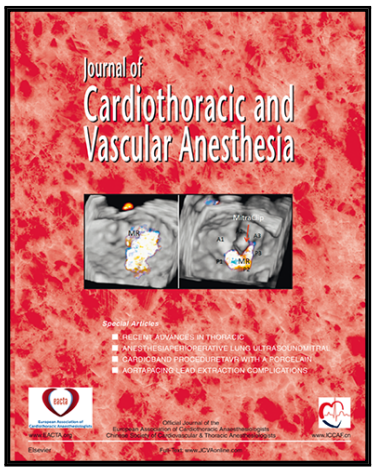

Comparison of four intensive care scores in prediction of outcome after Veno-Arterial ECMO: A single-center retrospective study

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Original Article

Comparison of four Intensive care scores in prediction of outcome after Veno-Arterial ECMO: A single center retrospective study

Suraj Sudarsanan, MD[1,*], drsurajsudarsan@gmail.com; Praveen Sivadasan, MD[1], psivadasan@hamad.qa; Prem Chandra[3], Pchandra@hamad.qa; Amr S Omar[1,2,4], a_s_omar@yahoo.com; Kathy Lynn Gaviola Atuel, MD[1], kathylynn_md@yahoo.com; Hafeez Ulla Lone[1], haf7275@gmail.com; Hany O Ragab[1], Hanyragab73@gmail.com; Irshad Ehsan[1], IEHSAN@hamad.qa; Cornelia S Carr[1,5], Ccarr@hamad.qa; Abdulrasheed Pattath[1], apattath@hamad.qa; Abdulaziz Al khulaifi[1,5], ABDULALKH@hamad.qa; Yasser Mahfouz Eltokhy Shouman[1], shouman@hotmail.com; A/Wahid Mahmoud A.A. Al Mulla[1], AALMULLA@hamad.qa

[1]Department of Cardiothoracic Surgery/Cardiac Anaesthesia & ICU, Heart Hospital, Hamad Medical Corporation, Doha, (PO: 3050), Qatar

[2]Department of Critical Care Medicine, Beni Suef University, Egypt

[3]Medical Research Center, Academic Health System, Hamad Medical Corporation, Doha, Qatar

[4]Weill Cornell Medical College, Doha,Qatar

[5]College of Medicine,Qatar University,Doha,Qatar

[*]Corresponding author. Department of Cardiothoracic Surgery/Cardiac Anaesthesia & ICU Section, Heart Hospital, Hamad Medical Corporation, Doha, (PO: 3050), Qatar

Abstract

Objective: Assess the capability of APACHE-II (Acute Physiology and Chronic Health Evaluation II), SOFA (Sequential Organ Failure Assessment scores), Cardiac Surgery Score

(CASUS), and SAVE (Survival After VA-ECMO) in predicting outcomes among a cohort of patients undergoing Veno-Arterial ECMO (VA-ECMO).

Design: This is an observational retrospective study of 142 patients who were admitted to the Cardiothoracic Intensive Care Unit (CTICU) after undergoing VA-ECMO insertion.

Setting: CTICU of a tertiary care center.

Participants: All patients admitted to the CTICU for a minimum duration of 24 h, post-VA ECMO insertion, between the years 2015 and 2022.

Interventions: Review of electronic patient records.

Measurements and Results: Scores for APACHE-II, SOFA, and CASUS were calculated 24 h after intensive care units (ICU) admission. The SAVE score was computed from the last available patient details within 24 h of ECMO insertion. Relevant demographic, clinical, and laboratory data for the study was retrieved from electronic patient records. Pre-ECMO serum levels of lactates and creatinine were significantly associated with mortality. Lower ECMO flow rates at 4 h and 12 h post-ECMO cannulation were significantly correlated with survival to discharge. The development of arrhythmias, acute kidney injury (AKI), and the need for continuous renal replacement therapy (CRRT) while on ECMO were significantly associated with mortality. The APACHE-II, SOFA, and CASUS scores, calculated at 24 h of ICU admission, were significantly higher amongst non-survivors. Following risk score categorization using receiver operating characteristic (ROC) curve analysis, it was found that APACHE-II, SOFA, and CASUS scores calculated at 24 h post-ICU admission after ECMO insertion demonstrated moderate predictive ability for mortality, whereas the SAVE score failed to predict mortality. APACHE-II > 27 (AUC of 0.66), calculated 24 h post-ICU admission after ECMO insertion, showed the greatest predictive ability for mortality.

Multivariate logistic regression analysis of the four scores showed that APACHE-II > 27 and SOFA > 14, calculated 24 h post-ICU admission after ECMO insertion, were independently significantly predictive of mortality.

Conclusion: The APACHE-II, SOFA, and CASUS, calculated at 24 h of ICU admission, were significantly higher among non-survivors compared to survivors. APACHE-II demonstrated the highest mortality predictive ability. APACHE-II scores of 27 or above, and SOFA scores of 14 or above, at 24 h of ICU admission after ECMO cannulation, can predict mortality and assist physicians in decision-making.

Keywords

VA-ECMO outcome prediction, risk scoring in VA-ECMO patients in ICU, mortality prediction post-VA ECMO

List of abbreviations: ACEF, Age, Creatine, Ejection Fraction; AKI, Acute kidney injury; AKIN, Acute Kidney Injury Network; AMI, Acute myocardial infarction; APACHE II, Acute Physiology and Chronic Health Evaluation II; aPTT, Activated partial thromboplastin time; AUC, Area under the curve; CABG, coronary artery bypass grafting; CASUS, Cardiac Surgery Score; CI, Confidence interval; CPB, Cardio-pulmonary bypass; CRRT, Continuous renal replacement therapy; CS, Cardiogenic shock; CTICU, Cardiothoracic Intensive Care Unit; ECLS, Extracorporeal life support; ECMO, Extra-corporeal Membrane oxygenation; ECPR, Extracorporeal cardio-pulmonary resuscitation; ELSO, Extra Corporeal Life Support Organization; ENCOURAGE, Prediction of Cardiogenic shock outcome for AMI patients salvaged by VA- ECMO; IABP, Intra-aortic balloon pump; ICU, Intensive Care Unit; IQR, inter-quartile range; LR+, likelihood ratio of a positive test; LR-, likelihood ratio of a negative test; LOS ICU, Duration of ICU stay; LOS HOSP, Duration of Hospital stay; LOV, Length of

Ventilation; MCS, Mechanical Circulatory support; MI, Myocardial infarction; NPV, Negative predictive value; POD, Post-operative day; POCT, point-of-care test; PPV, positive predictive value; REMEMBER, Predicting mortality in patients undergoing veno-arterial Extracorporeal membrane oxygenation after coronary artery bypass grafting; ROC, Receiver operating curve; SAPS II, Simplified Acute Physiology Score II; SAVE, Survival after VA-ECMO; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; VAV-ECMO, Veno-arterio-venous extracorporeal membrane oxygenation

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO), as part of extracorporeal life support (ECLS), is a standard therapy for short-term hemodynamic support in the context of cardiogenic shock (CS). It is especially useful for patients who are progressively deteriorating despite maximal medical treatment. Serving as a short-term ventricular assist device for mechanical circulatory support (MCS), VA-ECMO can be swiftly placed at the bedside, in the emergency room, intensive care unit, cardiac catheterization suite, or operating room. It can be used as a bridge to recovery or decision-making, providing clinicians with the opportunity for further treatment and evaluation (1,2). VA-ECMO has recently gained popularity for extracorporeal cardiopulmonary resuscitation (ECPR), where it maintains vital organ perfusion during and immediately after cardiac arrest (3). Post-cardiotomy VA-ECMO is used when weaning from cardiopulmonary bypass (CPB) is difficult, providing time for the ventricle to recover after complex surgeries. It is often electively instituted after heart transplantation as a bridge to recovery.

