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Research Paper

Machine learning based predictive modeling of readmissions following extracorporeal membrane oxygenation hospitalizations☆

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ABSTRACT

Background: Despite increasing utilization and survival benefit over the last decade, extracorporeal membrane oxygenation (ECMO) remains resource-intensive with significant complications and rehospitalization risk. We thus utilized machine learning (ML) to develop prediction models for 90-day nonelective readmission following ECMO.

Methods: All adult patients receiving ECMO who survived index hospitalization were tabulated from the 2016–2020 Nationwide Readmissions Database. Extreme Gradient Boosting (XGBoost) models were developed to identify features associated with readmission following ECMO. Area under the receiver operating characteristic (AUROC), mean Average Precision (mAP), and the Brier score were calculated to estimate model performance relative to logistic regression (LR). Shapley Additive Explanation summary (SHAP) plots evaluated the relative impact of each factor on the model. An additional sensitivity analysis solely included patient comorbidities and indication for ECMO as potential model covariates.

Results: Of ~22,947 patients, 4495 (19.6 %) were readmitted nonelectively within 90 days. The XGBoost model exhibited superior discrimination (AUROC 0.64 vs 0.49), classification accuracy (mAP 0.30 vs 0.20) and calibration (Brier score 0.154 vs 0.165, all $P < 0.001$) in predicting readmission compared to LR. SHAP plots identified duration of index hospitalization, undergoing heart/lung transplantation, and Medicare insurance to be associated with increased odds of readmission. Upon sub-analysis, XGBoost demonstrated superior disclination compared to LR (AUROC 0.61 vs 0.60, $P < 0.05$). Chronic liver disease and frailty were linked with increased odds of nonelective readmission.

Conclusions: ML outperformed LR in predicting readmission following ECMO. Future work is needed to identify other factors linked with readmission and further optimize post-ECMO care among this cohort.

Introduction

Over the past decade, the use of extracorporeal membrane oxygenation (ECMO) for severe cardiopulmonary dysfunction has dramatically increased [1]. While significant advancements in technology and surgical management have yielded notable improvements in outcomes, ECMO remains a resource-intensive therapy that is associated with significant complications [2]. Ultimately, patients who survive to discharge following ECMO frequently suffer from sequelae of acute illness and physical deconditioning, often requiring repeat hospitalization [3].

With the aim of directing efforts for quality improvement, prior work has sought to delineate clinical factors associated with nonelective rehospitalization following ECMO [4]. Current models, however, remain limited due to the use of older, highly selective, or pediatric cohorts, thus reducing generalizability without accounting for local variations in clinical practice. Furthermore, published models generally lack external validation and demonstrate poor predictive performance, limiting their clinical utility [5]. Machine learning (ML) algorithms which utilize nonlinear data structures hold the promise of yielding

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prediction models with superior performance relative to traditional regression methods [6]. Indeed, ML modeling for survival after ECMO has shown improved discrimination and calibration compared to the regression-based Survival After veno-arterial ECMO score [7]. Given rising costs, and increasing emphasis on value-based healthcare, a contemporary prognostication of nonelective readmission is warranted. This model could potentially be used to predict readmission dynamically across centers.

In the present work, we utilized ML techniques to develop prediction models for readmission following hospitalization for ECMO using a national cohort. We hypothesized that the ML model would improve upon traditional methods in predictive and discriminatory power.

Methods

Data source and study population

The present study utilized the 2016–2020 Nationwide Readmissions Database (NRD), the largest publicly available all-payer readmissions repository in the US. The NRD provides hospital-based discharge weights to generate accurate estimates for ~60 % of all inpatient hospitalizations [8]. Unique patient identifiers allow tracking of readmissions within each calendar year and state.

