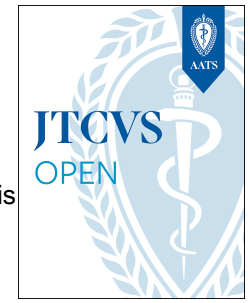

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Acute Brain Injury Risk Prediction Models in Venoarterial Extracorporeal Membrane Oxygenation Patients with Tree-Based Machine Learning: An ELSO Registry Analysis

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Abbreviations

ABG	arterial blood gas
ABI	acute brain injury
AUC-ROC	area under the receiver-operating characteristic curve
BMI	body mass index
CI	confidence interval
CNS	central nervous system
DBP	diastolic blood pressure
DPAP	diastolic pulmonary arterial pressure
ECMO	extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
ICH	intracranial hemorrhage

IQR	interquartile range
LOOCV	leave-one-out-cross-validation
ML	machine learning
MPAP	mean positive airway pressure
NPV	negative predictive value
$PaCO_2$	partial pressure of carbon dioxide
PaO_2	partial pressure of oxygen
PCWP	positive capillary wedge pressure
PEEP	positive end-expiratory pressure
PIP	positive inspiratory pressure
PP	pulse pressure
PPV	positive predictive value
SBP	systolic blood pressure
SD	standard deviation
SHAP	Shapley Additive Explanations
SPAP	systolic pulmonary arterial pressure
SvO_2	venous oxygen saturation
VA	venoarterial
VV	venovenous

Guarantor statement:

Andrew Kalra is responsible for the data analysis and all content of the manuscript.

Author contributions: Andrew Kalra: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. Preetham Bachina: Methodology, Validation, Formal analysis, Investigation, Writing – review & editing, Visualization. Benjamin L. Shou: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing. Jaeho Hwang: Validation, Writing – review & editing. Meylakh Barshay: Validation, Writing – review & editing. Shreyas Kulkrani: Validation, Writing – review & editing. Isaac Sears: Validation, Writing – review & editing. Carsten Eickhoff: Methodology, Validation, Visualization, Writing – review & editing. Christian A. Bermudez: Validation, Writing – review & editing. Daniel Brodie: Data curation, Writing – review & editing. Corey Ventetuolo: Validation, Writing – review & editing. Glenn J. R. Whitman: Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision, Project administration. Adeel Abbasi: Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision. Sung-Min Cho: Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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Central Picture Legend: Most important factors for predicting acute brain injury in 35,855 VA-ECMO patients.

Central Message. Machine learning predicted ABI in VA-ECMO patients with mediocre performance. Nevertheless, it identified longer ECMO duration and higher ECMO pump flow as the most important factors for ABI.

Perspective Statement: Predicting ABI with machine learning in the ELSO Registry was substandard due to lack of data granularity. Standardized neurological monitoring and more granular data collection across ELSO centers are important to detect the true prevalence of ABI. Nevertheless, machine learning identified longer ECMO duration and higher ECMO pump flow as the most important factors for ABI in VA-ECMO patients.

Abstract

Objective: We aimed to determine if machine learning (ML) can predict acute brain injury (ABI) and identify modifiable risk factors for ABI in venoarterial extracorporeal membrane oxygenation (VA-ECMO) patients.

Methods: We included adults (≥18 years) receiving VA-ECMO or extracorporeal cardiopulmonary resuscitation (ECPR) in the Extracorporeal Life Support Organization Registry (2009-2021). Our primary outcome was ABI: central nervous system (CNS) ischemia, intracranial hemorrhage (ICH), brain death, and seizures. We utilized Random Forest, CatBoost, LightGBM and XGBoost ML algorithms (10-fold leave-one-out cross-validation) to predict and identify features most important for ABI. We extracted 65 total features: demographics, pre-ECMO/on-ECMO laboratory values, and pre-ECMO/on-ECMO settings.

Results: Of 35,855 VA-ECMO (non-ECPR) patients (median age=57.8 years, 66%=male), 7.7% (n=2,769) experienced ABI. In VA-ECMO (non-ECPR), the area under the receiver-operator characteristics curves (AUC-ROC) to predict ABI, CNS ischemia, and ICH was 0.67, 0.67, and 0.62, respectively. The true positive, true negative, false positive, false negative, positive, and negative predictive values were 33%, 88%, 12%, 67%, 18%, and 94%, respectively for ABI. Longer ECMO duration, higher 24h ECMO pump flow, and higher on-ECMO PaO_2 were associated with ABI. Of 10,775 ECPR patients (median age=57.1 years, 68%=male), 16.5% (n=1,787) experienced ABI. The AUC-ROC for ABI, CNS ischemia, and ICH was 0.72, 0.73, and 0.69, respectively. Longer ECMO duration, older age, and higher 24h ECMO pump flow were associated with ABI.

