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CLINICAL RESEARCH
Myocardial disease

Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score

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Rationale Extracorporeal membrane oxygenation (ECMO) may provide mechanical pulmonary and circulatory support for patients with cardiogenic shock refractory to conventional medical therapy. Prediction of survival in these patients may assist in management of these patients and comparison of results from different centers.

Aims To identify pre-ECMO factors which predict survival from refractory cardiogenic shock requiring ECMO and create the survival after veno-arterial-ECMO (SAVE)-score.

Methods and results Patients with refractory cardiogenic shock treated with veno-arterial ECMO between January 2003 and December 2013 were extracted from the international Extracorporeal Life Support Organization registry. Multivariable logistic regression was performed using bootstrapping methodology with internal and external validation to identify factors independently associated with in-hospital survival. Of 3846 patients with cardiogenic shock treated with ECMO, 1601 (42%) patients were alive at hospital discharge. Chronic renal failure, longer duration of ventilation prior to ECMO initiation, pre-ECMO organ failures, pre-ECMO cardiac arrest, congenital heart disease, lower pulse pressure, and lower serum bicarbonate (HCO_3) were risk factors associated with mortality. Younger age, lower weight, acute myocarditis, heart transplant, refractory ventricular tachycardia or fibrillation, higher diastolic blood pressure, and lower peak inspiratory pressure were protective. The SAVE-score (area under the receiver operating characteristics [ROC] curve [AUROC] 0.68 [95%CI 0.64–0.71]) was created. External validation of the SAVE-score in an Australian population of 161 patients showed excellent discrimination with AUROC = 0.90 (95%CI 0.85–0.95).

Conclusions The SAVE-score may be a tool to predict survival for patients receiving ECMO for refractory cardiogenic shock (www.save-score.com).

Keywords Cardiogenic shock • Extracorporeal membrane • Outcome

Translational perspective

Using a large international cohort of 3846 patients treated with ECMO for cardiogenic shock, we identified prognostic factors for hospital survival and created a well calibrated and discriminatory survival prediction score comprising 13 pre-ECMO variables (the survival after veno-arterial-ECMO (SAVE)-score). It is the first validated international predictive mortality model based on a large population of acute refractory cardiogenic shock patients requiring ECMO. Based on these findings, the SAVE-score and its online calculator (www.save-score.com) offer a validated tool to predict survival for patients receiving ECMO for refractory cardiogenic shock.

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Introduction

Veno-arterial-extracorporeal membrane oxygenation (VA-ECMO) is an effective technique to support refractory cardiogenic shock while ensuring continuous organs perfusion to wait for cardiac function recovery, transplantation, or left ventricular assist device.[1] Most frequent indications include fulminant myocarditis,[2,3] acute myocardial infarction,[4] post heart transplantation,[5,6] or post-cardiotomy.[7] Despite notable advances in quality of the devices and in the overall intensive care unit (ICU) management, this rescue therapy is still marred by a high rate of complications such as bleeding,[8] infection,[9] or device complications.[8] Long-term physical and psychological impairment and high mortality rate have been consistently reported for these patients.[2,5,7] In addition, this technique requires considerable financial and human resources. For these reasons, VA-ECMO should be allocated to patients in an appropriate and resource efficient manner. Identifying pre-ECMO predictors of in-hospital survival is crucial to achieving this goal. Surprisingly, although cardiogenic shock cases represent the majority of adult patients on ECMO,[8] mortality risk factors for cardiogenic shock supported with ECMO have rarely been studied.[2,5,7,10] Reported adult data are either small cohort studies,[2,4,5,11] single-center studies,[2,4,5,11] or focus on specific sub-population such as myocarditis,[2] acute myocardial infarction,[12] or post-cardiotomy patients.[4,5,11] Despite the high burden of refractory cardiogenic shock requiring ECMO, predictive survival modelling has not been reported. However, five mortality prediction models for severe acute respiratory failure requiring ECMO have been published over the past 2 years.[13] Based on the large pre-ECMO assessment data extracted from the Extracorporeal Life Support Organization (ELSO) registry which prospectively includes data from 160 U.S. and 120 other international centres, we hypothesized that predictors of in-hospital survival following refractory cardiogenic shock requiring ECMO could be identified and that these findings would allow creation of survival prediction score namely the survival after veno-arterial-ECMO (SAVE)-score.

Materials and methods

Population studied

We queried the ELSO registry for adult patients who received ECMO primarily for cardiogenic shock from 2003 through 2013 (derivation cohort). Patients who received ECMO during cardio-pulmonary resuscitation (CPR) procedure were not included in our analysis. Validation of the model was performed on a cohort of patients who underwent veno-arterial-ECMO for refractory cardiogenic shock between 1 July 2006, and 31 December 2013, at the Alfred Hospital, Melbourne, Australia. The Alfred Hospital ICU operates an ECMO referral service and retrieves patients on ECMO from the southern states of Australia.

Data collection

Only data from the primary ECMO run were analysed including demographic data, pre-ECMO variables, ICD-09 diagnosis codes, procedure code, year of ECMO run, as well as hospital outcome. No patient or hospital identifying information was extracted. The pre-ECMO variables included CPR, chronic renal failure, time between ICU admission and cannulation, systolic and diastolic blood pressure values (DBP) within 6 h of cannulation, blood gases, and ventilator settings. Renal replacement therapy (RRT) and intra-aortic balloon pump (IABP) use at ECMO cannulation were reported. Extra-corporeal membrane oxygenation modes were reported as VA or mixed modes (i.e. combinations of veno-arterial and veno-venous). Two researchers (D.P. and M.S.) independently reviewed all ICD-09 diagnosis codes. Any discrepancies between the two reviewers were resolved by discussion. Diagnoses for cardiogenic shock were collapsed into the following groups: 'valvular heart disease', 'post-transplantation', 'congenital heart disease', 'aortic disease', 'other post-cardiotomy', -acute myocardial infarction', 'chronic heart disease', 'fulminant myocarditis', 'pulmonary embolism', 'sepsis', and 'refractory ventricular tachycardia (VT) or ventricular fibrillation (VF)'. Extra-cardiac organ failures, namely 'acute renal failure', 'central nervous system (CNS) dysfunction', 'liver failure' and 'respiratory failure' at ECMO cannulation were extracted. 'Acute renal dysfunction' was defined as a creatinine >1.5 mg/dL with or without RRT. 'Central nervous system dysfunction' combined neurotrauma, stroke, encephalopathy, cerebral embolism, as well as seizure and epileptic syndromes. 'Respiratory failure' included mixed chronic or acute pulmonary disorders, such as chronic obstructive pulmonary disease, associated pneumonia, severe hypoxemia, and pneumothorax. This analysis of de-identified data was approved by the Protocol and Registry Committees of ELSO.