All nonelective adult (≥18 years) hospitalizations entailing ECMO were identified using previously reported *International Classification of Diseases 10th Revision* (ICD-10) procedure codes [1]. Records missing data for age, sex, in-hospital mortality or hospitalization costs were excluded (<1 %). Only patients who survived index hospitalization were considered for analysis. Based on previously defined methodology, patients were categorized into the following groups for indication of ECMO: heart or lung transplant, postcardiotomy, cardiogenic shock, respiratory failure, and mixed cardiopulmonary failure [2].

Variable definitions and study outcomes

Patients hospitalized non-electively within 90 days of index ECMO discharge were considered the *Readmit* cohort, with all others grouped as *Non-Readmit* (Fig. 1). Patient and hospital characteristics, including age, sex, primary insurer, income quartile, hospital teaching status, hospital region and urban/rural location, were reported as defined by the Healthcare Cost and Utilization Project Data Dictionary [8]. The Elixhauser Comorbidity Index, a validated composite of 30 conditions, was used to quantify the burden of chronic conditions [9]. Patient frailty was ascertained using the binary Johns Hopkins Adjusted Clinical Groups tool, as previously detailed [10]. Individual comorbidities and perioperative complications were tabulated using previously reported ICD-10 diagnosis codes. Complications included cardiac (cardiac arrest, ventricular tachycardia, ventricular fibrillation, cardiac tamponade, myocardial infarction), respiratory (pneumothorax, pneumonia, acute respiratory failure, prolonged ventilation), neurologic (transient ischemic attack and cerebral infarction), renal (acute kidney injury), infectious (sepsis, septicemia, bacteremia, and central line bloodstream infection), and intraoperative (accidental puncture and hemorrhage) [11]. Hospitalization costs were calculated by the application of hospital-specific cost-to-charge ratios to overall charges and adjustment for inflation using the 2020 Personal Healthcare Index [12]. To account for institutional experience, centers were categorized into low-, medium-, and high-volume tertiles based on the total number of ECMO hospitalizations each year.

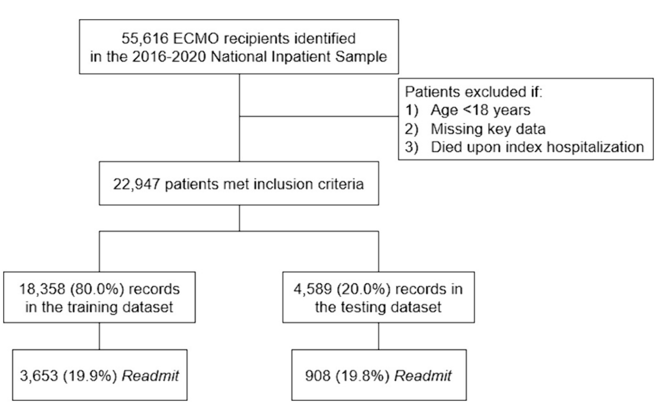

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of study cohort and survey-weighted sample size.

The primary outcome was the occurrence of at least one nonelective readmission within 90 days of discharge following ECMO hospitalization. Our main analysis considered patient demographics, comorbid conditions and indications for ECMO, as well as resource use complications and incurred during index hospitalization. We additionally performed a sensitivity analysis incorporating only patient demographics, concomitant comorbidities and indication for ECMO in the prediction model (Supplementary Table 1).

Model development and training

The study cohort was split randomly into training (80 %) and testing (20 %) sets. Models were derived using training data and evaluated using testing data. All variables included in the models are detailed in Supplementary Table 1. Categorical variables were split into binary classification to prevent variable misclassification and increase the granularity of discrete features [14].

Within the training set, ten-fold cross-validation was utilized for the identification of appropriate hyperparameters, which were used to optimize model performance. Briefly, this approach creates 10 random, equally-sized subgroups, and utilizes nine to train the model and one for validation. Within each subgroup, randomized search matrices identified hyperparameter values that maximize the c-statistic [15]. We report selected hyperparameters in Supplementary Table 2.