Conclusions: In the largest study predicting neurological complications with ML in ECMO, longer ECMO duration and higher 24h pump flow were associated with ABI in non-ECPR and ECPR VA-ECMO.

Keywords: machine learning; extracorporeal membrane oxygenation; acute brain injury; Extracorporeal Life Support Organization; neurological complications

Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly used for cardiopulmonary support.(1) Acute brain injury (ABI), which includes central nervous system (CNS) ischemia, intracranial hemorrhage (ICH) and hypoxic-ischemic brain injury, (HIBI) is reported to occur in up to 20% of adult venoarterial (VA)-ECMO patients(2) in the Extracorporeal Life Support Organization (ELSO) Registry. Furthermore, this rate is as high as 33% in VA-ECMO patients using noninvasive multimodal neuromonitoring at a single institution.(3) With greater ECMO usage and more cases of ABI, accurately predicting ABI with modifiable risk factors such as hyperoxia(4), low pulse pressure (PP)(5, 6), and hypercarbia(7) is important to lessen its occurrence.

In VA-ECMO, there have been several scoring systems developed to predict survival outcomes,(8-11) but their generalizability is limited as they stem from single-center studies, are focused in a specific subset of patients (e.g., only cardiogenic shock), and were created from logistic regression. Machine learning (ML) leverages big data to explore patterns and interactions without explicit programming from humans, thus offering distinct advantages to traditional regression.(12) Furthermore, coupled with the large sample size of the ELSO Registry, ML may be the most promising technique to adequately synthesize demographic and laboratory information to effectively predict ABI.(13) Additionally, identifying variables in the ML model that impact clinical outcomes will inform ECMO clinicians for mitigation of key risk factors for ABI.

Current literature applying ML to predict outcomes in ECMO patients is sparse and primarily focused on non-neurological outcomes such as thrombosis/hemorrhage and mortality.(14-16) An ELSO Registry analysis of VA-ECMO patients (n=23,812) demonstrated

ML yielded better prediction for in-hospital mortality (area under the receiver-operator characteristics curves, AUC-ROC=0.80) versus the SAVE score (AUC-ROC=0.61).(15) This study demonstrated the power of ML when applied to the ELSO Registry, and provided the impetus for this study designed to test the capability of ML to predict ABI.

Herein, we aimed to leverage ML to predict ABI in a large international cohort (the ELSO Registry) of ECMO patients.

Methods

Study design and population

The Johns Hopkins Hospital Institutional Review Board approved this retrospective observational study (IRB00216321) with a waiver of informed consent on 10/22/2019. "Retrospective Analysis of Outcomes of Patients on Extracorporeal Membrane Oxygenation" is the study title. All procedures were followed in accordance with the Helsinki Declaration of 1975 and the ethical standards of the responsible committee on human experimentation (institutional or regional). The ELSO Registry is an international multicenter database from over several hundred ECMO centers worldwide. It collects clinical characteristics and demographics, pre-ECMO and on-ECMO laboratory values such as arterial blood gas (ABG), on-ECMO complications, and outcomes like in-hospital mortality through voluntary participation. Comorbidity information was captured using the *International Classification of Diseases, 10th Revision (ICD-10)* codes.

We included patients who were 1) 18 years of age or older; and 2) supported with VA-ECMO for extracorporeal cardiopulmonary resuscitation (ECPR) and non-ECPR indications from 2009-2021. We excluded repeat ECMO runs within the same patient to avoid bias and complexity. VA-ECMO and ECPR cohorts were analyzed separately.

Data collection

In total, 65 variables were collected (**Figure 1)** for ML. The ELSO Registry collects ABG and hemodynamics pre-ECMO support and on-ECMO. Both pre-ECMO ventilator settings and ABGs were drawn within 6 hours of starting ECMO cannulation. If multiple ABGs existed within a specific period, the pre-ECMO ABG that was nearest to the start of ECMO cannulation was chosen. On-ECMO hemodynamic and ABG information were drawn closest to 24 hours of ECMO support. Values that were meant to be obtained simultaneously such as systolic and diastolic blood pressure and oxygen saturation by pulse oximetry and by arterial blood gas were abstracted by a trained ELSO data manager/abstracter from each center and were collected concurrently.