The prognosis and outcomes after the implementation of VA-ECMO are significantly influenced by underlying conditions, patient comorbidities, the severity of organ dysfunction at initiation, and complications or adverse events during MCS (4,5). Although VA-ECMO has lifesaving potential, it comes with associated complications, especially vascular ones from cannulation. In addition, patients on VA-ECMO are susceptible to neurologic injury, renal failure, liver failure, and sepsis as sequels of post-CS or cardiac arrest (6,7). Despite remarkable advances in the quality of devices and intensive care management of these patients, ECLS therapy is still linked with high rates of mortality and complications (1). Inappropriate or unwarranted application of VA-ECMO can lead to unnecessary prolongation of patients' and families' suffering, accompanied by significant costs and resource utilization (6,7). For these reasons, early prognosis is essential in patients undergoing treatment with VA-ECMO. Numerous survival prediction models are available for critically ill patients admitted to intensive care units (ICUs). However, these scores have not shown consistent results when applied to patients on ECLS (8–11).
Only a few such models, specifically those constructed for VA-ECMO, currently exist. Schmidt et al. developed the SAVE scoring system, utilizing the Extracorporeal Life Support Organization (ELSO) registry to predict survival to discharge in VA-ECMO patients (12). Chen et al. merged the serum lactate level with the SAVE score, creating the Modified SAVE score to predict outcomes in patients who underwent urgent VA-ECMO in the emergency department (13). The ENCOURAGE score, created from a bi-institutional database, predicts survival to ICU discharge for VA-ECMO patients (14). The REMEMBER score, consisting of six pre-ECMO variables, was designed to forecast in-hospital mortality for patients on VA-ECMO following isolated coronary artery bypass grafting (CABG) due to refractory CS (15).

We document our experience comparing the predictive accuracy of four prediction models in determining outcomes in a group of patients who underwent the initiation of VA-ECMO for CS or cardiac arrest. We evaluated two general ICU risk scores, APACHE-II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment), one score specific to cardiac surgery patients, CASUS (Cardiac Surgery Risk Score), and one score specifically for VA-ECMO, SAVE (Survival After Veno-Arterial ECMO).

Materials and Methods

This observational retrospective study was conducted in the cardiothoracic intensive care unit (CTICU) of a tertiary cardiac center and included all patients admitted to the CTICU for VA-ECMO insertion between 2015 and 2022. Patients with an ICU stay of less than 24 h post-ECMO insertion, and those not admitted to the CTICU following ECMO insertion, were excluded from the study. The study was approved by our institution's Institutional Review Board (study protocol # MRC-01-22-701), which waived the need for informed consent due to the retrospective nature of the review and the lack of individual patient identifications. The authors collected demographic, clinical, and laboratory data relevant to the study from the electronic patient records (Cerner Millennium, country required, and Dendrite Clinical Systems, London, United Kingdom). This included pre-ECMO patient demographics, clinical, laboratory, and hemodynamic parameters (both pre-ECMO and during ECMO), cannulation details (location, type, constitution), and procedures performed while on ECMO (such as revascularization - surgical or percutaneous, relook angiography, and definitive cardiac surgical procedures). It also included complications associated with ECMO and outcomes. Pre-ECMO variables were the latest values available within 24 h of cannulation.

Indications and contraindications for the insertion of VA-ECMO were determined by local protocols and ELSO guidelines. The VA-ECMO pumps utilized were either the CARDIOHELP (Maquet, Wayne, NJ) along with the Heart Lung Support (HLS) Set Advanced Oxygenator (Maquet Cardiopulmonary GmbH, Rastatt) or CentriMag (Levitronix, Waltham, MA) combined with the MEDOS Hilite Oxygenator (MEDOS Medizintechnik AG, Stolberg). The selection of cannulation strategies was influenced by the clinical scenario and the surgeon's preference. Arterial cannulation was typically established via the femoral, axillary, subclavian, or direct aortic route, while venous cannulation was typically established via the femoral, internal jugular, or central right atrial route. Some patients with concomitant poor lung function required a transition from VA-ECMO to veno-arterio-venous extracorporeal membrane oxygenation (VAV-ECMO) to combat hypoxia.

Patients were cannulated at their bedside. Percutaneous femoral cannulation was commonly employed during emergencies in the emergency room, cardiac catheterization suites, or inpatient wards following cardiac arrest, such as ECPR. Central cannulation, using the aortic and right atrial routes, was carried out in the operating room on selected post-cardiotomy shock patients requiring VA-ECMO support. The subclavian or axillary route was used for arterial cannulation when the femoral artery was determined to be unusable due to injury, small lumen, atherosclerosis, etc. All femoral arterial cannulations were accompanied by the placement of an ipsilateral antegrade limb perfusion cannula (either percutaneously or via surgical cut-down) to prevent ischemic complications; this is as directed by our institutional protocol. Patients were given heparin infusion to maintain an activated partial thromboplastin time (aPTT) between 40–60 seconds throughout the ECMO course. If there was excessive bleeding and/or coagulopathy, heparin infusion was

sustained and the duration of cessation of heparin was reviewed at the twice-daily multidisciplinary clinical rounds.

The APACHE-II, SOFA, and CASUS scores were tabulated 24 h after ICU admission. The SAVE score was computed from the patient's final details available within 24 h of ECMO insertion. When evaluating the SAVE score for ECPR patients who entered the emergency room with a cardiac arrest, the latest available patient details from electronic records were used. If no prior records were available, normal parameters were assumed.

Statistical analysis

Descriptive statistics were utilized to summarize and discern the characteristics and distribution of the sample data from participants. Results from normally distributed data were reported using mean and standard deviation (SD), whereas skewed data were presented utilizing the median and interquartile range (IQR). Frequencies and proportions served to summarize categorical data. APACHE-II, SOFA, SAVE, and CASUS scores were computed for every patient. The chief objective of our current data analysis was to evaluate the predictive accuracy of these four scores, APACHE-II, SOFA, SAVE, and CASUS, in forecasting non-survivors amidst patients undergoing VA-ECMO insertion for CS or cardiac arrest. The association between two or more qualitative variables was gauged via the chi-square ($\chi 2$) test or Fisher's exact test, as necessary. Unpaired t-tests or Mann–Whitney U tests, as appropriate, analyzed quantitative data between two independent groups (survivors and non-survivors). Both univariate and multivariate logistic regression methodologies were deployed to measure the predictive values of each score, along with other potential confounders and predictors linked with non-survivors. For the multivariate regression models, variables achieving statistical significance had $P < 0.10$ in the univariate

analysis or were deemed clinically significant. The discriminative ability of the logistic regression model was evaluated by the area under the receiver operating characteristic (ROC) curve.

The sensitivity, specificity, positive and negative predictive values, and likelihood ratios of these parameters were calculated. An ROC curve was constructed, and indices were computed to establish the most suitable cut-off values for the four aforementioned risk scores to evaluate model discrimination and predictive accuracy. Pictorial representations of essential results were created via relevant statistical graphs. All presented P values were two-tailed, and P values <0.05 were deemed statistically significant. All statistical analyses were conducted using the statistical packages SPSS version 29.0 (Armonk, NY: IBM Corp) and Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA).