Following hyperparameter preprocessing, eXtreme Gradient Boosting (XGBoost) models were developed to predict readmission, and compared to traditional logistic regression (LR). Briefly, XGBoost generates an ensemble of decision trees to optimize a final prediction model; using a boosting algorithm, trees can learn from previous iterations [16]. In comparison, LR uses a single weight vector, which is then converted into a probability between 0 and 1 that could be used for classification efforts [17].

Recursive feature elimination was employed to select covariates of greatest predictive performance. Independent variables were ranked by individual feature importance. SHapley Additive exPlanation (SHAP) values were calculated to measure the marginal influence of each covariate on the output of the decision tree model [18]. Derived from cooperative game theory, this method assigns credit in arbitrary units to each included factor for model output [19].

Modeling evaluation and performance

Model discrimination was primarily evaluated using the area under the receiver operating characteristic (AUROC) curve. The Brier score was used to evaluate the calibration of each model. Briefly, a Brier score of 0 indicates that all predicted probabilities perfectly match observed outcomes, while a maximum score of 1 represents the poorest calibration [20]. Furthermore, precision-recall curves were constructed to evaluate sensitivity and positive predictive value across all risk thresholds. The mean average precision (mAP) was calculated as the area under the precision-recall curve [21]. Calibration plots were created to assess how well predicted probabilities matched expected outcomes [22].

Statistical analysis

Continuous variables were reported as medians with interquartile range (IQR). Categorical variables were presented as frequencies (%). Baseline characteristics were compared using the χ^2 test and adjusted Wald or Mann-Whitney *U* tests. Cuzick's nonparametric test was applied to assess the statistical significance of nonparametric test of trends [13].

All statistical analysis was performed using Stata 16.1 (StataCorp, College Station, TX) and Python 3.11.6 (Python Software Foundation, Wilmington, DE). Statistical significance was set at $\alpha = 0.05$. This study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles, due to the de-identified nature of the data.

Results

Baseline demographics and outcomes

Of ~22,947 patients included for analysis, 4495 (19.6 %) were considered the *Readmit* cohort. Over the study period, the number of hospitals performing ECMO increased from 263 in 2016 to 384 in 2020, $P < 0.05$. However, the proportion of patients nonelectively readmitted decreased from 20.5 % to 17.2 % (2016 to 2020, $P < 0.01$). On average, the *Readmit* group was older (54 [41–63] vs 52 [38–62] years, $P < 0.001$) and less commonly privately insured (37.5 vs 44.7 %, $P < 0.001$), compared to *Non-Readmit* (Table 1). Those who underwent nonelective rehospitalization were more commonly placed on ECMO for heart or lung transplant (26.3 vs 14.2 %, $P < 0.001$) and cardiogenic shock (6.6 vs 6.2 %, $P < 0.001$), relative to *Non-Readmit*.

During index hospitalization, *Readmit* patients more frequently experienced intraoperative (7.0 vs 5.7 %, $P = 0.02$) and renal (56.7 vs 53.5 %, $P = 0.01$) complications, but less often developed respiratory sequelae (53.2 vs 56.3 %, $P = 0.01$). Further, the *Readmit* cohort demonstrated longer index LOS (45 [43–47] vs 35 [34–36], $P < 0.001$) and greater hospitalization costs (30 [28–31] vs 24 [23–25], $P < 0.001$), relative to *Non-Readmit* (Table 2).

Table 1
Demographic and clinical characteristics of patients undergoing ECMO were stratified by nonelective readmission within 90 days.