Definitions

ABI was defined as the presence of infarction (ischemic stroke), diffuse ischemia (HIBI), intra/extra parenchymal hemorrhage, intraventricular hemorrhage, seizures determined by electroencephalograph or clinically, and neurosurgical intervention (examples include intracranial pressure monitor, external ventricular drain, and craniotomy) during ECMO support. CNS ischemia was defined as ischemic stroke (determined by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI))) and HIBI (determined by CT or MRI). ICH was defined as intra/extra parenchymal hemorrhage and intraventricular hemorrhage (both determined by CT or MRI). Definitions for other variables included in our analysis are in the **Supplemental Methods.**

Outcomes

The primary outcome was the occurrence of ABI during ECMO support. Secondary outcomes included subtypes of ABI such as CNS ischemia and ICH.

Statistical analysis

Continuous variables were represented as median with interquartile range. Categorical variables were presented as frequency with percentages. The Wilcoxon rank-sum and Pearson's chi-square tests were utilized to compare continuous and categorical variables, respectively. Statistical significance was set at a p-value <0.05.

Data Pre-Processing

All categorical variables were one hot-encoded prior to running ML algorithms. Multiple imputation was used for missing data. All missing variables are shown in **Supplemental Table 1**.

Machine Learning Algorithm and Pipeline

We examined the suitability of 4 ML algorithms in predicting ABI from the ELSO Registry containing variables from pre-ECMO support and during ECMO support: Random Forest, CatBoost, LightGBM and XGBoost. For each algorithm, we fine-tuned the hyperparameters and used a Bayesian optimization onto our dataset split randomly into training (70%) and test (30%) sets. Further details are noted in the **Supplemental Methods.**

Feature Importance Scores in ML

To better understand how these ML models were constructed and to determine which variables were most important in predicting ABI, we analyzed which variables were of highest importance in correctly predicting ABI. Specifically, we examined the ranked feature importance in the best performing models, which discloses the contribution of each variables in the composition of the boosted decision trees within the model. We primarily focused on the top 3 most important features for ease of comparison and interpretability for the reader. Furthermore, Feature Importance Scores and Shapley Additive Explanations (SHAP) values depict the contribution of a variables on the predictions of the model (**Supplemental Methods).** Both Feature Importance Scores and SHAP values add interpretability to the model framework and reveal pertinent clinical variables

associated with ABI. All statistical analyses were performed using R Studio (R 4.1.2, www.r-project.org) and Python.

Results

VA-ECMO (non-ECPR)

Of 35,855 VA-ECMO (non-ECPR) patients, 2,769 (8%) had ABI (**Supplemental Table 2**, **Figure 2)**. The median age was 57.8 years (interquartile range, IQR:45.9-66.4) and 66% (n=23,542) were male. The median duration of ECMO support was 4.3 days (IQR:2-7.7).

Model Performance

Using the leave-one-out-cross-validation (LOOCV) 10-fold approach, for predicting ABI in VA-ECMO patients, the model achieved an AUC-ROC of 0.67 **(Figure 3A)**. The accuracy of the model was 83%. The true positive rate, true negative rate, false positive rate, and false negative rate were 33%, 88%, 12%, and 67%, respectively (**Table 1)**. The positive predictive value (PPV) and negative predictive value (NPV) were 18% and 94%, respectively. The area under the precision recall curve was 0.15. The precision, recall, and F1 were 0.15, 0.38, and 0.22, respectively.

For predicting CNS ischemia, the model achieved an AUC-ROC of 0.67 **(Figure 3B)**. The accuracy of the model was 86%. The true positive rate, true negative rate, false positive rate, and false negative rate were 33%, 88%, 12%, and 67%, respectively. The PPV and NPV were 11% and 97%, respectively. The area under the precision recall curve was 0.09. The precision, recall, and F1 were 0.11, 0.25, and 0.15, respectively.

For ICH, the model achieved an AUC-ROC of 0.62 **(Figure 3C)**. The accuracy of the model was 97%. The true positive rate, true negative rate, false positive rate, and false negative rate were 5%, 99%, 1%, and 95%, respectively. The PPV and NPV were 8% and 98%,

respectively. The area under the precision recall curve was 0.03. The precision, recall, and F1 were 0.05, 0.11, and 0.07, respectively.