Statistical analysis

Analyses were performed with STATA (StataCorp. 2011, Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP). Continuous variables were compared with Student's test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared using the χ^2 test for equal proportion.

The SAVE-score was constructed according to actual published recommendations.[14,15] Briefly, the following steps were used.

Step 1: Identification of 'Candidate variables'

Variables relating to patient, diagnosis, or associated organ dysfunction prior to initiation of ECMO were considered. Univariable comparison of all parameters between survivors and deaths was undertaken. Variables were subjected to a correlation matrix for analysis of co-linearity. Continuous variables were explored for linearity by considering as both quartiles and deciles before being converted into categorical variables for practical purposes. A separate 'missing' category was created for each continuous physiological variable to allow inclusion of patients with incomplete data. Variables with P-values ≤ 0.10, together with all diagnostic categories, were entered into a logistic regression model to identify candidate variables for inclusion in the SAVE-score.

Step 2: Construction of the survival after veno-arterial-extracorporeal membrane oxygenation-score

Beta parameters (regression coefficients)[16] were re-estimated using logistic regression with bootstrapping technique, sampling the whole dataset using 200 repetitions with replacement. This technique involved multiple re-sampling of the original data and facilitated use of the whole dataset without the need to split into derivation and validation samples. Inclusion criteria were set at $P \leq 0.10$. All associated refractory cardiogenic shock diagnoses were included in the model. Only variables with P-values ≤ 0.05 were retained for calculation of the score. Using the relative contribution of each β parameter,[17] practical weights, both positive and negative, were generated with a zero score approximately equating to a 50% risk of death.

Step 3: Internal validation

Logistic regression was used to reassess score performance in the original dataset. Model discrimination and calibration were assessed using the area under the receiver operating characteristics (ROC) curve and the

Hosmer-Lemeshow C-statistic with associated *P*-value, respectively. Further, sensitivity analyses were undertaken to determine the performance of the SAVE-score per year and in specific subgroups (early [pre-2010] and late period [2010–2013], fulminant myocarditis, post heart or lung transplantation, acute myocardial infarction, cardiac arrest prior to ECMO, and congenital heart disease).

Step 4: External validation

The external validation phase was performed completely independently and after the building of the SAVE-score from the derivation cohort. The external validation of the SAVE-score was performed on the dataset of 161 patients from the Alfred Hospital, Melbourne, Australia (validation cohort). Performance of the SAVE-score and the Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) II and APACHE III at ICU admission, the sepsis-related organ failure assessment (SOFA) score at ICU admission and at ECMO cannulation were assessed using the area under the ROC curve and the Hosmer-Lemeshow C-statistic with associated *P*-value, respectively.

Results

Populations

Three thousand nine hundred and sixty-three patients underwent 4128 VA-ECMO runs over the 13-year period. One hundred and seventeen patients in whom respiratory failure was the primary diagnosis were excluded. Three thousand eight hundred and forty six patients (age 54 (39–64) years, 67% male) were retained as the derivation cohort to create the SAVE-score (derivation cohort) (*Figure 1*). Their demographic and pre-ECMO characteristics are displayed in *Tables 1* and *2*. Briefly, 93% received VA-ECMO setting as sole support. Main diagnoses were chronic heart failure (33%), acute myocardial infarction (29%), and valvular heart disease (17%). Of note, cardiac arrest occurred before ECMO cannulation in 32% of the cohort. After 100 (49–169) hours on ECMO, 1601 patients (42%) were alive at hospital discharge. Characteristics of the validation cohort are provided in *Tables 1* and *2*. This 161 patient-cohort, aged of 51 (38–59) years with APACHE III at 76 ± 32 exhibited 67% survival rate at hospital discharge.

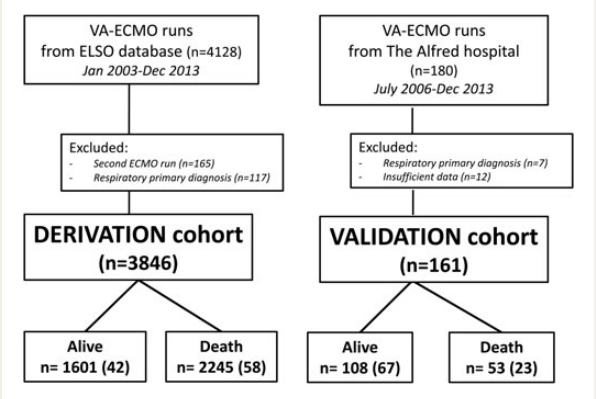


Figure 1 Study flow diagram. ECMO, extracorporeal membrane oxygenation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Predictors of in-hospital survival

Multivariable modelling performed on 3846 patients identified chronic renal failure, longer duration of mechanical ventilation prior to initiation of ECMO, others acute pre-ECMO organ failure, pre-ECMO cardiac arrest, congenital heart disease, lower pulse pressure, and lower serum bicarbonate as independent risk factors at the time of ECMO institution associated with hospital mortality (*Table 3*). Conversely, younger age, weight between 76 and 89 kg, acute myocarditis, post-transplant, refractory VT/VF, higher DBP, and lower peak inspiratory pressure were protective factors (*Table 3*).