Results

Between 2015 and 2022, all patients who had VA-ECMO insertions at our institution for either CS or cardiac arrest were observed. A total of 142 patients, who were managed in the CTICU after ECMO insertion for a minimum of 24 h, were included in the study. The study group's average age was 49.89 ± 11.70 years. Males significantly outnumbered females, constituting 88.73% of the study group, which had a diverse ethnic and racial profile. The reasons for VA-ECMO insertion in the study group include ECPR in 50% of cases, post-cardiotomy shock after cardiac surgery in 29%, CS in 17%, and other causes in 3.5%. Peripheral cannulation (femoral-femoral and femoral-axillary/subclavian) was used in 95% of the patients, while central cannulation was used in the remaining 5%. An intra-aortic balloon pump (IABP) was concurrently used in 76% of the patients. A reconfiguration of

VA-ECMO to veno-arterio-venous extracorporeal membrane oxygenation (VAV-ECMO) was required for 10% of the patients.

The outcome assessment of the study group showed that out of the 142 patients involved, 120 patients were successfully weaned from VA-ECMO (84%), however, only 59 patients were discharged alive from the hospital post-ECMO insertion (41.51%), whereas 83 patients died in the hospital (58.52%). Of the patients who died inside the hospital, 22 (26.52%) died while on ECMO, 47 (56.62%) died in the ICU post-ECMO removal, and 14 (16.86%) died after being transferred from the ICU to the ward.

Table 1a shows an evaluation of the quantitative predictors and their correlations with survivors and non-survivors. Of the pre-ECMO indicators recorded, only lactate and creatinine levels were significantly higher in non-survivors compared to survivors ($P<0.05$). This study found that the ECMO flow was significantly higher among non-survivors than among survivors at 4 h post-ECMO insertion (3.24 ± 0.78 L/min vs. 3.0 ± 0.60 L/min, $P=0.05$). A similar trend was noticed at 12 h post-ECMO insertion (3.17 ± 0.89 L/min vs 2.89 ± 0.67 L/min, $P=0.03$). Achieving lower flows at 4 h and 12 h post-ECMO demonstrates recovery of LV function in survivors. The duration of hospital stay (LOH) was significantly longer for survivors than non-survivors, with a median of 40; interquartile range (IQR) of 18–79 days vs a median of 14; IQR 6–34 days ($P=0.007$).

The results of the univariate logistic regression analysis, detailing the associations of categorical predictors with non-survivors, are shown in Table 1b. Patients who developed acute kidney injury (AKI) on ECMO exhibited a significantly higher risk of mortality compared to those who did not develop AKI, with an unadjusted odds ratio (OR) of 4.22, 95% CI 1.75–10.14; $P=0.001$. This study utilized the Acute Kidney Injury Network (AKIN)

criteria for AKI diagnoses. Likewise, those who underwent Continuous Renal Replacement Therapy (CRRT) had a significantly higher mortality rate than those who did not undergo CRRT (unadjusted OR 2.99, 95% CI 1.41–6.34; P=0.004). The study also found that patients who developed arrhythmias (Ventricular Tachycardia (VT), Ventricular Fibrillation (VF), or Atrial Fibrillation (AF)) on ECMO had significantly higher mortality rates as compared to those who did not (66.21% vs 50%, P=0.051). The mortality rate for patients who were administered ECMO following ECPR was higher than that of patients using ECMO following CS and post-cardiotomy (62% vs 52% and 51.2% respectively), but this difference was not statistically significant.

As depicted in Table 1a, among the four risk scores evaluated in this study, the SAVE score did not show significant differences between survivors and non-survivors. However, the values of the remaining three scores, as measured 24 h after ICU admission following VA-ECMO insertion, were significantly higher among non-survivors compared to survivors: CASUS (20.45 ± 4.15 vs 18.24 ± 4.11; P=0.003), APACHE-II (30.13 ± 6.53 vs 26.24 ± 6.82, P=0.001), and SOFA (16.22 ± 3.50 vs 14.05 ± 3.81, P=0.001). The categorization of risk scores through ROC curve analysis revealed that, among the four risk scores, an APACHE-II score >27 (unadjusted OR 3.19, 95% CI 1.59, 6.41; P=0.001) and a SOFA score >14 (unadjusted OR 3.77, 95% CI 1.85, 7.67; P<0.001) were significantly associated with a higher risk of mortality.

We performed two multivariate logistic regression analyses. Model one included four independent risk scores while model two incorporated potential predictors and confounding factors in addition to the four risk scores. The findings for each model are detailed in Table 2a and Table 2b, respectively. After adjusting for the potential predictors

and confounding factors, it was found that an APACHE-II score greater than 27 (adjusted OR 2.61, 95% CI 1.06, 6.44; P=0.037) and a SOFA score greater than 14 (adjusted OR 4.68, 95% CI 1.90, 11.55; P=0.001) were significantly predictive of mortality (Table 2b). We also evaluated the predictive accuracy of both regression models with the ROC curve and indices. The results indicated that the discriminative abilities of the models were comparable, and both demonstrated good accuracies (AUC 0.72, 95% CI 0.64, 0.80 vs 0.79, 95% CI 0.71, 0.86) as shown in Figure 1. Distributions of the four risk scores among survivors and non-survivors are illustrated in box plots (Figure 2).

ROC curves were plotted to determine the optimum cut-off value for these four risk scores when predicting mortality (Figure 3). The following cut-offs were found to be associated with mortality: CASUS>18, APACHE-II>27, SOFA>14, and SAVE> -6. The evaluation results from the diagnostic test, which used indices such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio of a positive test (LR+), and likelihood ratio of a negative test (LR-), are shown in Table 3 for various cut-off values of these four risk scores in predicting mortality. The absolute percentage of mortality across various cut-off scores for each risk score, as presented in Figure 4, indicates that higher risk score cut-off values are associated with a higher percentage of mortality.

Discussion

Many studies that analyze risk scores rely on calculations made at the initiation of ECMO. However, we decided against this, as values recorded at the onset of ECMO can be significantly skewed due to the prior cardiac arrest or low cardiac output state. These readings might not accurately reflect the support MCS provides for hemodynamics and

organ protection. We propose calculating the risk score 24 h after ICU admission following VA-ECMO insertion. This approach could trace the progress of organ system recovery, or the lack thereof, providing early insights into the efficacy of MCS. Anticipating a cut-off score at the 24-h mark of ICU admission for mortality could assist clinicians in customizing the treatment (escalating or de-escalating), reevaluating management strategies, and exploring definitive treatment options for the underlying pathology (percutaneous or surgical revascularization, escalating to durable ventricular assist devices/transplant, etc.).

The study population was unique compared with those of similar previous studies. The patients were comparatively younger (the mean age of non-survivors and survivors was approximately 50), had a diverse racial profile, and were predominantly male (11,16). The survival rate to discharge in our study was 41.5%, which aligns with the latest published international standard for adult patients undergoing VA-ECMO insertion, as derived from the ELSO registry (46% for CS and 31% for ECPR). An impressive 84.5% of the patients in our study survived ECLS compared with 61% in CS and 43% in ECPR from the ELSO registry (17). This is likely due to our study group consisting of relatively younger patients and having very few out-of-hospital cardiac arrests.

