

Predictors of Mortality and Discharge Location for Patients Supported by Venoarterial Extracorporeal Membrane Oxygenation

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University of Washington Abstract
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Background: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a form of advanced life support that is increasingly used to treat cardiac or pulmonary failure, however morbidity and mortality for patients supported by VA-ECMO remains high. Elucidation of predictors of mortality and discharge location for survivors may aid clinicians, patients, and families in prognostication for patients supported by VA-ECMO.

Methods: We performed a retrospective cohort study using registry data from the Extracorporeal Life Support Organization. Inclusion criteria were adults supported by VA-ECMO from 2017-2022. We calculated the relative risk of inpatient mortality in relation to patient demographic and clinical characteristics. Among survivors, we calculated the relative risk of discharge to a facility in relation to patient demographic and clinical characteristics.

Results: Data were extracted for 24,481 patients at 334 ESLO sites across North America. Patients were 33.2% female, 60.7% White, and had a mean age 55.6 years (SD 14.5). Inpatient mortality was 56%. The relative risk (RR) for inpatient mortality among patients in the oldest age category relative to youngest was 1.49 (CI 1.44 – 1.55). The age-adjusted RR for inpatient mortality for patients with a BMI ≥ 35 relative to 18.5 – 24.9 kg/m² was 1.25 (CI 1.17 – 1.33), for patients treated as a bridge to transplant was 0.50 (CI 0.44 – 0.58), for patients requiring renal replacement therapy was 1.31 (CI 1.24 – 1.38), for patients with a pH <7.14 at initiation relative to normal was 1.42 (CI 1.32 – 1.53), and for patient with an ECMO flow >4.7 L/min 24 hours after initiation was 1.23 (CI 1.14 – 1.33). Among survivors, 63.5% were discharged to a facility

rather than home. The relative risk for discharge to a facility among patients in the oldest age category relative to youngest was 1.53 (CI 1.45 – 1.61). The age-adjusted RR for discharge to a facility for patients with a BMI ≥ 35 kg/m² was 1.21 (CI 1.12 – 1.32), for patients on ECMO for ≥ 21 days was 1.33 (CI 1.21 – 1.46), for patients who suffered major complications was 1.39 (CI 1.25 – 1.56), and for patients who ambulated relative to those who were immobile was 0.55 (CI 0.45 – 0.67).

Conclusion: In this large cohort study of patients supported by VA-ECMO across North America, we found several patient demographic and clinical variables to be associated with inpatient mortality and discharge to a facility among survivors. These findings have potential to inform patients, family members, and clinicians regarding possible outcomes for patients started on VA-ECMO.

BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is a form of advanced life support that is increasingly being used to treat cardiac or pulmonary failure.¹⁻³ Utilization of veno-arterial (VA-) ECMO, which is specifically used in the setting of cardiovascular collapse, has increased more than 10 fold in the past 10 years in the US and around the world.⁴ With a growing list of indications for VA-ECMO and the potential of the technology to provide a critical bridge to recovery or durable treatment for patients with advanced heart failure,⁵⁻⁷ VA-ECMO has become and promises to continue as a cornerstone of life support for patients in the intensive care unit (ICU). However, inpatient mortality for patients supported by VA-ECMO is greater than 50%, and the frequency of complications is high.^{8,9} Due to the ability of VA-ECMO to sustain life nearly indefinitely, death for patients on VA-ECMO often occurs in the context of withdrawal of life-support when prognosis appears very poor.^{8,10} Among patients who are liberated from ECMO, many die prior to discharge and others have long-term disability.^{1,11,12}

Despite the relatively recent widespread adoption of VA-ECMO in ICUs and the rapid advancement of the technology in the past decade, literature is lacking regarding specific predictors of patient-centered outcomes. A few single center studies have observed pre-existing conditions (including elevated BMI) and markers of illness severity (such as the presence of shock and elevated blood levels of lactate) to be associated with inpatient mortality for patients started on VA-ECMO.¹³⁻¹⁶ Older age may also be associated with poor outcomes; however, the data are inconsistent.^{14,17} No large, multicenter study has yet evaluated predictors of survival to hospital discharge for patients initiated on VA-ECMO, or predictors of discharge home for those successfully liberated from VA-ECMO .

A clear understanding of which patients are at higher risk for certain adverse outcomes would be beneficial to patients, families, and medical providers. High quality care in the ICU necessitates alignment between these key stakeholders on patient goals and the likely outcomes of medical treatments.¹⁸ This alignment is facilitated by prognostic information and creates the foundation for shared decision-making between patients, families, and providers about treatment plans.¹⁹⁻²¹ More information regarding risk factors for poor patient outcomes after VA-ECMO, specifically those related to survival and recovery, could offer patients,

families, and clinicians important insight as they determine how to best align treatment and life support with patient values.