	Non-Readmit (n = 18,452)	Readmit (n = 4495)	P-value
Age, median (IQR)	52 (38–62)	54 (41–63)	<0.001
Female, %	36.7	36.3	0.75
Elixhauser (mean, SD)	3.9 ± 0.1	4.1 ± 0.1	<0.001
Income quartile, %			0.18
76th–100th	23.2	22.3	
51st–75th	25.0	23.6	
26th–50th	26.9	26.6	
0–25th	24.9	27.1	
Insurance coverage, %			<0.001
Private	44.7	37.5	
Medicare	26.5	35.8	
Medicaid	20.6	20.6	
Other[a]	8.2	6.1	
Indication for ECMO, %			<0.001
Post cardiotomy	13.2	12.6	
Cardiogenic shock	6.2	6.6	
Respiratory failure	53.3	41.3	
Mixed cardiopulmonary failure	13.1	13.2	
Heart or lung transplant	14.2	26.3	
Comorbidities, %			
Congestive heart failure	42.7	48.2	<0.001
Cardiac arrhythmia	39.4	41.1	0.19
Pulmonary circulatory disorder	17.5	20.2	0.01
Hypertension	31.5	32.8	0.31
Neurologic disorders	23.6	21.8	0.07
Chronic lung disease	14.0	14.4	0.61
Diabetes	14.3	16.0	0.05
Late-stage kidney disease	4.5	7.7	<0.001
Liver disease	19.6	22.7	0.001
Cancer	2.4	3.1	0.06
Coagulopathy	33.0	36.2	0.01
Hospital teaching status, %			0.05
Non-Metropolitan	0.5	0.2	
Metropolitan non-teaching	4.4	3.6	
Metropolitan teaching	95.2	96.2	

Abbreviations: *IQR*, interquartile range, *ECMO*, extracorporeal membrane oxygenation, *SD*, standard deviation.

[a] Includes self-pay, uninsured, and other

Model discrimination and performance

As shown in Fig. 2, XGBoost demonstrated superior discrimination (AUROC 0.64 vs 0.49, $P < 0.001$) compared to LR. XGBoost continued to exceed LR when evaluated by mAP and the Brier score (Table 3). Both models exhibited modest calibration, with increasing error at high estimates of risk (Fig. 3).

Feature importance

Features of greatest predictive importance were described through SHAP Summary plots (Fig. 4A). Undergoing heart or lung transplantation or developing acute renal injury were associated with increased risk of nonelective readmission. Certain comorbid conditions were additionally linked with increased nonelective readmission, including congestive heart failure and diabetes mellitus. In contrast, respiratory failure and postoperative acute respiratory distress syndrome were linked with lower odds of nonelective readmission.

Secondary analysis

As in our primary analysis, ML prognostic indices of pre-hospitalization features demonstrated improved performance compared to logistic regression (Supplementary Table 3). SHAP summary plots revealed patient frailty, concurrent cancer, and lowest income quartile were associated greater likelihood of nonelective readmission, while private insurance was linked with lower odds (Fig. 4B).

Discussion

Advances in selection and perioperative management of ECMO candidates have yielded steady improvements in survival over the last decade. Yet, readmission following hospitalization for ECMO remains both frequent and resource-intensive. In the present study, we applied

Table 2
Unadjusted clinical and financial outcomes of readmitted vs non-readmitted patients following ECMO.

	Non-Readmit (n = 18,452)	Readmit (n = 4495)	P-value
Clinical outcomes (%)			
Cardiac complication	37.8	37.6	0.92
Respiratory complication	56.3	53.2	0.01
Infectious complication	36.7	36.6	0.98
Intraoperative complication	5.7	7.0	0.02
Acute kidney injury	53.5	56.7	0.01
Financial outcomes			
Length of stay, median days [IQR]	35 [34–36]	45 [43–47]	<0.001
Costs, $1000 USD, median [IQR]	24 [23–25]	30 [28–31]	<0.001

Categorical outcomes reported as proportions (%) unless otherwise specified. Continuous outcomes reported as medians with interquartile ranges with units as specified.

Abbreviations: *ECMO*, extracorporeal membrane oxygenation, *USD*, United States Dollar; *IQR*, Interquartile Range.