Feature Importance

We identified the top 3 most important variables per Feature Importance Scores and depict the remaining variables (**Figure 4A, Supplemental Figure 1A, Supplemental Table 3**). The top 3 variables in predicting ABI were longer duration of ECMO support, higher ECMO pump flow rate at 24 hours, and higher on-ECMO PaO_2, in predicting CNS ischemia were higher ECMO pump flow rate at 24 hours, pre-ECMO cardiac arrest, and conventional ventilation at 24 hours of ECMO support, and in predicting ICH were longer duration of ECMO support, higher ECMO pump flow rate at 4 hours, and higher on-ECMO PaO_2 (**Supplemental Results, Figure 4B-C and Supplemental Figure 1, Supplemental Tables 3-5).**

ECPR

Of 10,775 ECPR patients, 1,787 (16.5%) had ABI (**Figure 1, Supplemental Table 6)**. The median age of the ECPR cohort was 57.1 years (IQR:45.5-65.9) and 68% (n=7,388) were male. The median duration of ECMO support was 2.63 days (IQR:0.88-5.33).

Model Performance

For predicting ABI in ECPR patients, the model achieved an AUC-ROC of 0.72 **(Supplemental Figure 2A)**. The accuracy of the model was 69%. The true positive rate, true negative rate, false positive rate, and false negative rate were 61%, 70%, 30%, and 39%, respectively (**Supplemental Table 7**). The PPV and NPV were 29% and 90%, respectively.

For predicting CNS ischemia, the model achieved an AUC-ROC of 0.73 **(Supplemental Figure 2B)**. The accuracy of the model was 81%. The true positive rate, true negative rate, false

positive rate, and false negative rate were 41%, 85%, 15%, and 59%, respectively. The PPV and NPV were 18% and 95%, respectively.

For ICH, the model achieved an AUC-ROC of 0.69 **(Supplemental Figure 2C)**. The accuracy of the model was 88%. The true positive rate, true negative rate, false positive rate, and false negative rate were 28%, 89%, 11%, and 72%, respectively. The PPV and NPV were 7% and 98%, respectively.

Feature Importance

The top 3 variables for predicting ABI were longer duration of ECMO support, older age, and higher ECMO pump flow rates at 24 hours and further details are depicted in the **Supplement** (**Supplemental Figures 3-4, Supplemental Tables 8-10, Supplemental Results)**.

Exploratory Analysis – Features and Mortality

A multivariable logistic regression model assessing mortality with the top 3 most important features for ABI in VA-ECMO patients was constructed for comparison. A longer ECMO duration (adjusted odds ratio=1.019, 95% confidence intervals=1.014-1.024) and higher on-ECMO PaO_2 (adjusted odds ratio=1.214, 95% confidence intervals=1.185-1.244, both $p<0.001$) level were both associated with increased mortality; higher ECMO pump flow rate at 24h (adjusted odds ratio=1.027, 95% confidence intervals=0.984-1.089, p=0.275) was not associated with mortality.

Discussion

This is the first ML study leveraging a large international database to predict ABI in ECMO patients, conveying novelty and generalizability of our study's results (**Figure 5**)

VA-ECMO vs. Venovenous (VV)-ECMO risk factors

ML uniquely identified longer duration of ECMO support (in hours), higher ECMO pump flow rate at 24 hours of ECMO support, and higher on-ECMO 24-hour PaO_2 as the top 3 most important

variables associated with ABI. Although ECMO duration is not necessarily a modifiable risk factor, it is still an important feature to monitor as a difference in 12 hours is a clinically significant difference, as previously shown in another ELSO Registry analysis.(17) As VV-ECMO patients have been shown to be cannulated longer than VA-ECMO patients,(18-20) the longer ECMO duration and lower risk of ABI associated may be attributed to the withdrawal of life-sustaining therapy for severely sick patients.(21, 22) Accordingly, this may have created a selection bias for patients who did undergo ABI and survived on ECMO support for longer. Furthermore, a higher ECMO pump flow rate and likely corresponding hemolysis(23, 24) was uniquely important for ABI in VA-ECMO and ECPR, but not in VV-ECMO. This finding may reflect the different hemodynamic/physiological states(23-25) and use/disuse of an aortic cannula(26) in VA- versus VV-ECMO populations and warrants further study. While pre-ECMO cardiac arrest is a known risk factor for CNS ischemia in ECPR patients,(2, 27) likely related to reperfusion injury and associated reactive oxygen species formation,(27, 28) we also note that this factor was highly important in VV-ECMO patients(29) which has not been previously reported. These comparisons suggest there are similar underlying but overall divergent risk factors between these populations, which necessitates further investigation with prospective observational studies. Hyperoxia (PaO_2 was treated as a continuous variable to avoid bias due to "data binning"(30)) is associated with increased risk of ABI due to generation of reactive oxygen species(28) and impairment of hippocampal oxidative energy metabolism(31) which accentuate reperfusion injury, as suggested in a previous ELSO Registry analysis(4) and at a tertiary academic ECMO center.(32) Notably, central cannulation was the 10^{th} most important feature for CNS ischemia, which is in line with previous literature demonstrating differences in rates of ABI based on cannulation strategy(33) although other studies demonstrate no significant differences in neurological injury between both