Prior studies have established age, pre-ECMO cardiac arrest, CPR duration, pre-ECMO serum lactate levels, and ECMO duration as survival predictors after VA-ECMO (12–15, 18,19). In our study, among the pre-ECMO variables, only serum lactate and serum creatinine levels had a significant association with mortality. Interestingly, age did not display a significant association with mortality in our study. This may be due to the relatively younger population we studied, with an average age of about 50 years among both survivors and non-survivors.

The APACHE-II and SOFA scores have been widely used to predict mortality following ICU admission and have undergone external validation (20–23). The CASUS system was introduced as a specialized cardiac surgery scoring system for prognostication and mortality prediction post-cardiac surgery, and it has been endorsed by various studies (24–26). Several specific predictive scores for VA-ECMO have been proposed. These include the SAVE, Prediction of CS Outcome for acute myocardial infarction (AMI) Patients Salvaged by VA-ECMO (ENCOURAGE), Predicting Mortality in Patients undergoing Veno-arterial Extracorporeal Membrane Oxygenation after CABG (REMEMBER), and modified SAVE scores (12–15). These scores focus on pre-cannulation variables for mortality prediction after VA-ECMO. However, these scores derive from select clinical subsets of CS, which may limit their optimal use across various clinical scenarios causing CS.

The SOFA score and APACHE-II score, despite not being originally intended or derived for use, have been leveraged to predict outcomes in patients using VA-ECMO. These scores have undergone external validation and exhibit comparable discriminatory ability when compared to certain scores specifically developed for ECMO patients (27). Numerous studies have demonstrated modest discriminatory capabilities of the SOFA and APACHE-II scores when anticipating mortality in patients on VA-ECMO (9,13,28,29), a result aligning with our findings. Unique from the aforementioned studies, which all calculated risk scores at the onset of VA-ECMO, our study recorded values and clinical parameters, while also determining scores 24 h post-admission into the ICU following the commencement of VA-ECMO.

CASUS, formulated as a specialized scoring system for post-cardiac surgery, has not seen extensive use in assessing outcomes for VA-ECMO patients; it has yet to be externally

validated. We chose to utilize CASUS in our study, thinking that since it was originally developed as a specific cardiac surgery score, its discriminatory ability would equate to the ECLS population. In the same vein, Hoffman, et al., retrospectively analyzed 90 adults who underwent VA-ECMO insertion and reported that CASUS, in comparison with SOFA (calculated 12 h post-ECMO initiation), exhibited superior discriminatory ability in mortality prediction (30). These results differ from our findings, where the SOFA score was a better predictor of mortality than the CASUS score. The disparity could stem from the fact that Hoffman's study comprised a larger portion of patients who received post-cardiac ECMO (75%) than our study (29%) did.

Schmidt et al. developed the SAVE scoring system, using the ELSO registry to predict survival until discharge in VA-ECMO patients (12). The main limitation of the SAVE score is its exclusion of patients who underwent ECPR. Several studies have reported that the SAVE score demonstrates modest discriminatory power in predicting mortality (17,27,30–32). Our study exposed a very poor discriminatory ability for the SAVE score (AUC 0.44), the poorest among the four scores under consideration. This result is likely due to the high proportion of ECPR cases in our study cohort (50%), as the SAVE score was conceived without factoring in ECPR patients.

The findings of our study are in line with those of various studies that have compared different risk scores among patients on VA-ECMO. B. Worku et al. conducted a retrospective analysis of data from 51 patients undergoing VA-ECMO support at their institution. They calculated the APACHE-II, SOFA, SAPS-II (Simplified Acute Physiology II), ENCOURAGE, SAVE, and ACEF (age, creatinine, ejection fraction) scores and assessed their ability to predict outcomes. The results revealed a modest discriminatory ability of the scores in the

patients' cohort, with the ACEF score performing the best (17). This study included patients who were slightly older and a larger proportion of females compared to our study. The performance of the APACHE-II score was similar to ours, the SOFA score performed worse, and the SAVE score was better. The superior performance of the SAVE score could be related to the smaller percentage of ECPR patients compared to our study group (41% vs 50%).

Wengenmayer et al. developed PREDICT VA-ECMO, a prediction model based on point-of-care test (POCT) measurements of lactate, pH, and standard bicarbonate concentration. It was compared with the SAVE, APACHE-II, SOFA, and SAPS scores for predicting hospital survival after VA-ECMO. The PREDICT VA-ECMO score reliably predicted hospital survival in both the derivation and validation cohorts, outperforming the other scores. The 12-h PREDICT VA-ECMO score integrates lactate, pH, and standard bicarbonate concentrations at 1, 6, and 12 h after ECMO insertion, offering improved prognostication (33). Unlike many ECMO risk scores that heavily rely on pre-ECMO variables and are calculated at the initiation of ECMO, PREDICT VA-ECMO depends on parameters measured after the initiation of ECMO at regular intervals. This approach aligns with our study methodology, where we calculated risk scores 24 h after ECMO initiation. The performance of the APACHE-II and SOFA scores in this study mirrored our findings, but the SAVE score performed better, even though the ECPR proportion was similar (51% vs. 50%). PREDICT VA-ECMO depends on just 3 POCT parameters of tissue perfusion to predict mortality, without addressing the recovery or lack of recovery of major organ systems (such as CNS, respiratory, renal), which play significant roles in risk prediction and prognostication.

Muller et al. formulated the ENCOURAGE score for patients undergoing VA-ECMO after AMI to predict mortality. This score was constructed based on seven pre-ECMO parameters, determined from multivariable logistic regression analyses. It performed better than the SAVE, SAPS-II, and SOFA scores (14). In comparison to our study, the SAVE score performed better in this study, while the SOFA score showed similar predictability.

Wang et al. proposed the REMEMBER score for predicting mortality after VA-ECMO in patients who underwent CABG. The REMEMBER score performed better than the SOFA, SAVE, EUROscore, and ENCOURAGE scores in this population (15). Compared with our study, their research focused solely on post-cardiotomy ECMO, included older patients and had a lower proportion of ECPRs. The mortality in their study was comparable to ours (55% vs 58.5%), but successful weaning from ECMO was much lower (64% vs 84.5%). In their study, the SOFA score and SAVE, determined at the time of ECMO initiation (unlike in our study), outperformed ours based on the AUC.

Pladet LCA et al. conducted a systematic review and meta-analysis of studies that focus on mortality prediction in ECMO settings (27). The discriminatory ability of frequently validated ECMO scores, SAVE and RESP, was found to be moderate, comparable to that of general ICU risk scores such as APACHE-II, SOFA, and SAPS-II. They reported that most models had a high risk of bias and were contingent on the fact that ECMO support had already been initiated.

The findings of our study align with previous studies that compared specific ECMO scores and general ICU scores, where only moderate predictive ability was associated with both general ICU and ECMO-specific scores. The common performance of ECMO-specific scores might be because they are predominantly calculated at the time of ECMO insertion and

cannot keep track of the clinical course of patients on ECMO. Our study demonstrated that the combined four risk scores had better predictive capability than each one individually. This predictive ability was further enhanced by adding other potentially clinically relevant predictors specific to non-survivors (ECMO duration, low-flow minutes, the reason for ECMO, cannulation location, and type of myocardial infarction associated with cardiac arrest). Another crucial finding in our study was the association of ECMO flow at 4 h and 12 h post-ECMO initiation with survival, with notably lower flow rates being significantly tied to survival. Achieving lower flow rates over time on ECMO indicates a recovery of left ventricular function. Thus, efforts should be made to lower the flow as early as possible by checking for signs of LV recovery (improvement of pulse pressure, echocardiographic parameters, etc.) every time a patient is placed on ECMO. Our study's poor mortality prediction correlation between scores based on pre-ECMO variables (SAVE) and scores calculated 24 h after ICU admission post-ECMO initiation indicates the importance of tracking organ system recovery on extracorporeal circulation. The serial assessment of parameters related to organ system recovery and their interpretation are vital in predicting outcomes in patients on VA-ECMO.