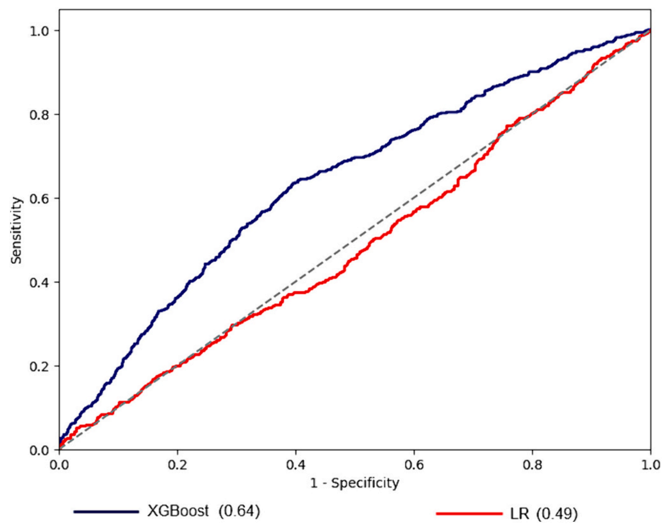

Fig. 2. Receiver Operating Characteristics of Logistic Regression and XGBoost. XGBoost exhibited greater discriminatory power in the prognostication of nonelective rehospitalization compared to LR within the testing dataset, demonstrated by incremental area under the Receiver Operating Characteristic Curve.

Table 3
Performance metrics between machine learning (XGBoost) versus logistic regression (LR).

Metric	LR (95 % CI)	XGBoost (95 % CI)
AUROC	0.488 (0.483–0.493)	0.636 (0.630–0.642)
Recall	0.490 (0.479–0.502)	0.609 (0.598–0.620)
Precision	0.200 (0.198–0.201)	0.272 (0.269–0.274)
Brier score	0.165 (0.162–0.168)	0.154 (0.151–0.158)

Performance metrics reported as mean with 95 % confidence intervals and obtained via 10-fold cross validation.
LR: Logistic Regression; *CI*, Confidence Interval; *AUROC*: Area Under the Receiver Operating Characteristic.

robust ML techniques to predict 90-day nonelective readmission following ECMO hospitalizations and made several important observations. Relative to logistic regression, machine learning demonstrated superior discrimination, calibration and predictive power. Furthermore, we identified several patient factors predictive of readmission. With implications towards ECMO-related practice and policy, several of these findings merit further discussion.

In the present work, ML models exhibited superior accuracy in evaluating nonelective readmission, compared with LR. Prior literature has validated the utility of ML techniques to predict outcomes following ECMO [23]. In a single-institution study of 282 patients, Ayers et al. implemented neural network learning to predict survival following VA-ECMO, reporting significant performance improvements compared to regression-based prognostic scores [7]. Similarly, Abassi and colleagues reported enhanced precision of XGBoost relative to LR in the prediction of severe hemorrhage and thrombosis during cannulation [24]. In line with this literature, our XGBoost model consistently outperformed LR modeling across various performance metrics. Ultimately, the superior predictive power of ML techniques is likely attributable to decision tree architecture, which adjusts for nonlinear interactions between covariates and outcomes of interest [6]. These factors may be especially significant in the context of readmission, which can result from complex interactions among a patient's in-hospital course, clinical disposition, comorbidities, and psychosocial environment [25]. While long-term follow-up data was unavailable for the present analysis, clinicians and centers could build on this work using more granular local datasets and validate our prognostic models for specific hospital contexts.

After evaluating SHAP values, we identified several patient factors that confer high readmission risk, including comorbid congestive heart failure and receipt of a heart or lung transplant during ECMO hospitalization. These conditions imply long-term chronic illness and decreased physiologic reserve, potentially increasing vulnerability to complications and readmission [26]. In particular, transplant patients may face poor functional status at baseline as well as the need for daily immunosuppression, limiting their ability to resist and recover from significant complications. Interestingly, we found acute respiratory distress syndrome and respiratory failure to be linked with lower odds of readmission. Generally, these patients present with respiratory failure secondary to acute illness; they are younger and face a lower burden of chronic disease, relative to the overall ECMO patient population [27]. Therefore, after adequate recovery, it is likely these patients are at lower risk for complications, disease sequelae, and eventual rehospitalization. Future studies should consider the role of post-discharge monitoring and follow-up care for patients facing greatest likelihood for readmission. These data could further reveal the longitudinal impact of ECMO beyond three months following initial hospitalization. Additionally, given patients who received ECMO may face unique sequelae of both their disease and treatment, the development of a specific post-discharge longitudinal care pathway could reduce readmission risk, while improving short- and longer-term recovery through targeted care.