strategies.(34, 35) Finally, older age was associated with an increased risk of ABI, which agrees with a 2017-2019 ELSO Registry analysis (n=15,172) of VA-ECMO patients that demonstrated that older age was associated with higher complication rates.(36)

Machine learning methodologies

We chose tree-based ML algorithms to predict ABI, which are becoming more commonly used in healthcare studies(37) as they provide an effective way to consider all different possible outcomes in a model. There are several specific advantages of tree-based ML algorithms over non-tree based models including 1) the ability to input a wide variety of data (i.e., both continuous and categorical), 2) the capability to handle data that is complex, non-linear, and not normally distributed, 3) the ability to easily visualize complex data through Feature Importance and SHAP value plots, 4) they do not require extensive data cleaning and preparation as data variable transformations are not required, and 5) their ability to capture subtle data patterns by separating features into mutually exclusive and distinctive regions.(38-41) Additionally, recent data has suggested that tree-based ML models may be statistically significantly superior than non-tree-based ML models with tabular data.(42) Furthermore, these tree-based ML models demonstrate high power, good accuracy, and provide interpretability to the models.(43) The primary difference between using Random Forest vs. gradient boosting tree methods is that Random Forest trees are constructed in an independent fashion while gradient boosting methods are created sequentially. Accordingly, Random Forest can determine their outputs without restriction of order while gradient boosting methods like XGBoost are restricted in a more fixed manner. There are also key differences within boosting methods: CatBoost may be most optimal for categorical data and can generate output more quickly than XGBoost or LightGBM. LightGBM demonstrates better

accuracy and speed than XGBoost, but XGBoost is the more established ML algorithm, perhaps making it a very reliable ML tree-based method. Nevertheless, despite implementing these 4 powerful and innovative methods with oversampling to enhance statistical power, ML could still not accurately predict ABI in the ELSO Registry. This finding may suggest that the ELSO Registry does not capture causative variables for ABI over the entire duration of ECMO support which are needed to fully glean the insights and advantages of ML and ultimately identify modifiable risk factors for ABI. Finally, we note that while ML did not predict ABI with high accuracy, it did produce a strong NPV (94% and 90% for ABI in VA-ECMO and ECPR, respectively), suggesting our models' true utility may lie in its high sensitivity and capability to rule out patients who truly did not have ABI. Furthermore, our models also demonstrated high true negative rates (88% and 70% for ABI, and 99% and 89% for ICH, in VA-ECMO and ECPR, respectively) which also suggests a high specificity and capability to rule patients in with ABI accurately. Therefore, implementing this model as a screening test may be warranted and useful for ECMO clinicians.

Lack of standardized neurological monitoring

Given the relatively mediocre performance in predicting ABI and its subtypes in both cohorts, we reveal certain limitations using a heterogenous, large dataset such as the ELSO Registry to predict ABI with ML. Specifically, unlike the institutional protocol at Johns Hopkins Hospital which uses standardized neurological monitoring with proven efficacy,(3) the protocols used to determine ABI across ECMO centers are neither standardized nor adjudicated/validated, and thus vary considerably. Accordingly, we only observed a 7.7% prevalence of ABI in VA-ECMO patients and 16.5% prevalence of ABI in ECPR patients within the ELSO Registry, which is considerably less than the prevalence of 33% at an experienced tertiary care ECMO center.(3) Therefore, this