METHODS

This was a retrospective cohort study using data from a registry maintained by the Extracorporeal Life Support Organization (ELSO). This registry includes data from patients supported by ECMO at 577 centers around the world. The Registry Database Development Committee oversees the quality and validity of the registry's entries. For this study specifically, patients were eligible for inclusion if they were over 18 years of age and were supported by VA-ECMO in at a center in North America between 2017 and 2022. Patients were excluded if they were on a different form of ECMO (e.g. venovenous or veno-arterio-venous).

Among patients who underwent VA-ECMO, we assessed inpatient mortality in relation to demographic characteristics, body mass index (BMI), the presence of specific indications for ECMO (trauma, bridge to transplant, or cardiac arrest), and markers of illness severity at the time of ECMO initiation (pH, ECMO flow rate in liters per minute, use of renal replacement therapy, and use of vasoactive agents). ECMO flow rate was measured within 24 hours of initiation.

Next, among the cohort of patients who survived to hospital discharge, we examined the above characteristics as predictors of being discharged to a location other than home. This included discharge to a long-term acute care facility, discharge to a skilled nursing facility, transfer to another hospital, or discharge to hospice. Additional clinical indicators examined were the presence of complications while supported by ECMO, the duration of ECMO support in days, and the maximal level of mobility achieved while on ECMO. Complications were categorized as "major" or "minor" by the ELSO registry. The maximal level of mobility achieved while on ECMO was determined using the ICU mobility scale and categorized as 0 (no mobility), 1-3 (sitting in bed), 4-6 (standing to marching in place), or 7-10 (walking with assistance or better).²² The predictive ability of each characteristic for each of the two outcomes, beyond their association with age, was measured using the approach of Mantel and Haenszel.²³

RESULTS

Data were extracted for 24,481 patients at 334 ESLO sites across North America. Patients were 33.2% female with a mean age of 55.6 years (SD 14.5 years) and mean BMI of 30.3 kg/m² (SD 7.1). Patients were 60.7% White, 15.2% Black, 5.9% Hispanic, 3.2% Asian, 0.7% Native American/Pacific Islander, 8.3% Other, and 6.0% Unknown. Trauma was cited as the indication for ECMO in 1.2% of patients. ECMO was used as a bridge to transplant for 5.9% of patients. Cardiac arrest occurred immediately prior to ECMO initiation in 48.2% of patients. Renal replacement therapy was required prior to ECMO initiation for 8.1% of patients and vasoactive agents were used prior to ECMO for 69.1% of patients. At the time of ECMO initiation (within 24 hours of cannulation), the mean pH for the cohort was 7.26 (SD 0.16) and the mean ECMO flow rate was 3.99 L/min (SD 0.91). These results are displayed in Table 1.

Of the entire cohort, inpatient mortality was 56%. The proportion of patients who died increased steadily as age increased, with an inpatient mortality of 44.5% in the youngest patients (18 – 43.0 years) and 66.4% in the oldest patients (68.3 years and older). The risk of inpatient mortality among persons in the oldest category was 1.49 (CI 1.44 – 1.55) times that in the youngest. The proportion of patients who died also steadily increased as BMI increased: 50.5% mortality for patients with a BMI of 18.5 – 24.9 kg/m² and 61.9% mortality for patients with a BMI of 35 kg/m² or higher (age-adjusted relative risk 1.25 for BMI of 35 kg/m² or higher, 95% CI 1.17 – 1.33). Inpatient mortality was lower in those who were started on ECMO as a bridge to transplant (28.4% versus 58.1% compared to those who were started on ECMO for other reasons), with an age-adjusted relative risk of inpatient mortality of 0.50 (CI 0.44 – 0.58). Inpatient mortality was higher in those who experienced cardiac arrest prior to ECMO initiation (62.8% versus 48.7% among those who did not experience cardiac) with an age-adjusted relative risk of 1.34 (CI 1.28 – 1.40). Inpatient mortality was higher in those who required renal replacement therapy (70.6% versus 54.7% among those who did not), with an age-adjusted relative risk of 1.31 (CI 1.24 – 1.38). Inpatient mortality increased as baseline pH decreased, with 50.2% of patients with a pH at ECMO initiation largely within the normal range (7.32 – 7.39) and 67.6% of patients in the lowest pH category (<7.14) dying in the hospital. The age-adjusted relative risk of inpatient mortality for those in the lowest fifth of the distribution of pH relative to those whose pH most closely approximated normal was

1.42 (CI 1.32 – 1.53). The risk of inpatient mortality also appeared to increase as ECMO flow requirements within the first 24 hours increased. The age-adjusted relative risk among those with a flow rate >4.7 L/min was 1.23 (CI 1.14 – 1.33) compared to those with a flow rate <3.25 L/min. These results are displayed in Table 2 .

