



Original Article

Predicting Survival After VA-ECMO for Refractory Cardiogenic Shock: Validating the SAVE Score

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ABSTRACT

Background: Venous-arterial extracorporeal membrane oxygenation (VA-ECMO) is used increasingly to support patients who are in cardiogenic shock. Due to the risk of complications, prediction models may aid in identifying patients who would benefit most from VA-ECMO. One such model is the Survival After Venous-Arterial Extracorporeal Membrane Oxygenation (SAVE) score. Therefore, we wanted to validate the utility of the SAVE score in a contemporary cohort of adult patients.

Methods: Retrospective data were extracted from electronic health records of 120 patients with cardiogenic shock supported with VA-ECMO between 2011 and 2018. The SAVE score was calculated for

RÉSUMÉ

Contexte : L'oxygénation extracorporelle veino-artérielle (ECMO-VA) est de plus en plus utilisée comme assistance pour les patients qui sont en choc cardiogène. En raison du risque de complications, des modèles de prédiction peuvent aider à déterminer quels patients bénéficieraient le plus d'une ECMO-VA. Le score SAVE (*Survival After Venous-Arterial Extracorporeal Membrane Oxygenation*) est un modèle de ce genre. Par conséquent, nous voulions valider l'utilité du score SAVE dans une cohorte contemporaine de patients adultes.

Méthodologie : Des données rétrospectives ont été extraites de dossiers médicaux électroniques de 120 patients atteints d'un choc cardiogène

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an increasingly common strategy to support patients who have refractory cardiogenic shock (rCS).¹ It creates a parallel venous-arterial circulation that bypasses the heart and lungs, maintaining organ perfusion and serving as a temporary bridge to myocardial recovery, transplantation, or durable mechanical circulatory support.¹⁻³ Use of VA-ECMO in

adults with acute and chronic cardiac failure has expanded rapidly in the past decade.⁴ In fact, the annual rate of ECMO cases per million adult discharges in the United States increased from 375 to more than 2000 between 2006 and 2011.⁵ Up to July 2019, data from the Extracorporeal Life Support Organization (ELSO) registry indicates that more than 22,000 adult cardiac VA-ECMO cases have been initiated, an exponential increase since 1990.⁶

Despite advances in ECMO management and improvement of survival in patients receiving VA-ECMO, complications from this rescue therapy remain a concern.⁷ These include bleeding, stroke, infection, and vascular access complications.⁷ Uncertain long-term outcomes and unknown cost effectiveness, particularly in the context of limited health care resources, are also important considerations.⁸ It is therefore vital to allocate this high-risk intervention to patients who are most likely to benefit.⁹

The Survival After Venous-Arterial Extracorporeal Membrane Oxygenation (SAVE) score is the first reported model

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Ethics Statement: This study was conducted and adhered to guidelines laid out by our institutional Research Ethics Board at the University Health Network.

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See page 80 for disclosure information.

each patient to predict survival to hospital discharge. We assessed the SAVE score calibration by comparing predicted vs observed survival at discharge. We assessed discrimination with the area under the receiver operating curve using logistic regression.

Results: A total of 45% of patients survived to hospital discharge. Survivors had a significantly higher mean SAVE score (-9.3 ± 4.1 in survivors vs -13.1 ± 4.4 , respectively; $P = 0.001$). SAVE score discrimination was adequate ($c = 0.77$; 95% confidence interval 0.69-0.86; $P < 0.001$). SAVE score calibration was limited, as observed survival rates for risk classes II-V were higher in our cohort (II: 67% vs 58%; III: 78% vs 42%; IV: 61% vs 30%; and V: 29% vs 18%).

Conclusions: The SAVE score underestimates survival in a contemporary North American cohort of adult patients with cardiogenic shock. Its inaccurate performance could lead to denying ECMO support to patients deemed to be too high risk. Further studies are needed to validate additional predictive models for patients requiring VA-ECMO.

for predicting survival to hospital discharge in adults with rCS supported with VA-ECMO.¹⁰⁻¹² The SAVE score is comprised of 12 variables, each one accounted for prior to and/or at the time of ECMO cannulation. Scores range from -35 to 17 , and they are divided into 5 risk classes. A SAVE score of zero is approximately equivalent to 50% survival.

Although previously validated in an Australian cohort with excellent discrimination ($c = 0.90$ [95% confidence interval {CI} 0.85-0.95]),¹⁰ to our knowledge, there is only one published study to date validating the utility of the SAVE score as a predictive tool in a North American cohort.¹³ We therefore sought to evaluate the performance of the SAVE score in a contemporary cohort of adult patients with rCS at a high-volume (> 30 VA-ECMO cases per year), tertiary academic centre in North America.

Materials and Methods

Patient population

We identified consecutive adult patients (aged ≥ 18 years) supported with VA-ECMO for rCS between January 2011 and July 2018 at our institution (Toronto General Hospital, Toronto, Canada). We included patients placed on hybrid ECMO configurations (venous-venous-arterial/venous-arterial-venous) for primary cardiac indications. All eligible patients were included regardless of whether they underwent central or peripheral cannulation and what primary institution initially performed cannulation. Patients placed on veno-venous (VV)-ECMO were excluded, as were patients with respiratory failure as their primary diagnosis. In patients who received more than one ECMO run, only data from the first ECMO run were analyzed.

Clinical variables

We extracted patient data retrospectively from the electronic health record. These data encompassed the 12 variables

ayant reçu une ECMO-VA entre 2011 et 2018. Le score SAVE a été calculé pour chaque patient afin de prédire la survie au congé de l'hôpital. Nous avons évalué la calibration du score SAVE en comparant la survie prédite au moment du congé et la survie observée. Nous avons évalué la discrimination par l'aire sous la courbe opérationnelle chez le receveur en faisant appel à la régression logistique.

