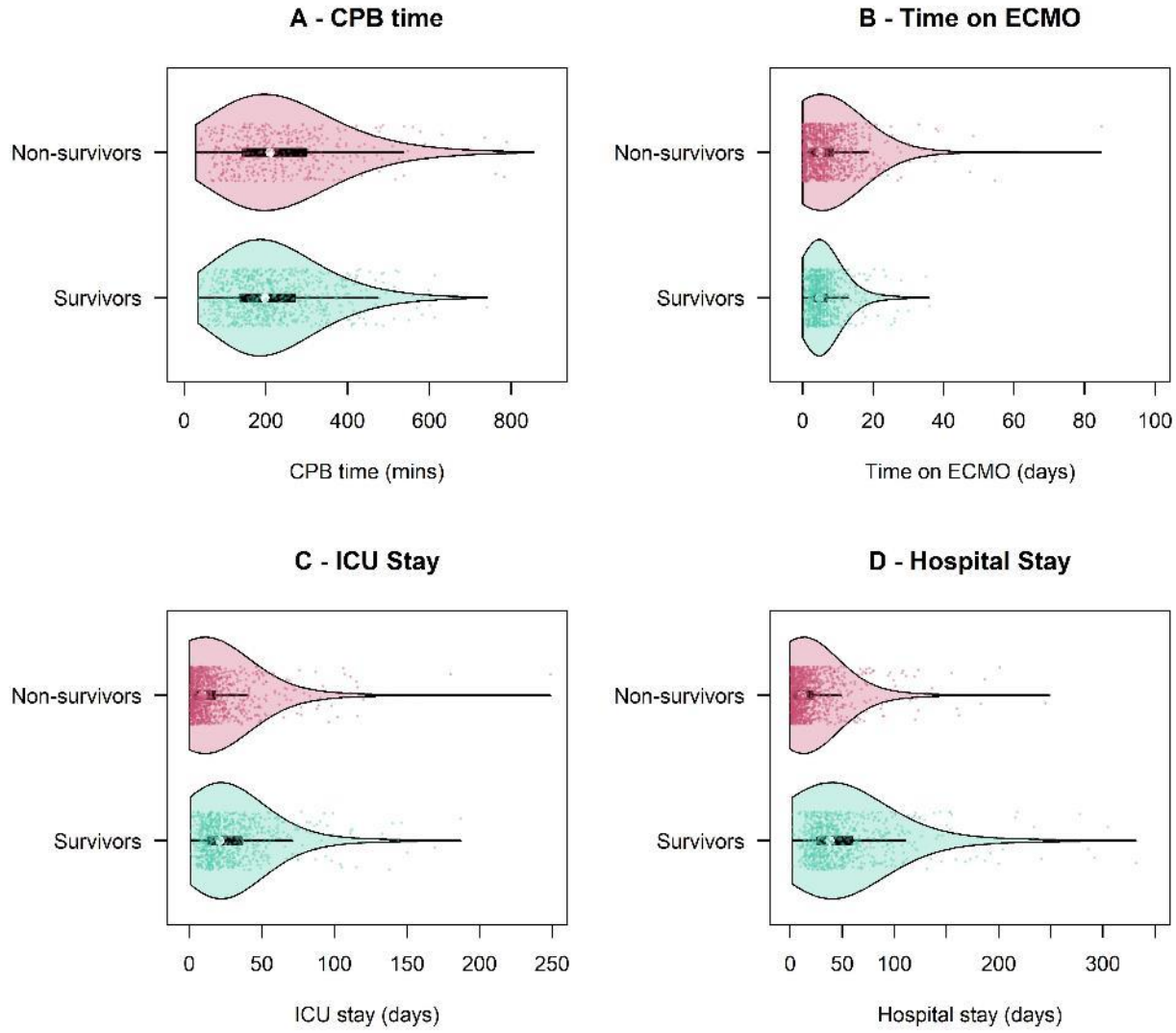
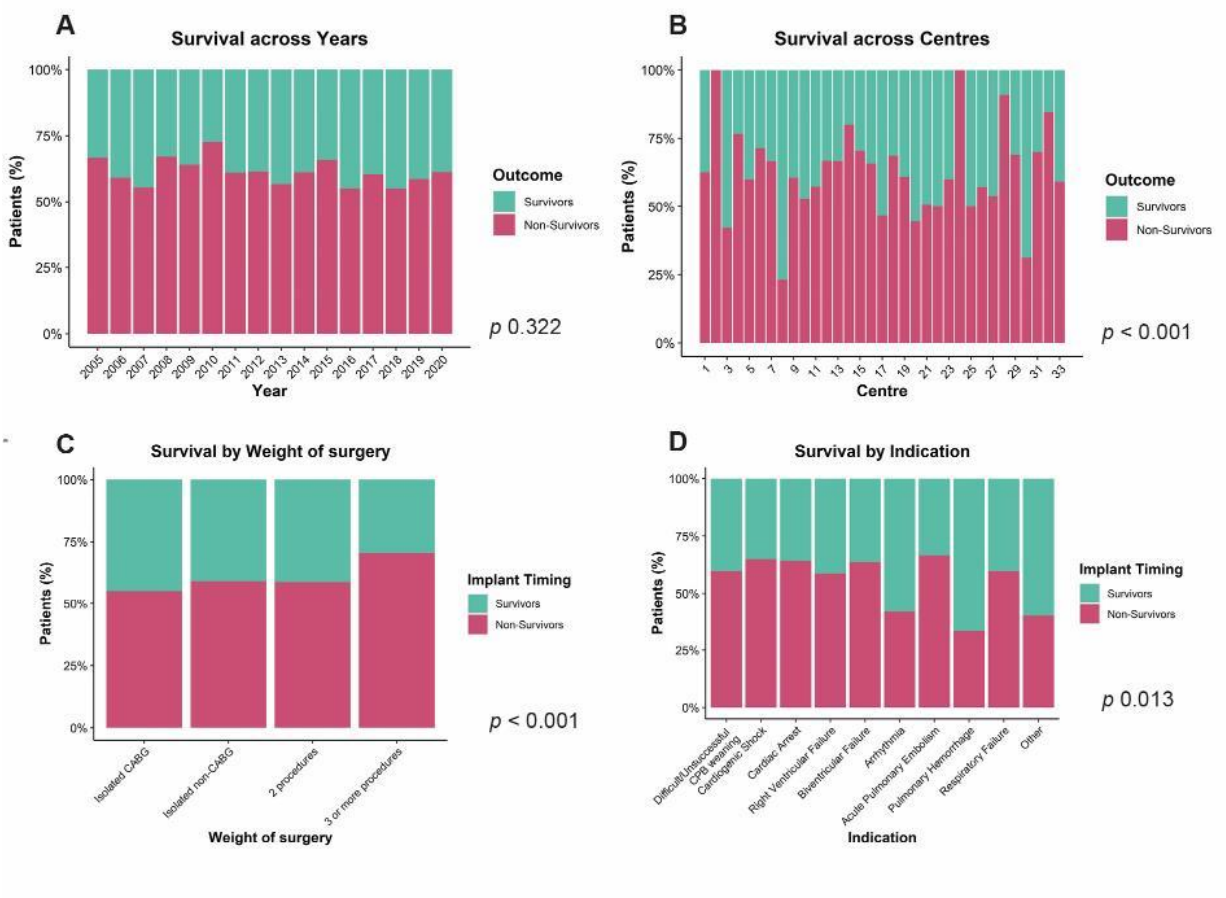


Figure S4. Violin plots.



Violin plots representing the duration of cardiopulmonary bypass (CPB) during surgery (A), the duration of extracorporeal membrane oxygenation (ECMO) support (B), the length of stay in intensive care unit (ICU, C) and the overall hospital stay (D) of survivors, patients deceased on ECMO and patients deceased after weaning.

Figure S5. Stacked bar plots.



Stacked bar plots representing in-hospital survival by several determinants: year of surgery (A), treating centre (B), weight of surgery (C) and indication for extracorporeal membrane oxygenation (D).