Out of the entire cohort of patients started on VA-ECMO, 10,843 patients survived to hospital discharge. Survivors had a mean age of 53.2 years (SD 14.7), were 33.3% female, and had a mean BMI of 29.6 kg/m² (SD 6.7). Among survivors, 16.3% were Black, 3.2% Asian, 6.0% Hispanic, 0.8% Native American or Pacific Islander, 8.5% other race, and 5.0% unknown race. Trauma was the indication for ECMO in 1.3% of survivors, bridge to transplant in 9.6%, and cardiac arrest preceded ECMO in 40.5% of survivors. Seventy-four percent of survivors were supported by ECMO for less than 7 days, 22.9% were supported between 7 and 21 days, and 3.1% of survivors were supported by ECMO for 21 days or more. Among survivors, 2.9% suffered major complications and 46% suffered minor complications while on ECMO. An ICU mobility score of 7 or greater was achieved by 4.7% of patients while supported by ECMO, while 51.5% of patients were immobile throughout their ECMO course (ICU mobility score 0). These results are displayed in Table 3 .

Among all survivors, 63.5% were discharged to a facility rather than home. The proportion of patients who were discharged to a facility increased steadily as age increased, 48.9% in the youngest patients (18 – 39.3 years) and 74.7% in the oldest patients (66.3 years and older) (Table 4). The relative risk for discharge to a facility was 1.53 (CI 1.45 – 1.61) for those in the oldest age category (66.3 years and older), compared to those in the youngest age category. The proportion of survivors who discharged to a facility in each BMI category increased as BMI increased, with 57.9% of survivors in the normal BMI range (18.5 – 24.9 kg/m²) and 69.2% of survivors in the highest BMI category (≥ 35 kg/m²) discharging to a facility. The age-adjusted relative risk for discharge to a facility was 1.21 (CI 1.12 – 1.32) for those with a with BMI of ≥ 35 kg/m² relative to those with a BMI of 18.5 – 24.9 kg/m². The proportion of survivors who were discharged to a facility was 76.1% among those who were supported for 21 days or more versus 60.4% among those who were supported by ECMO for 7 days or less (age-adjusted relative risk 1.33, CI 1.21 – 1.46). The proportion of survivors who were discharged to a facility was 57.4% among those who suffered no complications while supported by ECMO, in contrast to 78.0% of survivors who suffered major complications while supported by ECMO (age-adjusted relative risk 1.39, CI 1.25 – 1.56). Among survivors who achieved a maximal ICU mobility score of 7 or greater while supported by ECMO, the discharge to facility proportion was 36.1%, whereas survivors who were

immobile during their ECMO course had a discharge to facility proportion of 67.6% (age-adjusted relative risk of 0.55, CI 0.45 – 0.67). These results are displayed in Table 4.

DISCUSSION

We were able to identify some demographic and clinical characteristics of patients supported by VA-ECMO that predicted, to a modest extent, the likelihood of survival to hospital discharge and, among survivors, those who were discharged home and not to another medical facility. The risk of inpatient mortality increased as age increased, with nearly a 50% difference between the youngest and oldest age groups studied. A systematic review and meta-analysis of VA-ECMO for cardiogenic shock following cardiac surgery found age to be one of the most common adverse prognostic indicators,²⁴ and another of VA-ECMO for cardiogenic shock more broadly found that a 10 year increase in age was associated with a 9% higher risk of short term mortality in patients with underlying heart failure. One observational cohort study of 517 patients on VA-ECMO for refractory post-cardiotomy cardiogenic shock found that patients over age 70 had 1.6 the odds of death prior to discharge compared to those 70 years or younger (CI 1.01 – 2.69).²⁵ The very large size of our cohort suggests that positive relation of increasing age with inpatient mortality present in the studies of patients with cardiogenic shock likely applies to patients on VA-ECMO for a broader range of indications.