Résultats : Au total, 45 % des patients ont survécu au congé de l'hôpital. Les survivants affichaient un score SAVE moyen considérablement plus élevé ($-9,3 \pm 4,1$ chez les survivants vs $-13,1 \pm 4,4$; $p = 0,001$). La discrimination par le score SAVE était adéquate ($c = 0,77$; intervalle de confiance à 95 % : 0,69 à 0,86; $p < 0,001$). La calibration du score SAVE était limitée, car les taux pour les classes de risque II à V étaient plus élevés dans notre cohorte (II : 67 % vs 58 %; III : 78 % vs 42 %; IV : 61 % vs 30 %; et V : 29 % vs 18 %).

Conclusions : Le score SAVE sous-estime la survie dans une cohorte nord-américaine contemporaine de patients adultes atteints d'un choc cardiogène. L'inexactitude de ses résultats pourrait faire en sorte qu'une assistance par ECMO serait refusée à des patients jugés comme présentant un risque élevé. D'autres études sont nécessaires pour valider d'autres modèles de prédiction pour les patients ayant besoin d'une ECMO-VA.

needed to calculate the corresponding SAVE score, each accounted for prior to and/or at the time of ECMO cannulation. Definitions for all variables were kept consistent with the original derivation model.¹⁰ Etiologies for rCS were not mutually exclusive, and they included congenital heart disease, myocarditis, refractory ventricular tachycardia or ventricular fibrillation, post-heart or lung transplantation, and other diagnoses (valvular heart disease, acute myocardial infarction, sepsis, etc). For extra-cardiac organ failures, acute renal failure was defined as creatinine $> 133 \mu\text{mol/L}$, with or without renal replacement therapy. Chronic renal failure was defined as kidney damage or a glomerular filtration rate $< 60 \text{ mL/min per } 1.73 \text{ m}^2$ for ≥ 3 months. Liver failure was defined as total bilirubin $\geq 33 \mu\text{mol/L}$, or serum aminotransferases (aspartate transaminase or alanine aminotransferase) $> 70 \text{ UI/L}$ at ECMO cannulation. Central nervous system dysfunction was defined as neurotrauma, stroke, encephalopathy, cerebral embolism, seizure, and/or epileptic syndromes. Respiratory failure included mixed chronic or acute pulmonary disorders, such as chronic obstructive pulmonary disease, pneumonia, severe hypoxemia, and/or pneumothorax. The lowest serum bicarbonate value within 6 hours of cannulation was used.

One additional variable we collected, beyond those required to calculate the SAVE score, was whether a patient required pre-ECMO cardiopulmonary resuscitation (CPR). If so, we recorded whether they received conventional CPR or extracorporeal CPR (ECPR). We defined conventional CPR through return of spontaneous circulation (ROSC) prior to ECMO cannulation. We defined ECPR through the absence of ROSC prior to ECMO cannulation.

Patients with missing variables were excluded from analysis if the missing data precluded the ability to compute a SAVE score calculation. No quantitative data were estimated or imputed. For example, if pre-ECMO aspartate transaminase or alanine aminotransferase values were not available, but if bilirubin was found to be in the range of liver failure as defined by the SAVE score, then patients were marked to have pre-ECMO liver failure. If, however, no laboratory markers of liver function

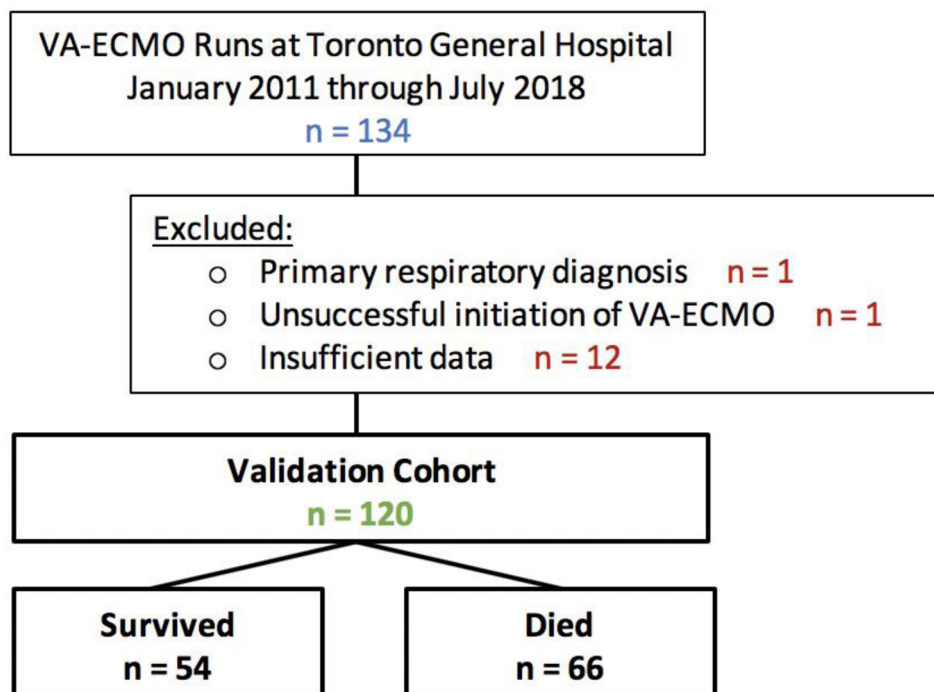


Figure 1. Study flow diagram. VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

were available prior to ECMO cannulation, then the patient was excluded from analysis. Assumptions were also made for 2 qualitative, binary variables in cases in which real-time physiologic data were not available. In cases in which patients suffered pre-ECMO cardiac arrest within 6 hours of cannulation, we assumed that diastolic blood pressure did not remain > 40 mm Hg, and that pulse pressure did not remain \geq 20 mm Hg prior to ECMO cannulation.