In our sensitivity analysis which solely utilized patient-level factors

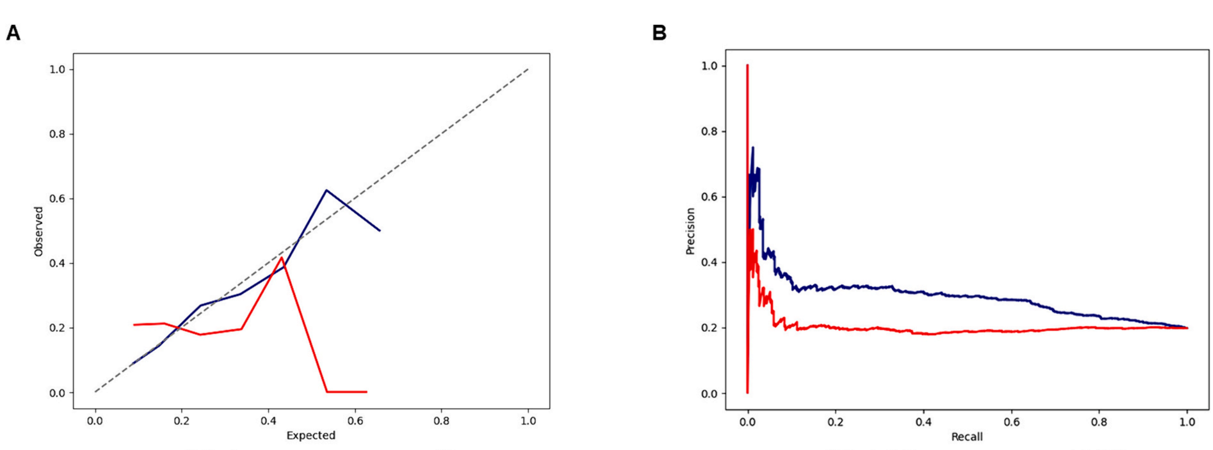

Fig. 3. (A) Calibration plot for XGBoost and Logistic Regression. XGBoost was more accurate in predicting nonelective readmission across higher risk thresholds. (B) Precision Recall Curves for Logistic Regression and XGBoost. The XGBoost model demonstrated greater classification accuracy, as indicated by enhanced mean average precision score.

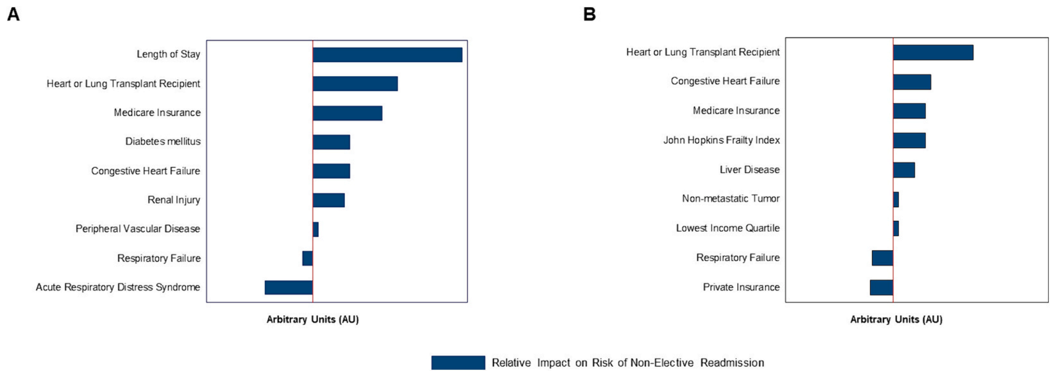

Fig. 4. (A) Feature importance of XGBoost model in predicting nonelective readmission following ECMO procedures. (B) Feature importance of XGBoost model in predicting nonelective readmission solely including patient comorbidities, demographics and indication for ECMO. SHAP Values were measured in arbitrary units and demonstrate the ten most important covariates on outcome prediction.