Conclusions

Our study, which compared the predictive performance of general ICU, cardiac surgery, and ECMO risk scores, demonstrated that the general ICU and cardiac surgery scores performed better than the ECMO-specific scores. The APACHE-II, SOFA, and CASUS calculations, determined 24 h after ICU admission, were significantly higher among non-survivors compared to survivors. Of these, APACHE-II, designed for general ICU patients, showcased the best mortality predictive ability in our cohort, albeit with moderate discriminatory

power. A score of 27 or above on APACHE-II, and 14 or above on SOFA, at 24 h post-ICU admission following ECMO cannulation can help predict mortality and assist physicians in decision-making. However, the SAVE score is ineffective in predicting mortality in ECPR. ECMO flow at 4 h and 12 h post-ECMO initiation can predict mortality on ECMO. Further studies are necessary to create dynamic scoring systems, with a focus on patients' clinical progression on ECMO, and monitoring the trend of mortality variables. This would help enhance the scores' discriminatory power for accurate prediction of VA-ECMO mortality.

Implications and future directions

The availability of indicators or parameters for the early prognostication of patients on VA-ECMO is of great significance. Despite the existence of various predictive models for estimating mortality on VA-ECMO, these mainly depend on pre-insertion variables and have only modest predictive capability.

Clinical and laboratory variables that track the course of a patient on VA-ECMO play a crucial role in providing clues about the recovery or malfunction of organ systems. Identifying a cut-off value for risk scores at 24 h post-ICU admission following VA-ECMO insertion can contribute objectivity to assessments of patient clinical status, prognostication, and related decision-making. Contemporary ICU risk scores may not precisely predict organ system dysfunction in patients maintained on extracorporeal circulation, as most of these scores were not developed with this patient subset in mind. Therefore, there is a need to develop risk scores that incorporate pre-insertion variables and early post-VA ECMO variables, facilitating more accurate outcome prediction. Future research should focus on developing such a scoring system that can be calculated at the

patient's bedside, aiding clinicians in objective prognostication, outcome prediction, and decision-making.

Limitations of the study

This was a single-center retrospective study. The most significant limitation of this study was that it could not identify pre-insertion variables responsible for a preferable outcome, which could potentially prevent unnecessary insertions. However, this study highlights several immediate post-ECMO insertion parameters (some are alterable) that could positively impact the overall results. Our study included very few post-cardiotomy patients and patients who suffered from out-of-hospital cardiac arrest. Another potential limitation is the moderate AUC of the predictors, necessitating future validation studies.

Ethics approval and consent to participate

The study was approved by the ethics committee of the institute- Medical Research Center, Hamad Medical Corporation, Doha, Qatar (reference number - MRC-01-22-701). The need for informed consent was waived as no specific intervention was being done, and sampling blood for lab investigations was part of routine post-operative care.

Consent for publication

The ethical committee of the institute - Medical Research Center, Hamad Medical Corporation, Doha, Qatar (reference number - MRC-01-22-701), approved to publish this manuscript

Declaration of competing interest

None of the authors received, in the past 5 years, reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript now, however Hamad Medical Corporation is going to fund for article processing charges. None of the authors hold any stocks or shares in an organization that

may in any way gain or lose financially from the publication of this manuscript, either now or in the future. None of the authors hold, nor are currently applying for any patents relating to the content of the manuscript. We did not receive reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript. None of the authors have any other financial competing interests. None of the authors have any other non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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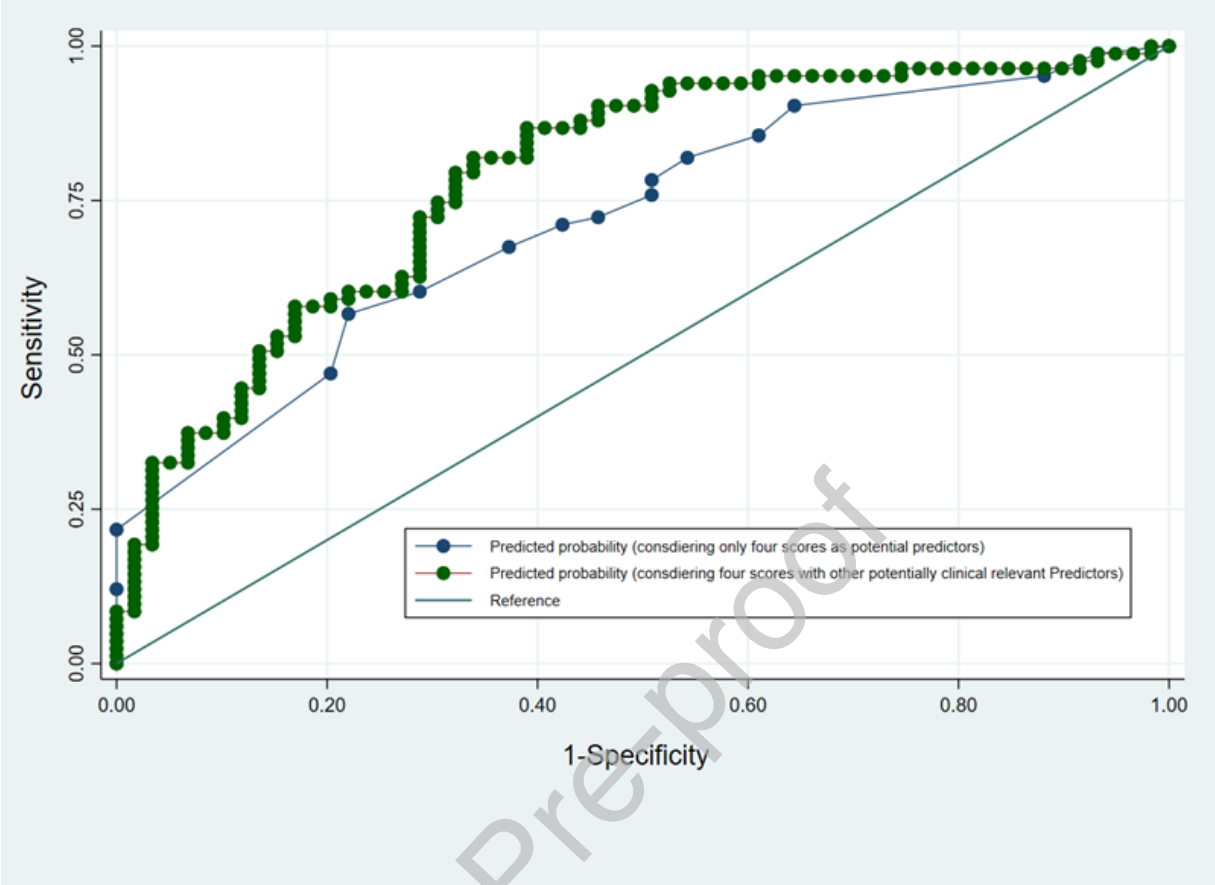