Outcomes

Two reviewers (F.A. and J.L.) independently calculated the SAVE score for each patient. Any discrepancies between the 2 reviewers were resolved by discussion. All SAVE scores were calculated by inputting the individual SAVE score variables into the online calculator available at <http://www.save-score.com>. The primary outcome was survival to hospital discharge. Patients that were repatriated to their original institutions were included as survivors. Patients that died at our hospital were deemed nonsurvivors.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation, or median and interquartile range (IQR), as appropriate. Student's *t* test or the Mann-Whitney *U* test were used for unpaired comparison between patients who did and did not survive post-ECMO. Categorical variables are presented as frequency or percentage, and they were compared by χ^2 or Fisher's exact test. The SAVE score survival rates were compared between the 5 previously defined SAVE score risk categories (class I [score \geq 5], II [1 to 5], III [-4 to 0], IV [-9 to -5] and V [\leq -10]).¹² Univariable logistic regression analysis was used to assess the value of the SAVE score in

predicting survival to hospital discharge or transfer post-ECMO, with results presented as the odds ratio and 95% confidence interval (OR [95% CI]).

Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. A receiver operating characteristic (ROC) curve was constructed to evaluate the SAVE score as a discriminator of survival post-ECMO. Additionally, a calibration curve was used to compare the observed SAVE score survival probabilities to the originally published predicted survival probabilities in quintile bins.¹² As the logistic regression equation of the original SAVE score survival curve could not be obtained, the predicted probabilities for each SAVE score were visually estimated from the published logistic regression curve using digital calipers. Predicted probabilities for SAVE score values below -17 (ie those beyond the negative terminus of the published curve) were estimated by linearly interpolating the negative end of the curve. All statistical analyses were performed using MATLAB (version 8.0, MathWorks, Natick, MA) or SPSS (version 20.0, SPSS Inc., Cary, NC). A 2-sided *P* < 0.05 was considered statistically significant.

Results

Population

A total of 134 patients requiring VA-ECMO for rCS were identified (Fig. 1). One patient was excluded due to a primary diagnosis of noncardiac respiratory failure. One patient was excluded due to failed cannulation. Finally, 12 patients were excluded from the final cohort due to insufficient data in their electronic health record to calculate their SAVE score. In all, 120 patients were ultimately retained as the validation cohort

Table 1. Patient characteristics

Characteristic	TGH Validation cohort	SAVE score Derivation cohort
Total N	120	3846
Age (Y)	49 (38-57)	54 (39-64)
Males	74 (62)	2548 (67)
Weight (Kg)	78 ± 20	79 ± 21
Diagnoses associated with cardiogenic shock*		
Chronic heart failure of other causes	39 (33)	1272 (33)
Post-cardiotomy	28 (23)	157 (4)
Refractory VT/VF	26 (22)	491 (13)
PGD post-heart transplantation	19 (16)	216 (6)
Acute myocardial infarction	19 (16)	1105 (29)
Myocarditis	15 (13)	242 (6)
Congenital heart disease	11 (9)	315 (8)
Valvular heart disease	10 (8)	636 (17)
Sepsis	4 (3)	317 (8)
Pulmonary embolism	3 (3)	151 (4)
Chronic renal failure†	17 (14)	112 (3)
Pre-ECMO cardiac arrest	55 (46)	1240 (32)
ECPR	26 (22)	—
Pre-ECMO diastolic blood pressure > -40 mm hg‡	23 (19)	—
Pre-ECMO pulse pressure ≤ -20 mm hg‡	90 (75)	—
Pre-ECMO intubation (h)	111 (93)	—
≤ 10	60 (54)	—
11-29	35 (32)	—
≥ 30	16 (14)	—
PIP ≤ 20 cmH ₂ O	27 (23)	—
ACUTE pre-ECMO organ failures		
Renal failure§	77 (64)	-529 (14)
Liver failure	89 (74)	178 (5)
Cns dysfunction¶	30 (25)	219 (6)
pre-ECMO laboratory values		
CR (mmol/L)	148 (99-198)	—
AST (UI/L)	208 (43-878)	—
ALT (UI/L)	141 (38-884)	—
TBILI (mmol/L)	25 (14-39)	—
HCO ₃ ⁻ (mmol/L)	16 ± 4.5	19.7 ± 6.3

Data are given as n (%), mean ± standard deviation, or median (quartile 1-quartile 3).

ALT, alanine aminotransferase; AST, aspartate transaminase; CNS, central nervous system; Cr, creatinine; CRF, chronic renal failure; ECMO, extracorporeal membrane oxygenation; ECPR, cardiopulmonary resuscitation; PGD, primary graft dysfunction; PIP, peak inspiratory pressure; rCS, refractory cardiogenic shock; SAVE, Survival After Venous-Arterial Extracorporeal Membrane Oxygenation; TGH, Toronto General Hospital; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Patients could fall into more than one category with respect to their rCS diagnoses.

† CRF defined as kidney damage or glomerular filtration rate < 60 mL/min per 1.73 m² for ≥ 3 months.

‡ Worst value within 6 hours prior to cannulation.

§ Acute renal failure defined as creatinine > 133 µmol/L with or without renal replacement therapy.

|| Acute liver failure defined as total bilirubin ≥ 33 µmol/L or serum aminotransferases (ALT or AST) > 70 UI/L at ECMO cannulation.

¶ Acute CNS dysfunction defined as neurotrauma, stroke, encephalopathy (confusion/decreased level of consciousness), cerebral embolism, seizure, and/or epileptic syndromes.

(Table 1; Fig. 1). Complete physiologic data were available for 93% (112 of 120), and complete SAVE score data were available for 98% (118 of 120). The primary etiologies of rCS were chronic heart failure (> 6 months), post-cardiotomy shock, refractory ventricular arrhythmias, and primary graft dysfunction after heart transplantation (Table 1). A total of 55 (46%) patients suffered a cardiac arrest prior to ECMO initiation. Of these, 26 (22%) patients received ECPR, defined as cannulation during CPR prior to ROSC. Most patients had evidence of extra-cardiac organ hypoperfusion prior to ECMO initiation (acute renal failure [64%], acute liver failure [74%], and central nervous system dysfunction [25%]).