In this study, increased body mass index also was associated with risk of inpatient mortality and risk of discharge to a facility among survivors, although only to a moderate extent. One prior study of 89 patients between 2011 and 2019 on VA-ECMO found that survivors had a lower BMI (27.9 ± 4.2 kg/m² vs. 32.3 ± 7.5 kg/m² among decedents), and that the odds of survival to hospital discharge was 0.37 (CI 0.15 – 0.94) for those with a BMI ≥ 30 kg/m² compared to those with a BMI < 30 kg/m². The study to develop the ENCOURAGE Score to predict mortality after cardiogenic shock from myocardial infarction in 138 patients found that a BMI > 25 kg/m² was associated 3.10 times the odds of mortality compared to those with a lower BMI (CI 1.21 – 7.92).²⁶ However, another study of 355 patients supported by VA-ECMO from 2009 to 2019 did not find a clear association between BMI and survival to hospital discharge, with an OR of 0.95 (CI 0.75 – 1.20) for an increase in BMI of 5 kg/m² on multivariable logistic regression.²⁷

Several clinical variables also demonstrated modest associations with inpatient mortality in our cohort, namely pre-ECMO cardiac arrest, pre-ECMO requirement for renal replacement therapy, arterial pH, and ECMO flow within 24 hours of initiation. These variables are all markers of illness severity and overall health. A few prior studies have investigated the role of specific variables as they pertain to survival outcomes via prediction models for patients on VA-ECMO. Candidate variables for these models were initially considered if they were thought to have plausible biological relevance to ECMO outcomes, and were tested for association with mortality prior to inclusion in the models. For example, the Survival After Veno-arterial ECMO (SAVE) Score²⁸ incorporated the presence of renal dysfunction (creatinine >1.5) into its model after it found an odds ratio of 1.6 for inpatient mortality in those with renal dysfunction ($p < 0.001$). SAVE also included blood levels of bicarbonate and ENCOURAGE incorporated blood levels of lactate, but neither include pH nor ECMO flow rate.

No prior studies have investigated functional outcomes or discharge location following VA-ECMO. In our cohort of survivors, mobility while on ECMO was one of the strongest predictors of discharge home versus a facility. Likelihood of discharge home increased as maximum mobility achieved while on ECMO increased, with a relative risk of 1.97 (CI 1.83 – 2.12). In this cohort study we can make no assumptions about whether this association is causative or correlative. It is possible that low overall illness severity is a confounder, leading to both higher mobility and greater ability to discharge directly home. However, multiple studies in non-ECMO critically ill patients have found that early mobilization results in improved mobility, functional status, and muscle strength after hospitalization.^{29,30} Given these findings in a similar population, it is feasible that promoting mobility for patients on ECMO may result in greater functional status and therefore higher likelihood of discharging home.

In our cohort of survivors, variables related to a more complicated ECMO course, such as longer duration of ECMO support or the development of major or minor medical complications, were associated with lower likelihood of discharge home. Regardless of whether these events directly affect discharge location or simply correlate with discharge location, these predictors of discharge home versus a facility are important to identify. Patients and family members face a long recovery process beyond just the critical illness period, and PTSD, anxiety, and depression after critical illness are common among both groups.³¹⁻³⁴ Understanding who is

at risk for extended care needs following discharge may provide an important opportunity to prepare patients, families, and medical providers for the road ahead.

There are a few limitations to consider in the interpretation of the study results. First, registries have inherent variability in data inputs due to the diversity of contributing sources, which may lead to inconsistencies within the cohort data. However, registry oversight by ELSO's Registry Database Development Committee helps to standardize data input and minimize the number of erroneous entries. Second, as mentioned above, the observations made do not allow for conclusions regarding causal associations between predictors and outcomes. This observational cohort study can only identify associations, and the possibility of unaddressed confounding precludes our ability to say whether these associations are or are not causative. Lastly, these findings were based on a cohort of people to whom ECMO was administered. Many people are denied ECMO either because they are deemed too sick or, conversely, are not considered to be sick enough to benefit from ECMO. Accordingly, our results pertain only to those initiated on ECMO.

CONCLUSION

These findings suggest associations between several clinical and demographic variables and our two outcomes, inpatient mortality and, for those who survive, discharge to a facility versus home. Older age, higher BMI, pre-ECMO cardiac arrest, pre-ECMO need for renal replacement therapy, low pH, and high flow requirements within 24 hours of ECMO initiation were all associated with increased inpatient mortality. Patients who were started on ECMO as a bridge to transplant had a substantially lower risk of inpatient mortality. Among survivors, older age, higher BMI, and pre-ECMO cardiac arrest were associated with higher likelihood of discharging to a facility. Variables associated with a more complicated ECMO course were also associated with higher likelihood of discharge to a facility. These findings have potential to inform patients, family members, and clinicians regarding possible outcomes for patients started on VA-ECMO. The existing predictive models leave room for optimization, and more specific and sensitive markers of both survival and functional capacity at discharge are needed.

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