Test Result Variable(s)	AUC	P-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Predicted probability (consdiering only four scores as potential predictors)	0.720	<0.0001	0.637	0.803
Predicted probability (consdiering four scores with other potentially clinicallyy relevant Predictors)	0.788	<0.0001	0.711	0.864

AUC: area under the curve

Figure 1. Predictive accuracy evaluation of both multivariate regression models using ROC curve and indicies

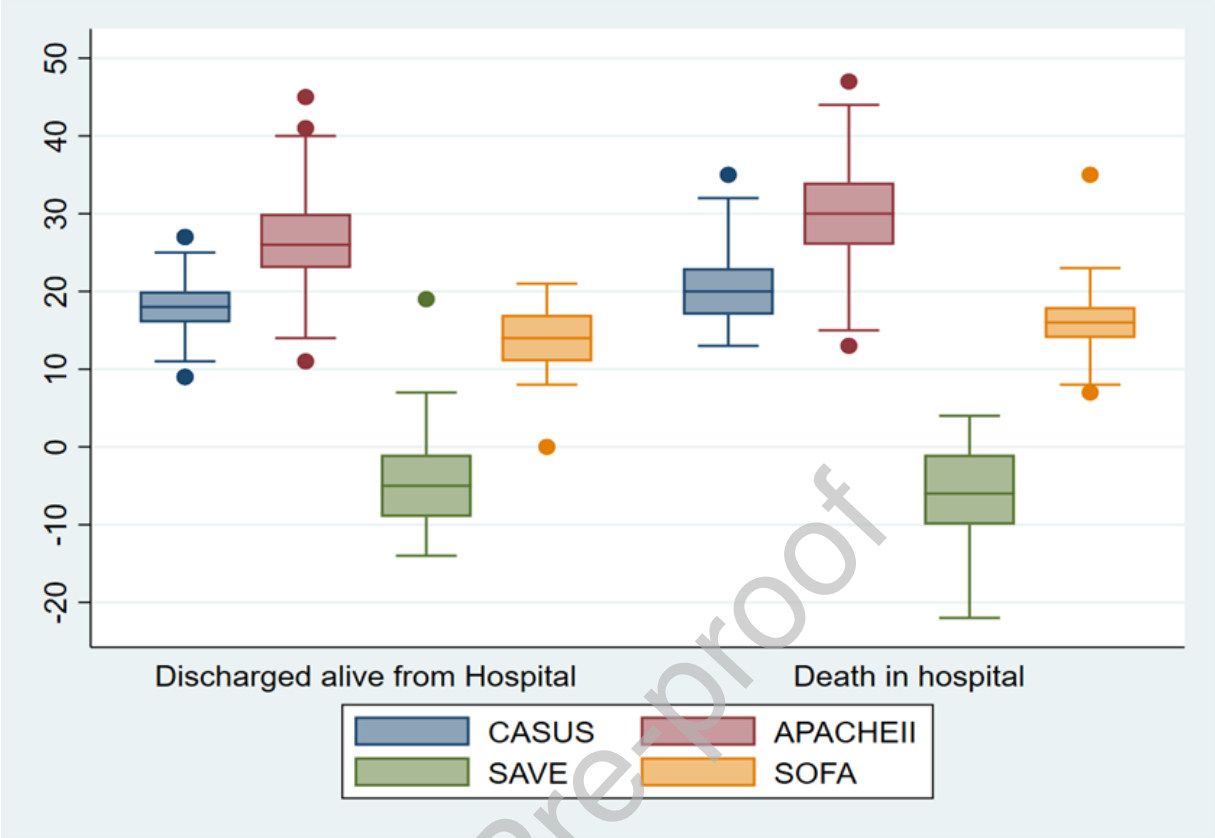

Figure 2. Box plots depicting distribution of four risk scores in survivors and non-survivors

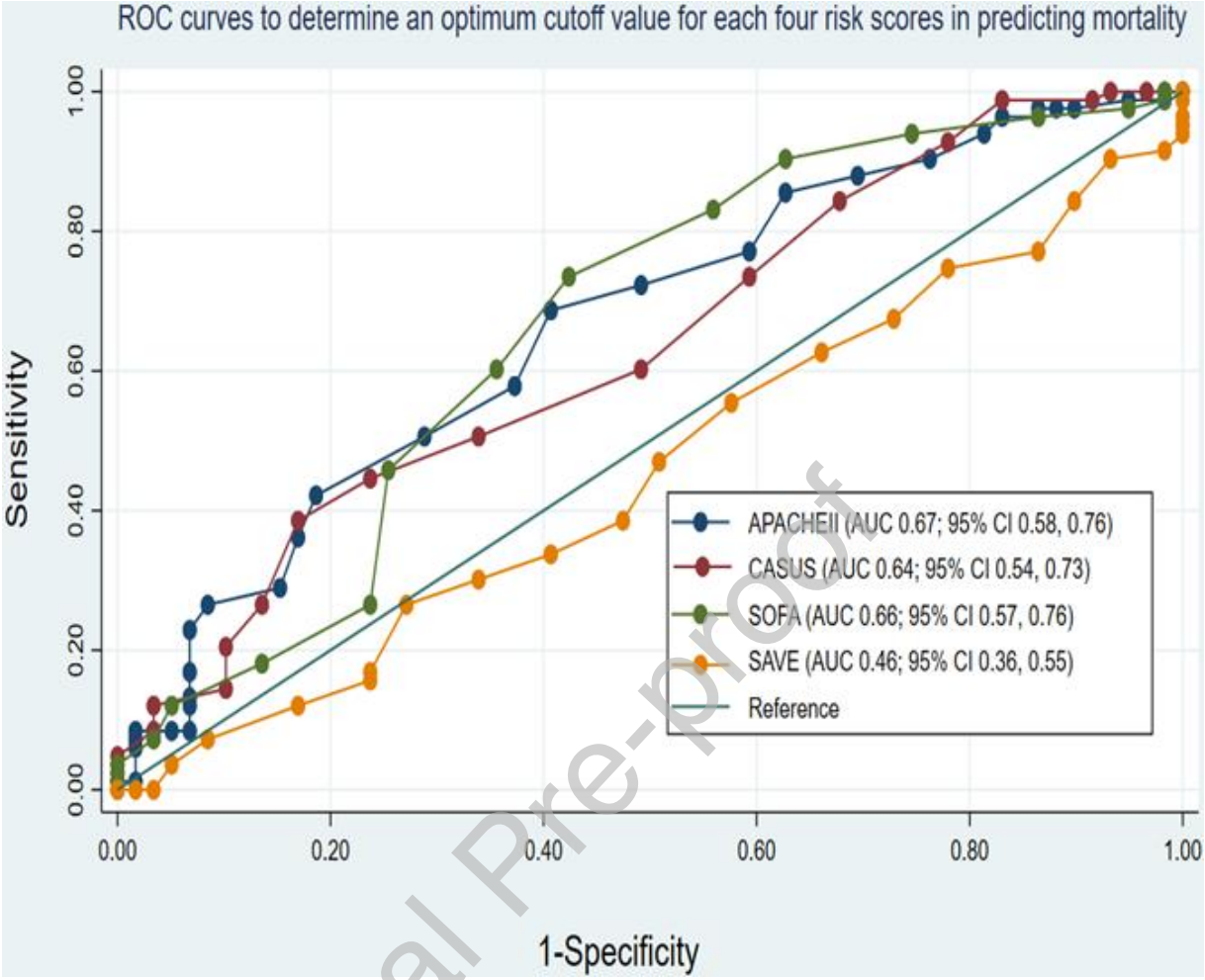

Figure 3. ROC curve to determine an optimum cutoff value for Scores in predicting mortality