Survival after veno-arterial-extracorporeal membrane oxygenation-score

Based on these findings, 12 items were retained to create the SAVE-score. The full description is provided in *Table 4*. In addition, an online calculator is available at www.save-score.com. Five risk classes, namely class I (SAVE-score: ≥5), class II (SAVE-score: 1 to 5), class III (SAVE-score: −4 to 0), class IV (SAVE-score: −9 to −5), and class V (SAVE-score: ≤−10) with their corresponding survival rate (75, 58, 42, 30, and 18%, respectively), were identified (*Figures 2* and *3*). A SAVE-score of zero was approximately equivalent to 50% survival with positive scores representing higher chances of survival. Survival in major diagnostic groups by risk class is shown in *Table 5* and model performance in each group is provided in Supplementary material online, *Table S1*. There were no significant changes in outcomes or SAVE-score over the time period of the study (see Supplementary material online, *Figure S1* and *Table S2* for detailed annual breakdown of survival and score characteristics).

Internal validation of the SAVE-score demonstrated modest discrimination ($c = 0.68$ [95% CI 0.66–0.69]) and good calibration with a Hosmer-Lemeshow C-statistic of 9.7 ($P = 0.29$). Discrimination was best in patients with more complete physiological data (see Supplementary material online, *Figure S2*). The performance of the SAVE-score in the validation cohort was excellent with $c = 0.90$ [95% CI 0.85–0.95] and Hosmer-Lemeshow C-statistic of 13.97 ($P = 0.08$). Discriminatory performance was greater than APACHE II, APACHE III, and SOFA scores at ICU admission or at ECMO cannulation (*Figure 4*).

Discussion

Using a large international cohort of 3846 patients treated with ECMO for cardiogenic shock, we identified prognostic factors for hospital survival and created a well calibrated and reasonably discriminatory in-hospital survival prediction score comprising 13 pre-ECMO variables (SAVE-score).

Prognostic factors of in-hospital survival

Although ECMO devices have steadily improved for two decades,[18] patients treated with ECMO for refractory cardiogenic shock still exhibit very high short-term mortality (40–75%).[5,7,19] For instance, survival at hospital discharge was only 42% in the ELSO cohort. Our study highlights the importance of the underlying diagnosis leading to cardiogenic shock in determining hospital survival. For

Table 1 **Patient characteristics in derivation and validation cohorts according to their hospital outcomes**

	Derivation ELSO cohort ($n = 3846$)				Validation cohort ($n = 161$)			
	Total ($n = 3846$)	Alive at hospital discharge ($n = 1601$)	Death in hospital ($n = 2245$)	*P*-value	Total ($n = 161$)	Alive at hospital discharge ($n = 108$)	Death in hospital ($n = 53$)	*P*-value
Age (years)	54 (39–64)	51 (35–61)	56 (43–65)	<0.001	51 (38–59)	50 (36–57)	56 (39–63)	0.033
Male	2548 (67)	1055 (67)	1493 (67)	0.73	121 (75)	83 (77)	38 (72)	0.48
APACHE II	–	–	–	–	22 ± 9	21 ± 8	26 ± 10	0.011
APACHE III	–	–	–	–	76 ± 32	71 ± 30	91 ± 34	0.003
SOFA at ICU admission	–	–	–	–	11 ± 4	10 ± 3	13 ± 4	<0.0001
SOFA at ECMO cannulation	–	–	–	–	12 ± 3	11 ± 3	14 ± 3	<0.0001
Weight (kg)	79 ± 21	77 ± 19	80 ± 24	<0.001	76 ± 17	76 ± 17	78 ± 16	0.39
Interval ICU admission-ECMO (h)	24 (7–106)	18 (4–77)	30 (9–122)	<0.001	0 (0–0)[a]	0 (0–0)[a]	0 (0–2)[a]	0.13
Duration of intubation prior to ECMO (h)	10 (4–26)	9 (2–22)	12 (5–31)	<0.001	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0.16
Type of ECMO								
Veno-arterial (only)	3576 (93)	1482 (92)	2094 (93)	0.40	161 (100)	108 (100)	53 (100)	1.0
Mixed modes	270 (7)	119 (7)	151 (7)		0 (0)	0 (0)	0 (0)	
Chronic renal failure	112 (3)	25 (2)	87 (4)	<0.001	22 (14)	13 (12)	9 (17)	0.39
Pre-ECMO cardiac arrest	1240 (32)	456 (28)	784 (35)	<0.001	66 (41)	31 (29)	35 (66)	<0.0001
Pre-ECMO IABP	410 (18)	151 (17)	259 (19)	0.4	28 (20)	18 (19)	10 (21)	0.83
Duration of ECMO support (h)	100 (49–169)	107 (63–165)	96 (42–173)	0.005	7 (4–10)	7 (4–9)	7 (3–13)	0.99
Diagnoses associated with cardiogenic shock[a]								
Acute myocardial infarction	1105 (29)	437 (27)	668 (30)	0.097	30 (19)	14 (13)	16 (30)	
Aortic disease	120 (3)	30 (2)	90 (4)	<0.001	1 (1)	1 (1)	0 (0)	
Congenital heart disease	315 (8)	102 (6)	213 (9)	0.001	9 (6)	5 (5)	4 (8)	
Myocarditis	242 (6)	145 (9)	97 (4)	<0.001	18 (11)	15 (14)	3 (6)	
Post heart or lung transplantation	216 (6)	112 (7)	104 (5)	0.002	52 (39)	40 (37)	12 (23)	
Pulmonary embolism	151 (4)	70 (4)	81 (4)	0.229	2 (1)	1 (1)	1 (4)	0.62
Refractory ventricular VT/VF	491 (13)	211(13)	280 (12)	0.517	6 (4)	6 (6)	0 (0)	
Sepsis	317 (8)	116 (7)	201 (9)	0.057	3 (2)	1 (1)	2 (4)	
Valvular heart disease	636 (17)	246 (15)	390 (17)	0.099	4 (3)	0 (0)	4 (8)	
Chronic heart failure of other causes	1272 (33)	536 (33)	736 (33)	0.652	28 (17)	23 (21)	5 (9)	
Other post-operative diagnoses	157 (4)	53 (33)	104 (46)	0.041	8 (6)	2 (2)	6 (11)	