Survival outcomes

Fifty-four (45%) patients in our cohort survived to hospital discharge and/or transfer after VA-ECMO. This compares to the 42% overall survival rate in the original SAVE score derivation cohort. The median (interquartile range) SAVE score was -10.0 (-13 to -6), and was greater among survivors than those who died (-7 [-10.0 to -3.0] vs -12.0 [-16.0 to -10.0]; *P* < 0.001; Fig. 2). In logistic regression analysis, the absolute SAVE score was significantly associated with in-hospital survival (OR [95% CI]: 1.20 [1.11-1.30]; *P* < 0.001). The Hosmer-Lemeshow test demonstrated

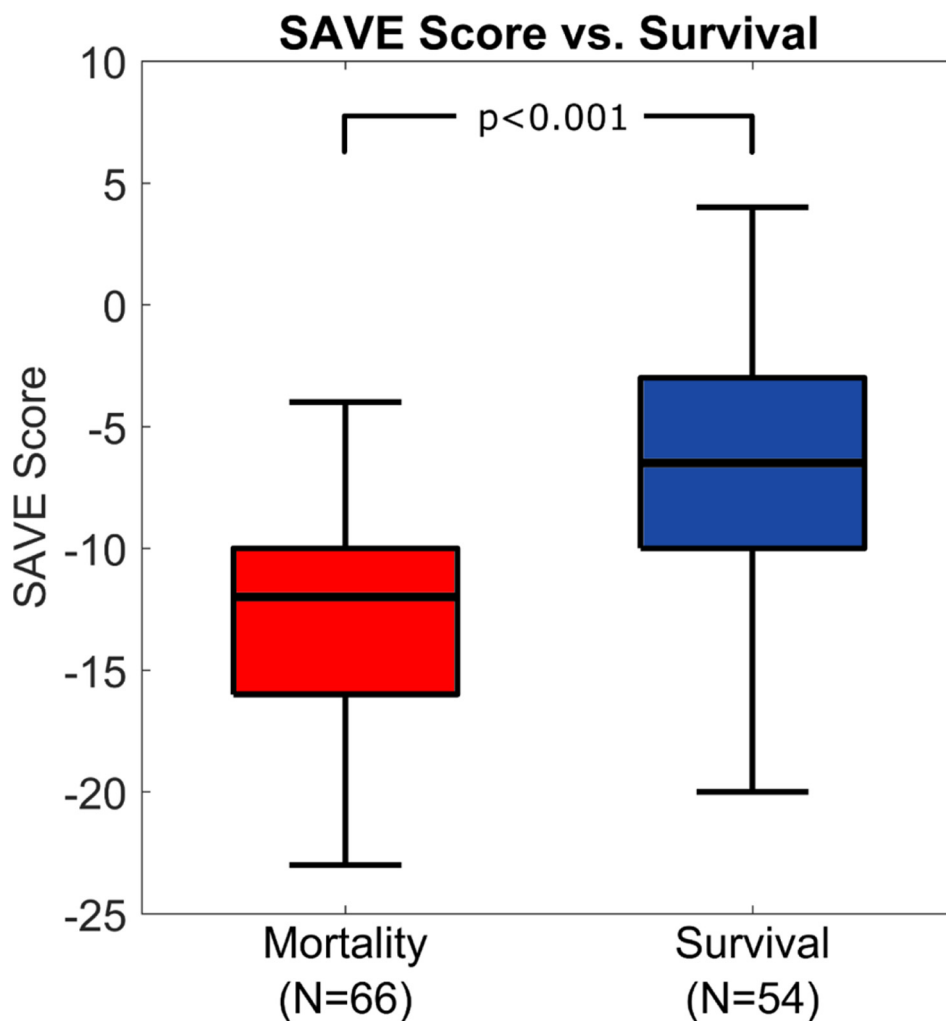


Figure 2. Median Survival After Veno-Arterial Extracorporeal Membrane Oxygenation (SAVE) score in survivors vs those who died. Median (inter-quartile range) values: -7 (-10 to -3) in survivors vs -12 (-16 to -10) in those who died ($P < 0.001$). Median SAVE score of the entire study population: -10.0 (-13 to -6).

adequate model calibration ($\chi^2 = 10.7$, $P = 0.22$), whereas the area under the ROC curve revealed fair discrimination for survival by the SAVE score ($c = 0.77$ [95% CI 0.69-0.86], $P < 0.001$; Fig. 3). However, the calibration curve revealed that the SAVE score consistently underestimated survival probability in our cohort (Fig. 4A). This bias was particularly apparent for patients with SAVE scores > -12 (ie, patients with predicted survival probabilities $> 18.4\%$ based on the original cohort). The observed survival rates for the established SAVE score risk classes II-V were also higher in our cohort than those of the original SAVE score derivation cohort (II: 67 vs 58%; III: 78 vs 42%; IV: 61 vs 30%; and V: 29 vs 18%; Table 3). We had no SAVE Class I patients in our cohort for comparison.

Outcomes based on etiology of cardiogenic shock

We examined survival based on the underlying etiology of rCS according to the pre-specified categories in the SAVE score calculator. Patients with cardiac failure due to common causes (acute myocardial infarction, idiopathic dilated cardiomyopathy, sarcoidosis, toxin-induced cardiomyopathy, and

others) had the highest survival rate at 62%. Patients with acute myocarditis also had comparably favorable outcomes on VA-ECMO, with a survival rate of 60%. Patients requiring VA-ECMO for post-cardiotomy shock and sepsis had the lowest survival likelihood (29% and 0%, respectively). Patients who survived, compared with those who died, were younger (43 [30-56] vs 52 [44-62] years, respectively; $P = 0.004$), more often maintained a pre-ECMO diastolic blood pressure > 40 mm Hg (15 [28%] vs 8 [12%]; $P = 0.03$), and less often experienced pre-ECMO acute renal failure (27 [50%] vs 50 [76%]; $P = 0.003$; Table 2).