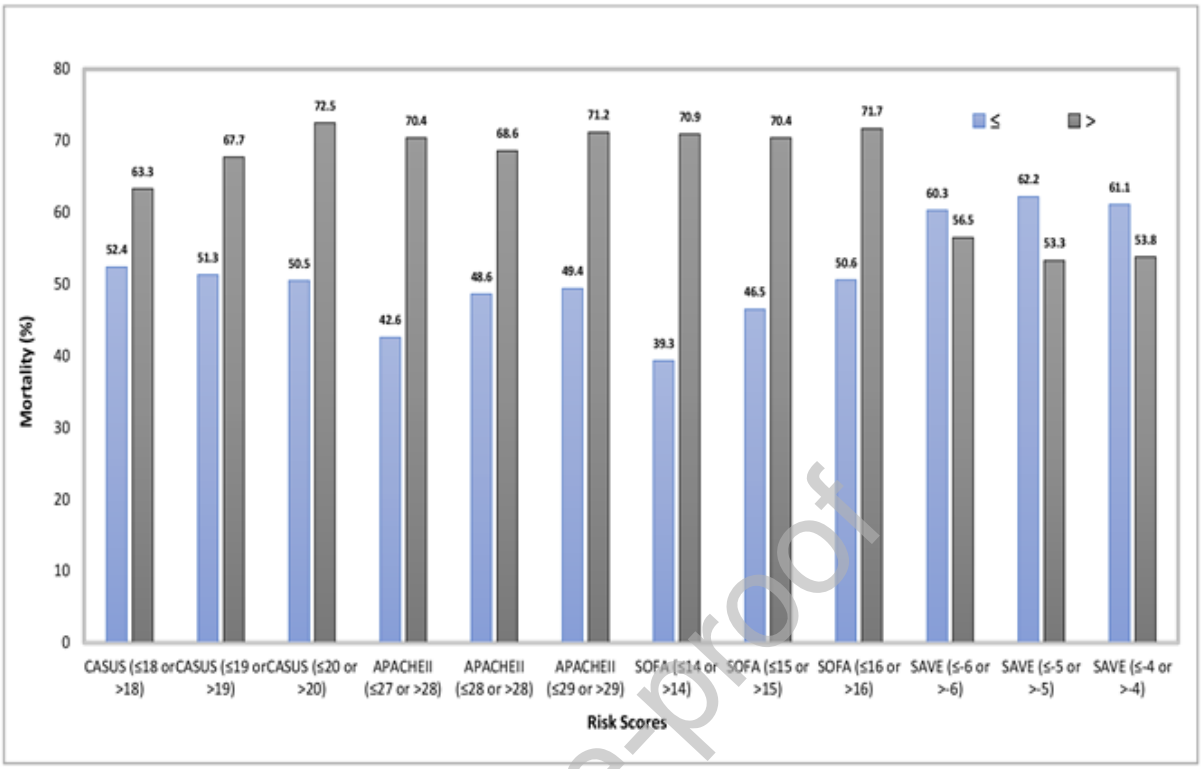

Figure 4: Mortality across different cut-offs for each risk score

Table 1a: Predictors and their association with survivors and non-survivors. Quantitative predictors and their association with survivors and non-survivors

Parameters	**Non-survivors, (n=83) mean ± SD / Median (IQR)**	**Survivors, (n=59) mean ± SD / Median (IQR)**	**Unadjusted OR (95% CI)**	**P-value**
Age (years)	50.47 ±12	49.07 ±11.30	1.01(0.98,1.04)	0.48
BMI (kg/m^2)	26.82 ±5.32	26.05 ± 4.61	1.03(0.96,1.10)	0.36
EF (%)	35.42 ±17	35.55 ±16.42	1.01(0.97,1)	0.96
ECMO Duration (hours)	125(125,193)	116 (51,170)	1.01(0.99,1)	0.14
Pre-ECMO				
Low Flow Time(minutes) *	19 (2,35)	10 (0,30)	1.01(0.99,1)	0.57
Ventilation (hours)	3 (1,10)	2 (1,6)	1.01(0.99,1)	0.93
Lactate (mmol/L)	7.2 (3.32,13.91)	5.9 (3.91,10)	1.02(0.99,1.12)	**0.07**
WBC (X 10^9/L)	14.25 ±6.28	13.48 ± 6.87	1.01(0.96,1)	0.50
Platelets (X 10^9/L)	224 (131.5,312.5)	203.5(135.6,265.3)	1.01(0.99,1)	0.60
Bilirubin (micromol/L)	13 (7, 36.75)	11.95(6.55,28.75)	1.02(0.99,1)	0.27
Creatinine (micromol/L)	143(100.51,240.52)	102 (79.25,134.53)	1.01(0.99,1)	**0.07**
ALT (Units/L)	69 (24,240.52)	33 (20,136)	1.01(0.99,1)	0.55
On ECMO				
ECMO flow(L/min) @4 hrs,	3.24 ±0.78	3.0 ±0.60	1.6 (0.99,2.74)	**0.05**
ECMO flow (L/min) @ 12 hrs	3.17 ±0.89	2.89 ±0.67	1.6 (1, 2.72)	**0.03**
LOV (hours)	216 (96,360)	255 (150,528)	1.02(0.99,1)	0.41
LOS-ICU (days)	12 (5,23)	16 (11,30)	1.01(0.99,1)	0.67
LOS-Hospital (days)	14 (6,34)	40 (18,79)	0.98(0.97,0.99)	**0.007**
Risk Scores				
CASUS	20.45 ± 4.15	18.24 ±4.11	1.15(1.04,1.26)	**0.003**
APACHE-II	30.13 ± 6.53	26.24 ±6.82	1.09(1.03,1.16)	**0.001**
SOFA	16.22 ±3.50	14.05 ±3.81	1.20(1.07,1.34)	**0.001**
SAVE	-5.86 ± 5.62	-4.49 ±6.12	0.96(0.90,1.01)	0.16

CI: Confidence interval; OR: Odds ratio.

Table 1b: Categorical Predictors and their association with non-survivors (Univariate Logistic regression analysis)

Predictors	**Non-survivors n/N (%)**	**Unadjusted OR (95% CI)**	**P-value**
Gender			
Male	74/126 (58.71%)	1 (reference)	0.850
Female	9/16 (56.32%)	0.90 (0.31,2.58)	
Ethnicity			
Indian	54/92 (58.72%)	1 (reference)	
Arab	20/35 (57.11%)	0.93(0.42,2.06)	0.874
Asian	3/4 (75%)	2.11(0.21,21.06)	0.524
Others	6/11 (54.52%)	0.84(0.24,2.96)	0.792
Cardiac arrest location			
No Cardiac arrest	26/50 (52%)	1 (reference)	
In hospital	52/87 (59.83%)	1.37(0.68,2.76)	0.370
Out of Hospital	5/5 (100%)	-	0.990
Indication for ECMO			
ECPR	44/71 (62%)	1 (reference)	
Cardiogenic shock	13/25 (52%)	0.66(0.26,1.66)	0.381
Post-cardiotomy shock	21/41(51.22%)	0.64(0.29,1.40)	0.262
Others	5/5 (100%)	-	0.990
Location of cannulation			
Operating Room	22/44 (50%)	1 (reference)	
Cath-Lab	32/49 (65.3%)	1.88(0.81,4.33)	0.137
ICU	23/35 (65.70%)	1.91(0.76,4.78)	0.163
ER	5/11 (45.51%)	0.83(0.22,3.13)	0.788
HDU/Floor	1 /3(33.33%)	0.5 (0.04,5.92)	0.583
Surgery while on ECMO			
No Surgery	49/80 (61.32%)	1 (reference)	
CABG	19/37 (51.41%)	0.66(0.30,1.46)	0.312
Valve Surgery	7/9 (77.82 %)	2.21(0.43,11.35)	0.340
CABG + Valve	2/5 (40%)	0.42(0.06,2.66)	0.351
Others	6/11 (54.51%)	1.05(0.23,4.72)	0.940
Predictors	**Non-survivors n/N (%)**	**Unadjusted OR (95% CI)**	**P-value**
Type of MI preceding ECMO			
No MI	18/33 (54.51%)	1 (reference)	
NSTEMI	24/41 (58.52%)	1.17(0.47,2.96)	0.731
STEMI	41/68 (60.30%)	1.26(0.54,2.93)	0.580
Type of VA-ECMO			
Femero-femoral	72 (86.72%)	1 (reference)	