Data are given as *n* (%), mean ± standard deviation or median (interquartile range).
APACHE, Acute Physiology, Age, and Chronic Health Evaluation II; ELSO, Extracorporeal Life Support Organization; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IABP, intra-aortic balloon pump; MV, mechanical ventilation; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; SOFA, sepsis-related organ failure assessment, VT, ventricular tachycardia; VF, ventricular fibrillation.
[a]Diagnoses were not mutually exclusive in the derivation ELSO dataset but only one diagnosis per patient was present in the validation cohort.

Table 2 Pre-extracorporeal membrane oxygenation organ failure and main pre-extracorporeal membrane oxygenation variables in derivation and validation cohorts according to their hospital outcomes

	Derivation ELSO cohort ($n = 3846$)				Validation cohort ($n = 161$)			
	Total ($n = 3846$)	Alive at hospital discharge ($n = 1601$)	Death in hospital ($n = 2245$)	*P*-value	Total ($n = 161$)	Alive at hospital discharge ($n = 108$)	Death in hospital ($n = 53$)	*P*-value
Others acute pre-ECMO organ failure								
Liver failure	178 (5)	47 (3)	131 (5)	<0.001	46 (37)	9 (11)	37 (82)	<0.0001
Respiratory failure[a]	476 (12)	162 (10)	314 (14)	<0.001	32 (20)	15 (14)	17 (32)	0.007
Central nervous system dysfunction[b]	219 (6)	66 (4)	153 (7)	<0.001	25 (17)	2 (2)	23 (46)	<0.0001
Renal failure[c]	529 (14)	160 (10)	369 (16)	<0.001	46 (43)	15 (18)	41 (91)	<0.0001
Pre-ECMO blood pressure[d]								
Systolic pressure (mmHg)	80 (65–95)	81 (67–96)	77 (63–92)	<0.001	75 (50–80)	80 (70–85)	50 (0–60)	<0.0001
Diastolic pressure (mmHg)	49 (40–59)	50 (40–60)	47 (38–58)	<0.001	50 (40–55)	52 (45–55)	40 (0–40)	<0.0001
Pulse pressure (mmHg)	30 (20–40)	30 (20–40)	29 (19–40)	0.26	20 ± 13	25 ± 13	12 ± 11	<0.0001
Pre-ECMO ventilator settings								
PaO_2/FiO_2	129 (67–272)	134 (69–275)	123 (66–270)	0.20	169 (102–352)	167 (118–353)	185 (91–350)	0.61
PIP, cmH_2O	26 (21–31)	24 (20–30)	26 (22–32)	<0.001	22 (20–25)	20 (18–23)	24 (22–27)	<0.0001
PEEP, cmH_2O	5 (5–10)	5 (5–10)	6 (5–10)	0.09	10 (8–10)	10 (9–10)	10 (7–10)	0.45
Pre-ECMO blood gas								
pH	7.30 (7.19–7.39)	7.31 (7.21–7.40)	7.30 (7.18–7.39)	0.002	7.24 (7.13–7.38)	7.29 (7.21–7.43)	7.16 (7.06–7.23)	<0.0001
$PaCO_2$, mmHg	41 ± 18	41 ± 18	41 ± 18	0.63	42 ± 28	44 ± 34	38 ± 12	0.26
PaO_2, mmHg	95 (62–186)	96 (62–186)	95 (62–187)	0.73	116 (79–265)	119 (79–247)	99 (80–300)	0.52
HCO_3, mmol/L	19.7 ± 6.3	20.1 ± 5.8	19.3 ± 6.7	0.001	17 ± 6	18 ± 6	13 ± 5	<0.0001
SaO_2, %	91 ± 14	92 ± 13	90 ± 15	0.03	100 ± 10	100 ± 8	97 ± 3	0.12

Data are given as *n* (%) or median (interquartile range). ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.

[a]Respiratory failure mixed chronic or acute pulmonary disorders such as chronic obstructive pulmonary disease, associated pneumonia, severe hypoxaemia, or pneumothorax.

[b]CNS dysfunction combined neurotrauma, stroke, encephalopathy, cerebral embolism, as well as seizure and epileptic syndromes.

[c]Renal dysfunction is defined as chronic or acute renal insufficiency (e.g. creatinine >1.5 mg/dL) with or without RRT.

[d]Worse value within 6 h prior ECMO cannulation.

Table 3 Results of multivariable logistic regression for survival prediction model from the derivation cohort