Pre-ECMO cardiac arrest and ECPR

In our cohort, 55 (46%) patients experienced pre-ECMO cardiac arrest. Twenty-six (47%) of these patients survived to hospital discharge or transfer. Survivors had a significantly higher mean SAVE score compared to those who died (-9.3 ± 4.1 vs -13.1 ± 4.4 ; $P = 0.001$; Table 4). Among the 55 patients who experienced pre-ECMO cardiac arrest, 23 (22% of the total cohort, 42% of the cardiac arrest cohort) received ECPR. There was no difference observed in the SAVE scores

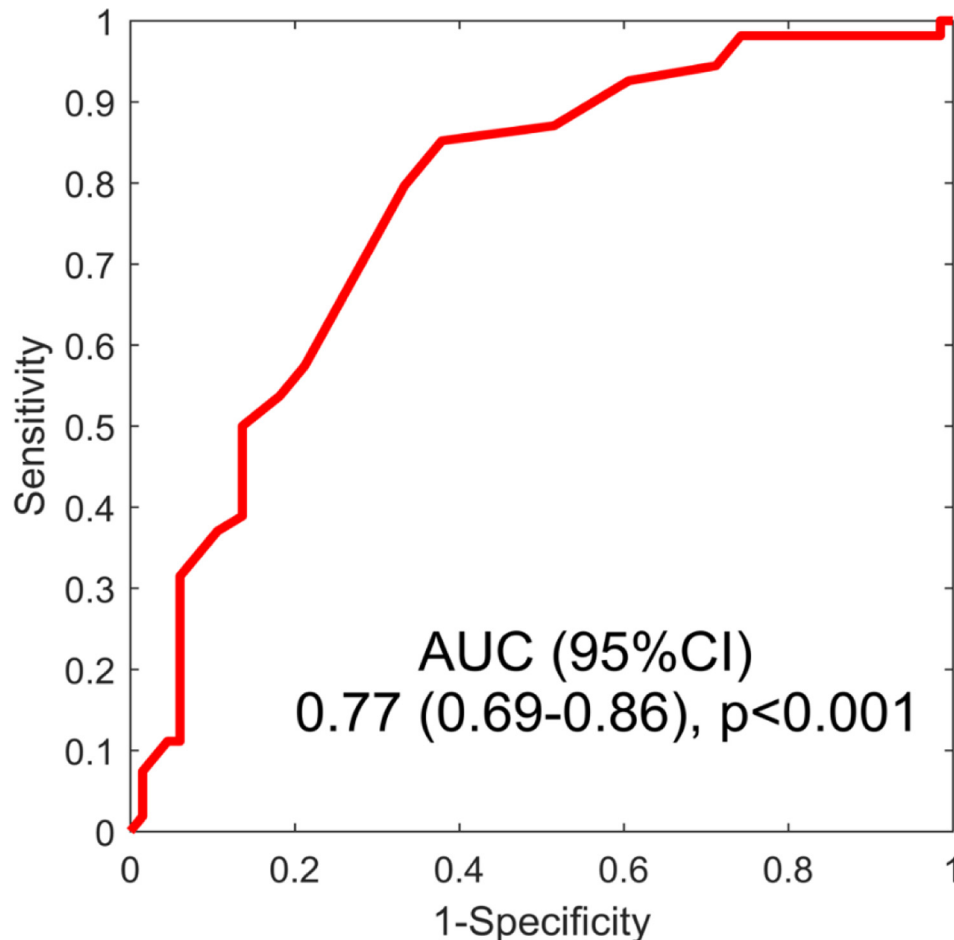


Figure 3. Receiver operating characteristic curve for Survival After Veno-Arterial Extracorporeal Membrane Oxygenation (SAVE) score prediction of survival. Area under the curve (AUC) (95% confidence interval [CI]): 0.77 (0.69-0.86), $P < 0.001$.

of ECPR patients who did vs did not survive (-10.2 ± 4.0 vs -12.8 ± 5.2 ; $P = 0.198$). Among the 32 patients who received conventional CPR, SAVE scores were significantly higher in survivors than nonsurvivors (-8.7 ± 4.2 vs -13.4 ± 4.0 ; $P = 0.003$; Table 4). Comparing ECPR vs conventional CPR, there was no significant difference in survival between patients with pre-ECMO cardiac arrest that received ECPR (11 of 23, or 48%) vs those that did not receive ECPR (15 of 32, or 47%; $P = 0.944$).

It is important to note that the SAVE score was not validated in patients receiving ECPR. When excluding patients who received ECPR ($n = 94$), the absolute SAVE score remained significantly associated with in-hospital survival (OR 1.23 [1.12-1.36]; $P < 0.001$). Calibration also remained adequate ($\chi^2 = 7.0$, $P = 0.54$), whereas the area under the ROC curve revealed good discrimination for survival ($c = 0.80$ [95% CI 0.71-0.89], $P < 0.001$). In addition, the calibration curve remained similar in underestimating the survival probability in the non-ECPR cohort (Fig. 4B). Overall, there was no significant difference in the predictive ability of the SAVE score (Hanley and McNeil test: $P = 0.65$).

Discussion

In a cohort of 120 patients at a high-volume North American ECMO centre, we have demonstrated that the SAVE score predicts survival in patients requiring VA-ECMO for rCS, with fair discrimination. However, compared to the initial derivation cohort that included patients until 2013, the SAVE score performed more poorly in our contemporary population (area under ROC curve 0.90 vs 0.77, respectively).