Femro- Axillary/Subclavian	5/6 (83.34%)	0.26(0.10,3.65)	0.321
Central	6/7 (85.72%)	0.26(0.03,2.30)	0.220
Miscelleneous variables			
IABP on ECMO			
No	18/34 (52.94%)	1 (reference)	0.456
Yes	65/108 (60.21%)	1.34(0.61,2.91)	
Conversion to V-AV			
No	72/128 (56.25%)	1 (reference)	0.121
Yes	11/14 (78.63%)	2.85(0.76,10.71)	
Additional ECMO runs			
No	73/128 (57%)	1 (reference)	0.306
Yes	10/14 (71.42%)	1.88(0.56,6.32)	
Arrythmias on ECMO			
No	34/68 (50%)	1 (reference)	0.051
Yes	49/74 (66.21%)	1.96(0.99,3.86)	
Acute Kidney Injury			
No	9/29(31.03%)	1 (reference)	**0.001**
Yes	74/113 (65.50%)	4.22(1.75,10.14)	
CRRT on ECMO			
No	45/91 (49.45%)	1 (reference)	**0.004**
Yes	38 /51(74.53%)	2.99(1.41,6.34)	
Predictors	**Non-survivors n/N (%)**	**Unadjusted OR (95% CI)**	**P-value**
Open chest on ECMO			
No	27/40 (67.5%)	1 (reference)	0.173
Yes	56/102 (55%)	0.59 (0.27, 1.26)	
ICU readmission post ECMO			
No	69/115 (60%)	1 (reference)	0.441
Yes	14/27 (51.9%)	0.72(0.31,1.67)	
Complications on ECMO			
No	4/9 (44.4%)	1 (reference)	0.384
Yes	79/133 (59.4%)	1.83(0.47,7.12)	
Risk Score			
CASUS ≤ 18	33/63 (52.41%)	1 (reference)	0.190
CASUS > 18	50/79 (63.32%)	1.56(0.79,3.07)	
APACHE-II ≤27	26/61 (42.62%)	1 (reference)	**0.001**
APACHE-II >27	57/81 (70.40%)	3.19(1.59,6.41)	
SOFA ≤ 14	22/56 (39.3%)	1 (reference)	**<0.001**
SOFA >14	61/86 (71%)	3.77(1.85,7.67)	
SAVE ≤ -6	44/73 (60.31%)	1 (reference)	0.650

SAVE > -6	39/69 (56.55%)	0.85(0.43,1.67)	

CI: Confidence interval; OR: Odds ratio
'n' is the total number of non-survivors cases whereas 'N' is the total number of participants included against each specific variable/parameter

Table 2a: Predictive assessment of risk scores. Predictive assessment of risk scores with non-survivors (multivariate logistic regression analysis)

Risk Scores	Adjusted Odds ratio (aOR)	95% CI for aOR	P-value
CASUS > 18	1.07	0.50, 2.32	0.857
APACHE-II >27	2.74	1.23, 6.12	**0.014**
SOFA >14	3.05	1.42, 6.52	**0.004**
SAVE > -6	1.51	0.68, 3.36	0.311

CASUS ≤ 18, APACHE-II ≤27, SOFA ≤ 14, SAVE ≤ -6 were considered as reference categories.
CI: Confidence interval; OR: Odds ratio.

Table 2b: Predictive assessment of risk scores with other specific potentially clinically relevant predictors with non-survivors (multivariate logistic regression analysis)

Risk Scores/potential predictors	**Adjusted, Odds ratio (aOR)**	**95% CI for aOR**	**P-value**
CASUS > 18	1.14	0.48, 2.74	0.765
APACHE-II >27	2.61	1.06, 6.44	0.037
SOFA >14	4.68	1.90, 11.55	0.001
SAVE > -6	2.08	0.85, 5.08	0.107
ECMO duration	1.01	1.00, 1.01	0.013
Low flow minutes	1.00	1.00, 1.00	0.994
Indication			
ECPR	Reference		
Cardiogenic shock	0.40	0.12, 1.30	0.126
Others	0.73	0.15, 3.67	0.705
Location of cannulation			
Operating Room	Reference		
Cath-Lab	2.31	0.41, 12.88	0.341
ICU	1.83	0.40, 8.35	0.438
ER	1.21	0.14, 10.41	0.865
HDU/Floor	1.03	0.04, 27.55	0.985
Type of MI associated			
No MI	Reference		
NSTEMI	1.82	0.61, 5.46	0.282
STEMI	1.64	0.57, 4.71	0.360
Additional ECMO runs (yes)	1.04	0.24, 4.58	0.957
Definitive procedure on ECMO (yes)	0.33	0.12, 0.90	0.031

CASUS ≤ 18, APACHE-II ≤27, SOFA ≤ 14, SAVE ≤ -6 were considered as reference categories.

Table 3: Diagnostic test evaluation of various cut-off values of Scores in predicting mortality.

Risk Scores	Cut-off score	AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR^+ (95% CI)	LR^- (95% CI)
CASUS	>18	0.63 (0.53,0.73)	60.2 (49.48,70.09)	50.85 (38.43,63.16)	63.29 (52.28, 73.)	47.62 (35.78, 59.73)	1.23 (1.12, 1.35)	0.78 (0.69, 0.88)
APACHE-II	>27	0.666 (0.56,0.74)	68.67 (58.06,77.64)	59.32 (46.59,70.91)	70.37 (59.69, 79.21)	57.38 (44.9, 68.98)	1.69 (1.53, 1.86)	0.53 (0.47, 0.59)
SOFA	>14	0.664 (0.57,0.77)	73.49 (63.11,81.8)	57.63 (44.93,69.39)	70.93 (60.6, 79.47)	60.71 (47.63, 72.42)	1.73 (1.59, 1.90)	0.46 (0.40, 0.53)
SAVE	>-6	0.455 (0.36.0.55)	46.99 (36.62,57.62)	49.15 (36.84,61.57)	56.52 (44.79, 67.57)	39.73 (29.29, 51.19)	0.92 (0.82, 1.04)	1.08 (0.96, 1.21)

PPV: Positive Predictive Value, NPV: Negative Predictive Value, LR^+: Likelihood ratio of a Positive Test, LR^-: Likelihood ratio of a Negative Test CI : Confidence Intervals computed using Wilson's method.