	OR (95% CI)	β-Coefficient	*P*-value
Age ≤38 years[a]	2.57 (2.07–3.18)	0.943	<0.0001
Age between 39 and 52 years[a]	1.67 (1.37–2.04)	0.515	<0.0001
Age between 53 and 62 years[a]	1.43 (1.17–1.75)	0.357	<0.0001
Weight ≤65 kg[b]	1.22 (0.99–1.5)	0.196	0.026
Weight between 66 and 75 kg[b]	1.33 (1.08–1.64)	0.285	0.003
Weight between 76 and 89 kg[b]	1.41 (1.16–1.71)	0.34	<0.0001
Chronic renal failure	0.42 (0.26–0.68)	−0.872	0.001
Duration of intubation prior to ECMO between 11 and 29 h	0.73 (0.62–0.87)	−0.31	0.001
Duration of intubation prior to ECMO ≥ 30 h	0.55 (0.46–0.67)	−0.591	<0.0001
Others acute pre-ECMO organ failure			
Liver failure	0.63 (0.42–0.94)	−0.46	0.018
Central nervous system dysfunction[c]	0.63 (0.44–0.89)	−0.465	0.008
Acute renal failure[d]	0.64 (0.51–0.8)	−0.446	<0.001
Pre-ECMO cardiac arrest	0.75 (0.65–0.86)	−0.29	<0.001
Congenital heart disease	0.63 (0.48–0.84)	−0.461	<0.0001
Acute myocarditis	1.58 (1.18–2.13)	0.46	0.003
Heart and lung transplants	1.52 (1.16–2)	0.421	0.004
Refractory ventricular arrhythmias—VT/VF	1.34 (1.09–1.64)	0.29	0.005
Diastolic blood pressure 40–48 mmHg[e]	1.42 (1.16–1.74)	0.348	<0.0001
Diastolic blood pressure 49–58 mmHg[e]	1.47 (1.19–1.81)	0.383	<0.0001
Diastolic blood pressure ≥59 mmHg[e]	1.61 (1.32–1.95)	0.473	<0.0001
Pulse pressure ≤20 mmHg[e]	0.76 (0.61–0.94)	−0.277	0.009
HCO_3 ≤15 mmol/L	0.7 (0.58–0.83)	−0.364	<0.0001
PIP ≤20 cmH_2O	1.46 (1.2–1.79)	0.381	0.001

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PIP, peak inspiratory pressure; VT, ventricular tachycardia; VF, ventricular fibrillation.
[a]Reference category age >62 years.
[b]Reference category weight >90 kg.
[c]CNS dysfunction combined neurotrauma, stroke, encephalopathy, cerebral embolism, as well as seizure and epileptic syndromes.
[d]Renal dysfunction is defined as chronic or acute renal insufficiency (e.g. creatinine >1.5 mg/dL) with or without RRT.
[e]Worst value within 6 h prior ECMO cannulation (reference category <40 mmHg).

instance, the better prognosis of myocarditis has been reported by Combes *et al.* who described 81 patients with refractory cardiogenic shock treated by ECMO.[5] Similarly, other causes of myocardial injury such as refractory VT/VF or primary graft failure after heart transplantation have also been associated with better outcomes (*Tables 3* and *4*). A quickly reversible cause of cardiogenic shock is also recognized as an important predictor of survival.[2,5] Conversely, although primary percutaneous coronary angioplasty,[20,21] IABP,[22,23] and ECMO[12,24,25] may improve the poor outcomes of acute myocardial infarction complicated with cardiogenic shock,[21,26] this diagnosis was still associated with a lower survival in our study (*Table 4*).

Although the derivation and the validation cohorts both excluded patients who received ECMO instituted during CPR, the high prevalence of cardiac arrest pre-ECMO (which has a high risk of brain damage and multi-organ failure) highlights the magnitude of severity of illness in these patients.[27–29] This was reflected in its negative weighting (−2) in the SAVE-score (*Table 4*). We also demonstrated that increasing duration of mechanical ventilation prior to ECMO cannulation was independently associated with mortality (*Table 3*). A similar finding has been demonstrated in respiratory ECMO[30–32] but to the best of our knowledge has rarely been reported with ECMO for cardiac failure. This reinforces the need to initiate ECMO before occurrence of irreversible multi-organ failure. To shorten this delay, many of the high-volume centres now have a mobile ECMO team able to operate a portable and quick-to-prime ECMO circuit just after the emergency call.[33] A lower predictive chance of survival in the SAVE-score for each extra-cardiac associated organ failure—renal, liver, and neurological—at ECMO initiation illustrates the crucial impact of the ECMO timing. Prothrombin activity ≤50% and 24-h urine output ≤500 mL have been consistently previously reported as associated with ICU mortality.[5] Similarly, severity of the shock identified by lower diastolic pressure, lower pulse pressure, and lower serum bicarbonate was expected risk factors of hospital mortality (*Table 3*). These findings highlight the need to target the 'right time window' for ECMO initiation. Extracorporeal membrane oxygenation initiation too early in a patient's course may lead to an uncontrolled use of ECMO, which might disproportionately raise hospital costs and resource consumption while exposing patients to unnecessary ECMO complications, whereas late ECMO initiation may be futile. The SAVE-score and its online tool (www.save-score.com) may help clinicians to overcome this difficulty.

Table 4 The survival after veno-arterial-extracorporeal membrane oxygenation-score

Parameter	Score	
Acute cardiogenic shock diagnosis group (select one or more)		
Myocarditis	3	
Refractory ventricular VT/VF	2	
Post heart or lung transplantation	3	
Congenital heart disease	−3	
Other diagnoses leading to cardiogenic shock requiring VA-ECMO	0	
Age (years)		
18–38	7	
39–52	4	
53–62	3	
≥63	0	
Weight (kg)		
≤65	1	
65–89	2	
≥90	0	
Acute pre-ECMO organ failures (select one or more if required)		
Liver failure[a]	−3	
Central nervous system dysfunction[b]	−3	
Renal failure[c]	−3	
Chronic renal failure[d]	−6	
Duration of intubation prior to initiation of ECMO (h)		
≤10	0	
11–29	−2	
≥30	−4	
Peak inspiratory pressure ≤20 cmH_2O	3	
Pre-ECMO cardiac arrest	−2	
Diastolic blood pressure before ECMO ≥40 mmHg[e]	3	
Pulse pressure before ECMO ≤20 mmHg[e]	−2	
HCO_3 before ECMO ≤15 mmol/L	−3	
Constant value to add to all calculations of SAVE-score	−6	
Total score	−35 to 23	
Total SAVE-score	Risk class	Survival (%)
Hospital survival by risk class		
>5	I	75
1–5	II	58
−4 to 0	III	42
−9 to −5	IV	30
≤−10	V	18

An online calculator is available at www.save-score.com
VT, ventricular tachycardia; VF, ventricular fibrillation.
[a]Liver failure was defined as billirubin ≥33 μmol/L or elevation of serum aminotransferases (ALT or AST)>70 UI/L.
[b]CNS dysfunction combined neurotrauma, stroke, encephalopathy, cerebral embolism, as well as seizure and epileptic syndromes.
[c]Renal dysfunction is defined as chronic or acute renal insufficiency (e.g. creatinine >1.5 mg/dL) with or without RRT.
[d]Chronic kidney disease is defined as either kidney damage or glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months.
[e]Worse value within 6 h prior ECMO cannulation.