as readmission predictors, XGBoost continued to exceed LR across performance metrics. In line with research evaluating the impact of socioeconomic disadvantage on outcomes following ECMO for cardiogenic shock, we found lowest income and public insurance to confer greater readmission risk [5]. Furthermore, we identified patient frailty and comorbid liver disease as independent risk factors for rehospitalization. Notably, this finding accords with prior work that has linked liver dysfunction with inferior clinical outcomes during and after ECMO. In a single institution study of 187 ECMO runs, Sandrio et al. found both pre-ECMO liver impairment or high Model for End-Stage Liver Disease score to confer significantly greater mortality risk [28]. While pre-existing hepatic dysfunction is currently incorporated in existing ECMO mortality prediction models, our investigation suggests it may also be impactful for readmission [29]. We recognize many of these factors may not be modifiable, and certainly not during an acute hospitalization. Ultimately, the incorporation of these factors could help identify patients at greatest risk for rehospitalization early in their hospital course. Indeed, multi-disciplinary clinical teams could take this risk into account when discharge planning and coordinating follow-up care. Yet, efforts are needed to ensure sociodemographic risk factors do not negatively influence patient selection and further contribute to known disparities in receipt of this life-saving modality [30].

The present study has several limitations related to its retrospective nature. ICD coding may be influenced by physician-level and institutional billing practices. The NRD does not offer granular clinical, radiographic, or laboratory data to assess the disease severity of each individual patient. Moreover, ECMO-specific data points including flow rate, ventilator settings, and cannulation sites could not be ascertained in the NRD. Surgeon ECMO experience was unavailable for analysis, as were certain hospital metrics, such as nurse-to-patient ratios or utilization of standardized recovery pathways. The NRD does not capture out-of-hospital complications or follow-up care, nor does it report admitting diagnoses, preventing the adjustment of our models to these features. Future studies could consider the impact of such information on the AUROC and performance of readmission prediction models. Additionally, while we were unable to compare our machine-learning models to published algorithms, we utilized logistic regression with traditional methods for covariate selection for comparison. Nonetheless, the present study utilized a nationally representative sample and thorough statistical methods to present a robust ML-based analysis of readmission following ECMO.

In conclusion, we report that ML outperforms traditional LR in the prediction of nonelective readmission within 90 days following hospitalization for ECMO. With continued adoption and utilization of ECMO, the implementation of more accurate readmission risk assessments, such as the model detailed in the present work, could enhance care transitions and post-discharge follow-up. Altogether, improved readmission prediction and appropriately targeted interventions could improve both the value and quality of care for these complex patients.

Study type

Retrospective cohort study.

Ethics approval statement

The data that support the findings of this study are available from the Healthcare Cost and Utilization Project (HCUP). Restrictions apply to the availability of these data, which were used with permission for this study. Data are available from the authors with the permission of the Healthcare Cost and Utilization Project. This study was deemed exempt from full review by the Institutional Review Board at the University of California, Los Angeles, due to the de-identified nature of the data.

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CRediT authorship contribution statement

Jeffrey Balian: Conceptualization, Data curation, Methodology, Writing – original draft. **Sara Sakowitz:** Methodology, Validation, Writing – review & editing. **Arjun Verma:** Conceptualization, Validation. **Amulya Vadlakonda:** Conceptualization, Validation. **Emma Cruz:** Validation. **Konmal Ali:** Writing – review & editing. **Peyman Benharash:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have no related conflicts of interest or disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2024.04.003.

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