Among the 12 SAVE score elements, only patient age, pre-ECMO diastolic blood pressure > 40 mm Hg, and pre-ECMO acute renal failure significantly differed between patients who survived and patients who died (Table 2). The SAVE score also consistently underestimated survival in our cohort of patients, particularly for those in the low- and moderate-risk categories. These findings were recently replicated in a smaller validation study at another North American ECMO centre, in which the SAVE score significantly underestimated survival in Risk Class IV patients (predicted survival 30% vs observed survival 67%, $P < 0.05$).¹³ In addition, we did not observe a clear trend, linear or otherwise, in survival between the separate risk classes based on SAVE score, suggesting that the SAVE score alone may not be

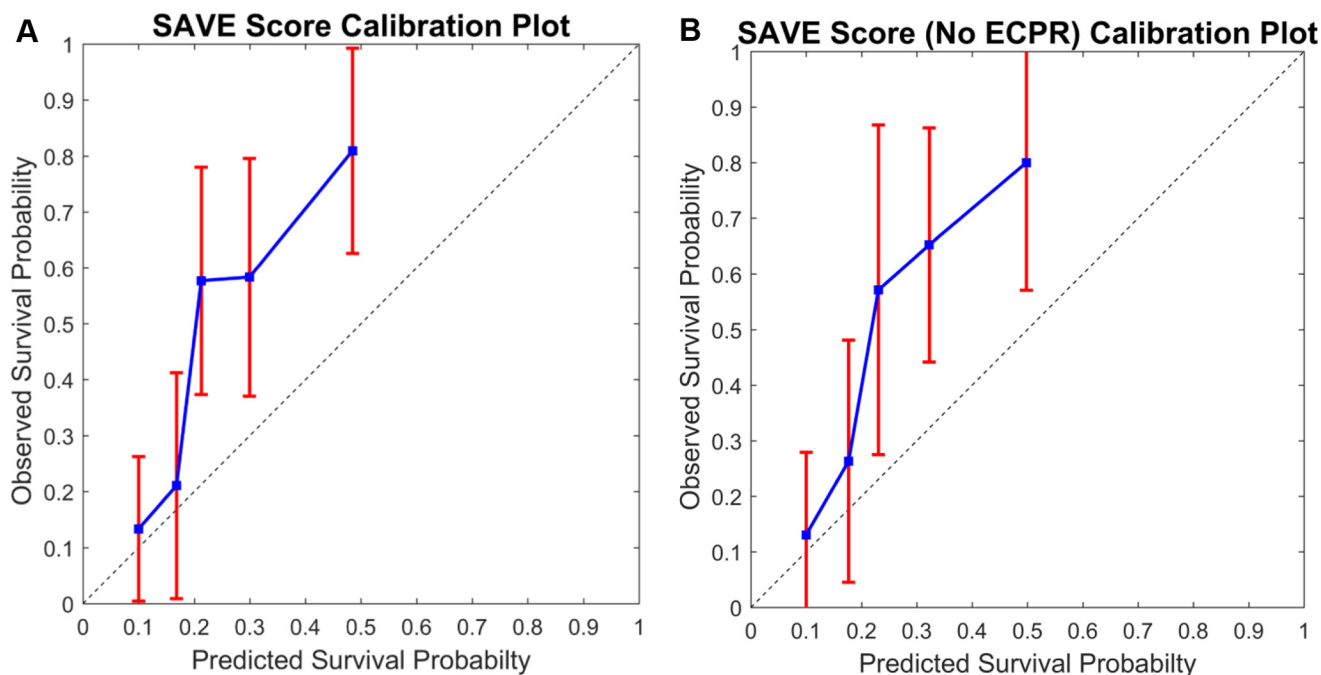


Figure 4. Calibration curve comparing the Survival After Venous-Arterial Extracorporeal Membrane Oxygenation (SAVE) score observed survival probabilities of our cohort to the predicted survival probabilities of the original model using quintile bins (A) including patients that received extracorporeal CPR (ECPR), and (B) excluding patients that received ECPR. The observed survival probability at each quintile is greater than the predicted survival probability. The dashed line represents the line of perfect calibration, whereas the red bars indicate the 95% confidence interval at each quintile.

sufficient in prognosticating patients with rCS when considering VA-ECMO.

One important reason for this may be that when the SAVE score was originally derived using the ELSO registry, complete physiologic data were available in only 23% of patients.¹⁰ Additionally, the ELSO registry comprises a large international cohort, mixing high- and low-volume ECMO centres. Important centre-specific discrepancies in VA-ECMO management that may impact survival outcomes have been reported, such as management of mechanical ventilation, anticoagulation, and weaning protocols.^{14,15} Additionally, Barbaro et al. have demonstrated a volume-outcome relationship in ECMO centres.¹⁶ Specifically, compared with adults receiving ECMO at low-volume (< 6 cases per year) centres, adult patients receiving ECMO at high-volume (>30 cases per year) centres had a significant reduction in mortality [adjusted OR 0.61; 95% CI 0.46-0.80].^{16,17} At our centre, we have performed more than 30 ECMO cases for several consecutive years, which may partly explain the better outcomes observed in our cohort than those predicted by the SAVE score. In addition, we employ a consistent, multidisciplinary team-based approach to patient selection, a process which has itself been shown to improve survival in patients with rCS.¹⁸

Another proposed limitation of the SAVE score is that its development stemmed from a patient cohort with a variety of cardiac diagnoses and VA-ECMO indications. The distribution in our patient cohort differed. The top 3 diagnoses associated with rCS in the SAVE score derivation cohort were chronic heart failure of other causes (idiopathic dilated

cardiomyopathy, sarcoidosis, toxin-induced cardiomyopathy), acute myocardial infarction, and valvular heart disease.¹⁰ The top 3 most common etiologies for rCS in our patient cohort were chronic heart failure of other causes (idiopathic dilated cardiomyopathy being the most common), post-cardiotomy shock, and refractory ventricular tachycardia/ventricular fibrillation. Importantly, primary graft dysfunction after cardiac transplantation comprised 16% of our total patient cohort, compared to 6% in the original SAVE score derivation cohort. VA-ECMO support for primary graft dysfunction is associated with better survival than most other etiologies of cardiogenic shock¹⁹ and may partly reflect an etiology-based interaction favoring better survival in our cohort. On the other hand, our patient cohort had a significantly higher prevalence of extra-cardiac end-organ hypoperfusion compared to the SAVE score derivation cohort (Table 1). Although one would expect a lower survival based on a more critically ill group of patients, our survival rates were better. This finding suggests that there may be other prognostic variables that need to be weighed, in addition to those suggested by the SAVE score.