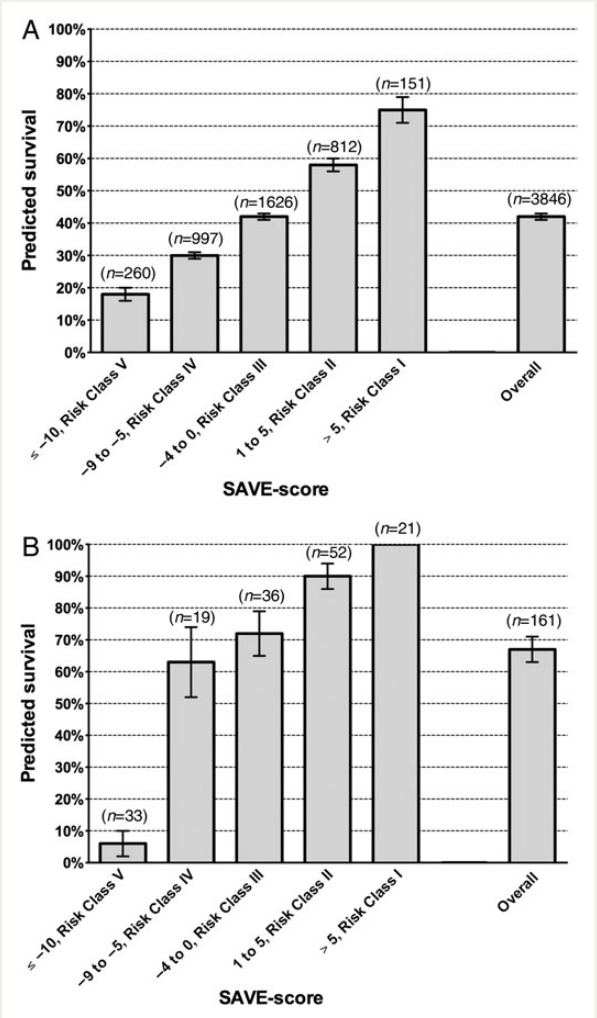


Figure 2 (*A*) Hospital survival percentage in derivation cohort according to the survival after veno-arterial-extracorporeal membrane oxygenation-score at extracorporeal membrane oxygenation initiation for severe cardiogenic shock. (*B*) Hospital survival percentage in the validation cohort according to the survival after veno-arterial-extracorporeal membrane oxygenation-score. Survival percentage is expressed as mean ± standard deviation. *N* = number of patients in the study who had particular survival after veno-arterial-extracorporeal membrane oxygenation-score values.

Derivation and validation of the survival after veno-arterial-extracorporeal membrane oxygenation-score

Survival prediction models have recently been developed to help clinicians in their decision-making processes for ECMO for respiratory indications.[13] In the field of the cardiac operative risk evaluation, the EuroSCORE[34,35] and the Parsonnet score[36] are both widely implemented. Surprisingly, the SAVE-score is the first reported in-hospital survival prediction model for ECMO use in cardiogenic shock. The score has been created in such a way (where 'zero' equates to a 50/50 chance of survival) to provide clinicians with an

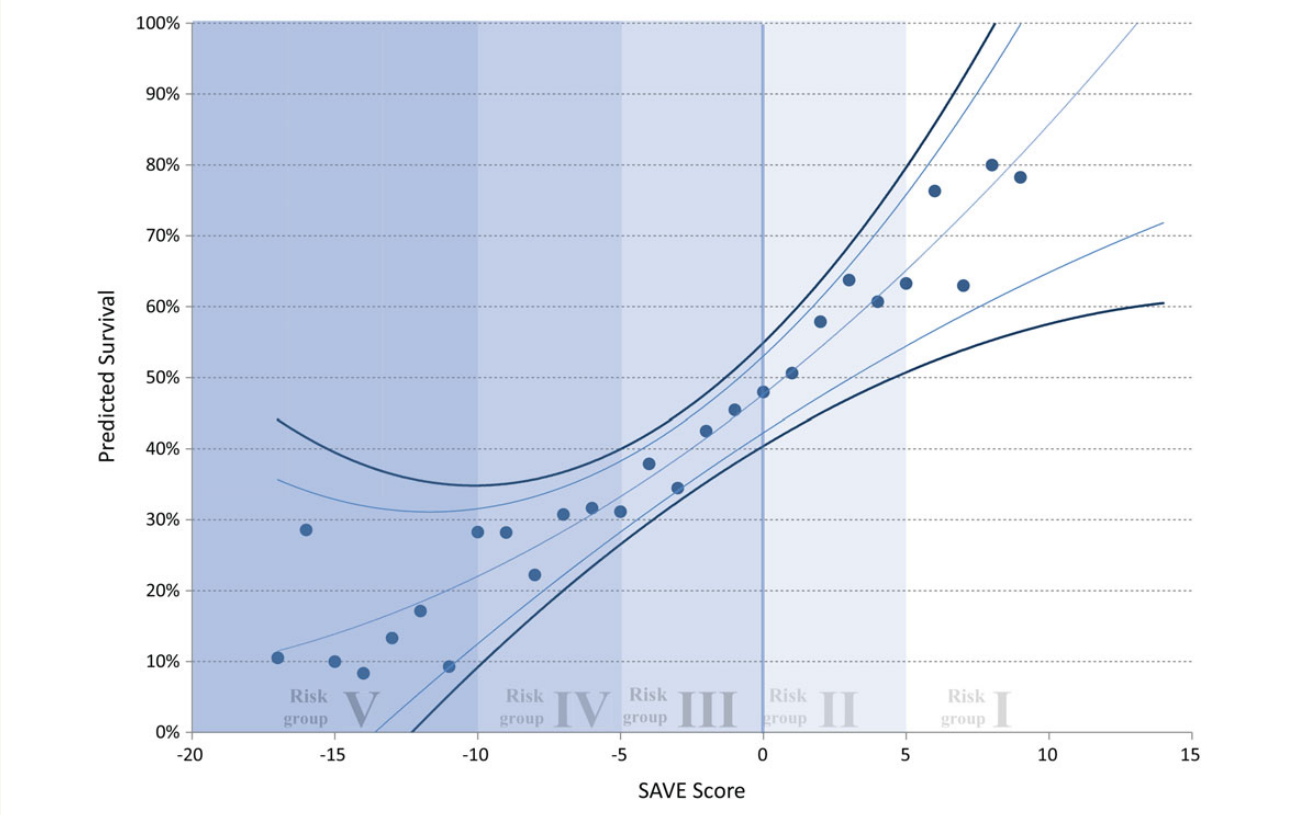
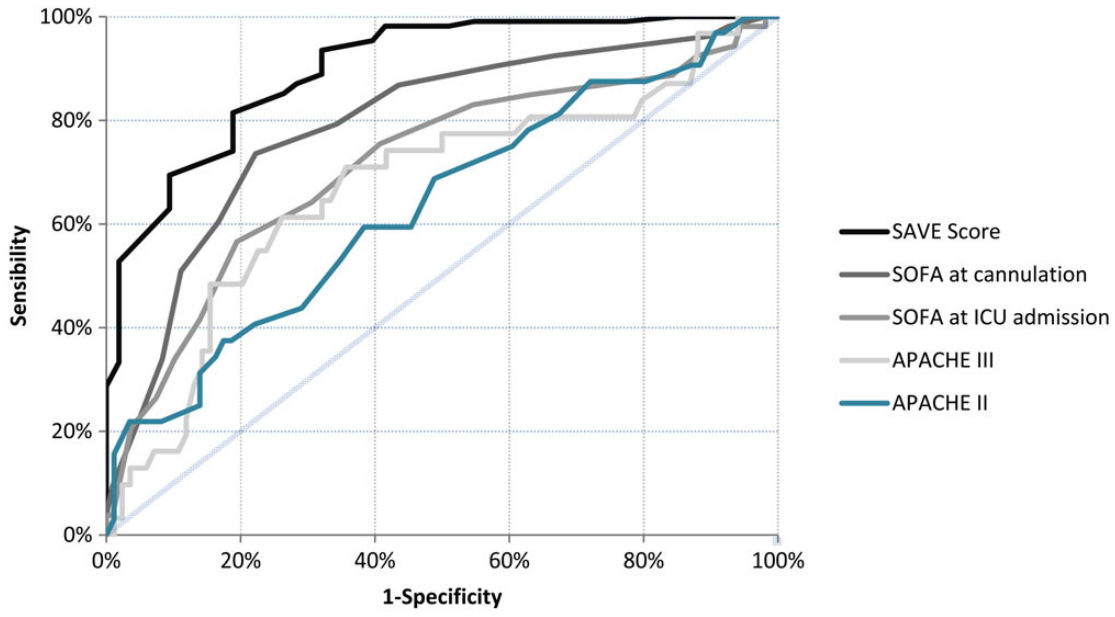


Figure 3 Individual observed survival regarding the survival after veno-arterial-extracorporeal membrane oxygenation-score within 95% confidence interval. Each dot represents the observed survival proportion at each score value in the study population ($n = 3846$) used to derive the survival after veno-arterial-extracorporeal membrane oxygenation-score. Curved black lines represent 95 and 99% confidence intervals for predicted survival at each score level.

Table 5 Hospital survival rate in the most prevalent diagnostic groups (acute myocardial infarction, valvular heart disease, other causes of cardiogenic shock and sepsis) and in diagnostic groups independently related to survival (myocarditis, heart and lung transplants, refractory ventricular tachycardia/ventricular fibrillation, cardiac arrest prior to extracorporeal membrane oxygenation, and congenital heart disease) according to the survival after veno-arterial-extracorporeal membrane oxygenation-score risk category at extracorporeal membrane oxygenation initiation

Risk category	V	IV	III	II	I	All patients
SAVE-score	(≤ −10)	(−9 to −5)	(−4 to 0)	(1–5)	(>5)	
Myocarditis	100% (1/1)	29% (4/14)	47% (27/57)	61% (68/111)	76% (45/59)	60% (145/242)
Heart and Lung transplants	25% (1/4)	24% (6/25)	43% (34/79)	61% (43/71)	76% (28/37)	52% (112/216)
Refractory VT/VF	24% (9/37)	29% (32/109)	42% (84/202)	58% (68/118)	72% (18/25)	43% (211/491)
Acute myocardial infarction	19% (20/107)	31% (108/353)	43% (201/471)	61% (100/163)	73% (8/11)	40% (437/1105)
Other causes of cardiogenic shock	17% (14/81)	28% (84/297)	44% (190/431)	57% (95/168)	94% (16/17)	40% (399/994)
Valvular heart disease	16% (9/58)	35% (59/167)	36% (95/266)	57% (73/128)	59% (10/17)	39% (246/636)
Cardiac arrest prior to ECMO	15% (20/130)	31% (131/428)	41% (201/495)	53% (88/165)	73% (16/22)	37% (456/1240)
Sepsis	26% (8/31)	24% (23/95)	39% (51/130)	55% (30/55)	67% (4/6)	37% (116/317)
Congenital heart disease	21% (7/33)	27% (29/109)	31% (37/121)	55% (27/49)	67% (2/3)	32% (102/315)

Diagnoses not mutually exclusive.
VT, ventricular tachycardia; VF, ventricular fibrillation; ECMO, extra-corporeal membrane oxygenation.