Other prognostic predictive models for VA-ECMO have been proposed.²⁰⁻²² The ENCOURAGE (Prediction of Cardiogenic Shock Outcome for AMI Patients Salvaged by VA-ECMO) risk score performed well (area under the ROC curve 0.84 [95% CI 0.77-0.91]), but it was validated only in patients with cardiogenic shock secondary to acute myocardial infarction.²⁰ Similarly, the Predicting Mortality In Patients Undergoing Venous-Arterial Extracorporeal Membrane Oxygenation After Coronary Artery Bypass Grafting

Table 2. Survival rate according to SAVE score risk class

SAVE score risk class	TGH		SAVE score derivation cohort		
	Count	Survival rate (%)	Count	Observed survival rate (%)	Predicted survival rate (%)
I (> 5)	0	—	151	75	> 65
II (1 to 5)	9	67	812	58	48-65
III (-4 to 0)	19	78	1626	42	34-47
IV (-9 to -5)	23	61	997	30	23-33
V (\leq -10)	70	29	260	18	< 23

SAVE, Survival After Veno-Arterial Extracorporeal Membrane Oxygenation; TGH, Toronto General Hospital.

(REMEMBER) risk score was validated using 6 pragmatic clinical and biochemical variables (area under the ROC curve 0.85 [0.79-0.91]). This study included 106 patients restricted to those undergoing coronary artery bypass grafting.²¹

Recently, Wengenmayer et al.²² have validated a dynamic predictive model using point-of-care biomarkers (pH, lactate, serum bicarbonate) over 12 hours in a diverse group of patients requiring VA-ECMO support, including those receiving

Table 3. Patient characteristics in TGH validation cohort according to hospital outcome

Characteristic	Overall	Survived	Died	<i>P</i>
	120	54 (45)	66 (55)	
Age (Y)	49 (38-57)	43 (30-56)	52 (44-62)	0.004
Males	74 (62)	34 (63)	40 (33)	0.791
Weight (Kg)	77 (66-89)	77 (62-90)	77 (67-87)	0.723
Diagnoses associated with cardiogenic shock*				0.116
Chronic heart failure of other causes	39 (33)	24 (62)	15 (38)	
Post-cardiotomy	28 (23)	8 (29)	20 (71)	
Refractory VT/VF	26 (22)	12 (46)	14 (54)	
PGD post-heart transplantation	19 (16)	7 (37)	12 (63)	
Acute myocardial infarction	19 (16)	6 (32)	13 (68)	
Myocarditis	15 (13)	9 (60)	6 (40)	
Congenital heart disease	11 (9)	5 (45)	6 (55)	
Valvular heart disease	10 (8)	5 (50)	5 (50)	
Sepsis	4 (3)	0 (0)	4 (100)	
Pulmonary embolism	3 (3)	1 (33)	2 (67)	
Chronic renal failure†	17 (14)	4 (7)	13 (20)	0.055
Pre-ECMO cardiac arrest	55 (46)	26 (47)	29 (53)	0.645
ECPR	26 (22)	11 (20)	15 (23)	0.755
Pre-ECMO diastolic blood pressure > 40 mm hg‡	23 (19)	15 (28)	8 (12)	0.030
Pre-ECMO pulse pressure \leq 20 mm hg‡	90 (75)	40 (74)	50 (76)	0.832
Pre-ECMO intubation (h)	111 (93)	49 (91)	62 (94)	0.508
\leq 10	60 (54)	31 (63)	29 (47)	
11 to 29	35 (32)	14 (29)	21 (34)	0.135
\geq 30	16 (14)	4 (8)	12 (19)	
Pip \leq 20 cmH ₂ O	27 (23)	15 (28)	12 (18)	0.210
Acute pre-ECMO organ failures				
Renal failure§	77 (64)	27 (50)	50 (76)	0.003
Liver failure	89 (74)	37 (69)	52 (79)	0.201
CNS dysfunction¶	30 (25)	9 (17)	21 (32)	0.057
Pre-ECMO laboratory values				
CR (mmol/L)	148 (99-198)	131 (89-188)	152 (117-216)	0.084
AST (UI/L)	208 (43-878)	115 (33-468)	245 (78-1226)	0.205
ALT (UI/L)	141 (38-884)	126 (43-721)	159 (32-1059)	0.795
TBILI (mmol/L)	25 (14-39)	25 (14-32)	28 (17-46)	0.100
HCO ₃ ⁻ (mmol/L)	16 \pm 4	16 \pm 5	15 \pm 4	0.292

Data are given as n (%), mean \pm standard deviation, or median (quartile 1-quartile 3).

ALT, alanine aminotransferase; AST, aspartate transaminase; CNS, central nervous system; Cr, creatinine; CRF, chronic renal failure; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; PGD, primary graft dysfunction; PIP, rCS, refractory cardiogenic shock; SAVE, Survival After Veno-Arterial Extracorporeal Membrane Oxygenation; TGH, VF, ventricular fibrillation; VT, ventricular tachycardia.

* Patients could fall into more than one category with respect to their rCS diagnoses.

† CRF defined as kidney damage or glomerular filtration rate < 60 mL/min per 1.73 m² for \geq 3 months.

‡ Worst value within 6 hours prior to cannulation.

§ Acute renal failure defined as creatinine > 133 μ mol/L with or without renal replacement therapy.

|| Acute liver failure defined as total bilirubin \geq 33 μ mol/L or serum aminotransferases (ALT or AST) > 70 UI/L at ECMO cannulation.

¶ Acute CNS dysfunction defined as neurotrauma, stroke, encephalopathy, cerebral embolism, seizure, and/or epileptic syndromes.

Table 4. Survival data surrounding pre-ECMO cardiac arrest and ECPR

	Count	SAVE score	<i>P</i> [§]	P
Pre-ECMO cardiac arrest*	55 (46)	-11.3 ± 4.6	0.001	—
Survived [†]	26 (47)	-9.3 ± 4.1		
Died [†]	29 (53)	-13.1 ± 4.4		
ECPR [‡]	23 (42)	-11.5 ± 4.7	0.198	0.814
Survived [†]	11 (48)	-10.2 ± 4.0		
Died [†]	12 (52)	-12.8 ± 5.2		
NO ECPR [‡]	32 (58)	-11.2 ± 4.7	0.003	0.944 [¶]
Survived [†]	15 (47)	-8.7 ± 4.2		
Died [†]	17 (53)	-13.4 ± 4.0		

Data are given as n (%) and mean ± standard deviation.

ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; SAVE, Survival After Venous-Arterial Extracorporeal Membrane Oxygenation.

* Percentage displayed as percentage of entire study population (n = 120).

[†] Percentage displayed as percentage of total number of patients within that treatment category.

[‡] Percentage displayed as percentage of total pre-ECMO cardiac arrest patients (n = 55).

[§] *P* represents difference in SAVE scores between patients who died vs patients who survived.

^{||} Represents difference in SAVE scores between patients who received ECPR and patients who did not.

[¶] Represents difference in outcome between patients who received ECPR and patients who did not.

ECPR. A comparative study between published predictive models may shed more light on the most relevant prognostic variables in this population.

Pre-ECMO cardiac arrest, conventional CPR, and ECPR

In our cohort, 46% of patients experienced pre-ECMO cardiac arrest. All of these instances were in-hospital events. Among these patients, receiving ECPR did not manifest a difference in their chances of survival (Table 4). These results add to mixed data surrounding the use of ECPR. Although the original SAVE-score validation cohort did not include patients receiving ECPR, we did not find a significant interaction in the overall performance of the SAVE score when including or excluding these patients in our cohort. In a small study that assessed the survival benefits of ECPR compared to conventional CPR after a witnessed arrest, ECPR provided a significantly higher return of spontaneous circulation, and an approximately 20% increase in survival to discharge.²³ Other studies on ECPR have shown improved survival at 12 and 24 months after discharge compared to conventional CPR.^{21,22} Furthermore, a study by Zakhary et al.²⁴ found arrest-to-ECMO cannulation time to be one of the factors most strongly associated with mortality.

Survival rates for ECPR at our centre appear promising, although it was performed in a highly selected group of patients. However, due to the small number patients in our ECPR subgroup, we cannot draw any specific conclusions on the utility of the SAVE score as a predictive model in patients undergoing ECPR. Clinical trials evaluating the efficacy of ECPR are ongoing and will shed light on this population.

Limitations

Our study has a number of important limitations. First, our study comprised a moderate sample size of patients at a single centre that did not incorporate risk adjustment. Second, the SAVE score was derived as a tool to predict survival to hospital discharge. In our study, some patients were repatriated from our facility to another hospital, requiring ongoing

supportive medical care and rehabilitation. The specific number of these patients is unknown, as we did not separate the primary outcome between discharge from hospital and repatriation, similar to other studies in this field. Although all of these patients survived their VA-ECMO run, we do not have data on other potential in-hospital events that may have occurred after the patients were discharged from our hospital. Additionally, some of the patients included in this analysis were initiated on ECMO at another facility and then transferred to our institution. Although our team would not interfere with remote hospital decision making, the ultimate decision for accepting patients from peripheral hospitals rests with the accepting centre, which could introduce an element of selection bias into our data.

Other limitations in the data we present are inherent to the use of predictive models in heterogeneous populations. For example, echocardiographic features and biomarkers proposed for risk stratification in patients undergoing ECMO support, such as serum troponins, were not included in the SAVE score algorithm, nor in our study.¹⁵ Additional data may therefore enhance the accuracy of the SAVE score, and may be of particular value in the contexts of pre-ECMO cardiac arrest and/or ECPR, within which outcomes are especially challenging to predict.¹²

Although we have included patients receiving ECPR as part of our external validation cohort, it is important to note that the SAVE score was not derived to include this population. Therefore, we cannot draw any conclusions with respect to the utility of this tool in patients undergoing ECPR.

Finally, it is worth remembering that the SAVE score was developed on patients already receiving ECMO. It has not been validated for rCS patients in whom ECMO has not yet been instituted.¹²

Investigation and validation of the SAVE score in a greater number of patients at more ECMO centres remain essential to ensuring its more widespread applicability.

Although the survival rates of patients receiving VA-ECMO for rCS have improved, the care of such patients remains complex, and it is associated with a number of potential complications.³⁻⁷ Although the SAVE score showed utility as a

prognostic tool in earlier-generation patients with rCS, its utility for predicting survival in a large North American cohort is limited, precluding its widespread adoption. As VA-ECMO becomes a routine part of the clinical pathway in management of rCS, prospective validation and evaluation of additional prognostically important clinical variables should be the focus of future studies. Although current ELSO guidelines for management of cardiogenic shock²⁵ do not incorporate use of prediction tools, further development of clinical guidelines incorporating the use of VA-ECMO will help clinicians provide appropriate use of this high-risk intervention in a critically ill population.

Appropriate patient selection for VA-ECMO is challenging. Although most clinicians rely on a team-based decision-making model when offering VA-ECMO to patients with rCS, these decisions are usually made based on overall clinical judgment. With its adequate model calibration and fair discrimination for survival, we have shown that the SAVE score can serve as an adjunct to clinical assessment when deciding on who should be offered this high-risk intervention. However, we cannot recommend application of the SAVE score to determine individual patient management, or to serve as the sole decision-making tool when deciding on whether VA-ECMO is futile. Similarly, other risk scores used in various critically ill patients (eg, sepsis, trauma) serve as additional tools, but they cannot replace clinical judgment at the bedside, especially in a complex, high acuity, and dynamically evolving situation.

Conclusions

When considering VA-ECMO for patients with rCS, the SAVE score can be used as an adjunctive tool to a team-based decision relying on clinical judgment. However, similar to other risk scores in critically ill patients, the SAVE score should not be the sole guide for clinical decisions, and it does not replace clinical judgment. Future work will focus on the development of a pre-ECMO prognostication tool using contemporary variables, including biomarkers and imaging. Ultimately, guidelines for appropriate clinical use of VA-ECMO will help guide clinicians when they are faced with challenging decisions around this high-risk, life-saving intervention.

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