Score	*c* (95% CI)	HLC-statistic	HLC-*p* value
SAVE-score	0.90 (0.85-0.95)	14.0	0.082
SOFA at cannulation	0.79 (0.72-0.87)	4.9	0.67
SOFA at ICU admission	0.71 (0.62-0.80)	8.0	0.43
APACHE II	0.58 (0.48-0.68)	11.7	0.19
APACHE III	0.59 (0.48-0.69)	14.7	0.07

Figure 4 Graphic representation of the survival after veno-arterial-extracorporeal membrane oxygenation-score, the SAPS II and the sepsis-related organ failure assessment performances in the validation cohort ($n = 161$). Model discrimination and calibration were assessed using the area under the receiver operating characteristics curve (i.e. *c*) and the Hosmer-Lemeshow C-statistic with associated *P*-value, respectively.

easy reference point to calibrate their own expectation of patient outcome. However, the SAVE-score will require further validation and investigation by other centres and in a wider ECMO population (*Table 3*). Although, its area under the ROC curve was only 0.68 in the derivation cohort, the performance of the SAVE-score in the 'external' validation cohort was unexpectedly high ($c = 0.90$). Several points may explain this. Validation was performed on a single-center population which uses a consistent, protocolized approach to the care of patients receiving ECMO and, despite a higher proportion of patients with other organ failures and cardiac arrest prior to cannulation, exhibited a greater hospital survival (67 vs. 42%, respectively, *Figure 1*). The greater area under the ROC curve in this group may be a direct artefact of the higher survival rate, and result from a smaller proportion of middle and high scores now being associated with death. In addition, there was a marked difference in the distribution of diagnoses leading to ECMO between the validation and the derivation cohort which may have influenced the SAVE-score performance. For instance, the main risk factor for cardiogenic shock was post-transplant support in the derivation cohort while it was one of less frequent in the derivation cohort (*Table 1*). Extracorporeal membrane oxygenation management, especially for refractory cardiogenic shock, is a bundle of associated measures such as mechanical ventilation and anticoagulation management, cardiac surgery, and its associated complication, mobilization, and end-of-life decision-making. The processes associated with 'how do you do ECMO' are mostly center specific and important discrepancies have already been reported[37,38] which may impact on the outcome.[39] This large international cohort, mixing high and low ECMO volume centres from 280 countries, probably represents considerable heterogeneity in the management of these patients. Unfortunately, removal of site

location was a requirement for release of the data so the relative contribution of the origin of the ECMO sites, as well as their ECMO case volume could not be assessed. Nevertheless, our homogeneous validation cohort might overcome this limitation because all patients received similar ECMO management. The Alfred Hospital in Melbourne has contributed to the ELSO registry since late 2008. Thus there is likely to be overlap with some patients represented in both the derivation and the validation cohorts. This undoubtedly limits the accuracy and the robustness of this 'external' validation. These patients could not be identified or excluded from the derivation process due to de-identified nature of data provided by ELSO. Consequently, the performance of the SAVE-score in the validation cohort from The Alfred Hospital should be viewed with caution and further external validation is needed. However, the SAVE-score performed better than several standard ICU severity scores. The poor performance of the APACHE score as well as the greater performance of the SOFA score to predict hospital survival in this population were consistent with previous study.[40]

Limitations

In addition to the specific limitations relative to the validation of the SAVE-score, interpretation and use of such score should be tempered by several considerations. The SAVE-score reflects data currently available in the ELSO registry and we cannot rule out that additional data may have enhanced the accuracy of our model. For instance, myocardial biomarkers such as serum butyrylcholinesterase or troponin, which have been proposed for risk stratification in patients undergoing ECMO support, were not included in our survival predictive model.[2,41] Because the score is retrospective, it looks at variables collected around the time of ECMO implementation, which may not perfectly correspond with medical decision-making in real-time. Although survival rates by SAVE risk class were similar before and after 2010, we cannot assess the impact of other changes in the management of cardiogenic shock during the whole period. Information on whether ECMO cannulation was performed centrally or peripherally was also not available. Complete physiological data were available for only 23% (876/3846) patients in the ELSO dataset. The effect of missing data on the development of the score cannot be fully assessed. Since patients who received ECMO during CPR were not included the data used to develop the SAVE-score, the applicability of the SAVE-score to these patients remains unknown. Finally, it is worth remembering that the SAVE-score has been developed on patients already receiving ECMO. It has not been validated for prediction of survival in a more general population of cardiogenic shock patients where ECMO has not yet been instituted. The objectives of the SAVE-score can be summarized as: (i) offering population management information; (ii) facilitating risk adjusted comparison of outcomes between institutions, regions, and time periods; and (iii) offering moderate improvements in objective prognostication. The score does not remove the inherent uncertainty that is part of critical illness and the authors do not recommend its application to determine individual patient management or decide on futility (particularly given that even at the extreme scores ($\leq$10), survival was still 18%).

In conclusion, the overall hospital survival of 3846 cardiogenic shock patients, extracted from an international cohort over a 13-year period, was only 42%. Age, weight, chronic renal failure, time with mechanical ventilation before initiation of ECMO, extracardiac organ failures, cardiac arrest, congenital heart disease, cause of the cardiogenic shock, haemodynamic data, serum bicarbonate value, and peak inspiratory pressure were identified as pre-ECMO prognosis factors of in-hospital survival. Based on these findings, the SAVE-score is a potential tool to predict in-hospital survival for patients receiving ECMO for refractory cardiogenic shock. Further, large prospective studies aiming to include patients not placed on ECMO and to evaluate the performance of the SAVE-score are now warranted.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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