study calls for more sensitive and accurate detection of ABI and more granular collection of variables across ECMO centers. ABI can precede mortality and therefore identifying risk factors for ABI can help clinicians mitigate their occurrence and their associated mortality risk. In fact, a single-center study of 106 VA-ECMO and 68 VV-ECMO pediatric patients using ML to predict CNS ischemia and ICH showed a superior AUC-ROC (0.76) than ours with the ELSO Registry (0.67).(44) This result may not be surprising given the institution's rigorous advanced neuroimaging technique to determine ABI and adjudication system by multiple clinicians. Accordingly, their prevalence of ABI (51% in VA/VV-ECMO mixed population) was much higher than ours with the ELSO Registry (7.7% in VA-ECMO and 16.5% in ECPR). Overall, an ELSO Registry addendum for neurological monitoring and imaging protocols may improve performance for ML to predict ABI. Furthermore, we suggest that all ELSO centers use standardized neurological monitoring protocols to better detect the true prevalence of ABI (and capture it more accurately in the ELSO Registry) and ultimately mitigate this devastating outcome for patients.

Limitations

The primary limitation of our analysis was the lack of standardized neurological monitoring protocols across ECMO centers and lack of ABI adjudication in the ELSO Registry. Since ABI is defined by imaging findings in the Registry, the quality control of ABI is likely very good. However, there is still underestimation of ABI in the Registry as many patients do not obtain proper neuroimaging studies in the first place. A fundamental limitation of this study was that model performance in VA-ECMO for predicting ABI, CNS ischemia, and ICH was poor due to low PPV. Given the relatively low outcome rates of ABI and its subtypes, these outcome variables likely have substantial class imbalance and thus make ML models predicting ABI very challenging. Accordingly, we saw improved performance with ML predicting ABI and CNS

Ischemia vs. ICH in VA-ECMO patients likely due to their higher prevalence; similarly, ECPR patients observed improved ML performance which is logical due to their much higher prevalence of ABI overall and its subtypes relative to non-ECPR VA-ECMO patients. Furthermore, the ELSO Registry lacks granularity with laboratory measurements as ABGs are only collected at a singular time point instead of multiple times throughout the ECMO run and were not collected at the same exact time point at each center. We also acknowledge that cross-sectionally the ECMO pump flow rates were small and may not be clinically meaningful, but these differences were still statistically significant in our model and should be noted. Finally, as this was a retrospective study, only associations could be determined.

Conclusions

Using the largest database of ECMO patients globally, we present the first study to predict neurological outcomes on sufficiently powered international ECMO patient cohorts. Machine learning identified ECMO duration and higher pump flow rates as the most important risk factors for ABI in both VA-ECMO and ECPR cohorts. Overall, performance of ML models to predict ABI in VA-ECMO and ECPR patients was suboptimal likely due to lack of data granularity in the ELSO Registry. This finding suggests that the detection and sensitivity rates for capturing ABI in ECMO patients across ECMO centers worldwide is substandard. Accordingly, standardized neurological monitoring and imaging protocols are urgently needed.

Table 1. Model performance in the 30% test set of venoarterial extracorporeal membrane oxygenation patients for predicting acute brain injury, central nervous system ischemia, and intracranial hemorrhage.

	Acc	TPR	TNR	FPR	FNR	PPV	NPV
ABI	83% (8928/ 10757)	33% (3550/ 10757)	88% (9466/1075 7)	12% (1291/107 57)	67% (7207/1075 7)	18% (1963/107 57)	94% (3550/1075 7)
CNS Ischemia	86% (9251/1075 7)	33% (3550/107 57)	88% (9466/1075 7)	12% (1291/107 57)	67% (7207/1075 7)	11% (1183/107 57)	97% (10434/107 57)
ICH	97% (10434/107 57)	5% (538/1075 7)	99% (10649/107 57)	1% (108/1075 7)	95% (10219/107 57)	8% (861/1075 7)	98% (10542/107 57)

Machine learning produced a strong NPV but a poor PPV. ABI: acute brain injury. Acc: Accuracy. CNS: central nervous system. ICH: intracranial hemorrhage. FNR: False Negative Rate. FPR: False Positive Rate. PPV: Positive Predictive Value. NPV: Negative Predictive Value. TPR: True Positive Rate. TNR: True Negative Rate. Accuracy = true positive + true negative / true positive + true negative + false positive + false negative. TPR = true positive/true positive + false negative. TNR = true negative/true negative + false positive. FPR = false positive/false positive + true negative. FNR = false negative/false negative + true positive. PPV = true positive/true positive + false positive. NPV = true negative/true negative + false negative.

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Figure Legends.

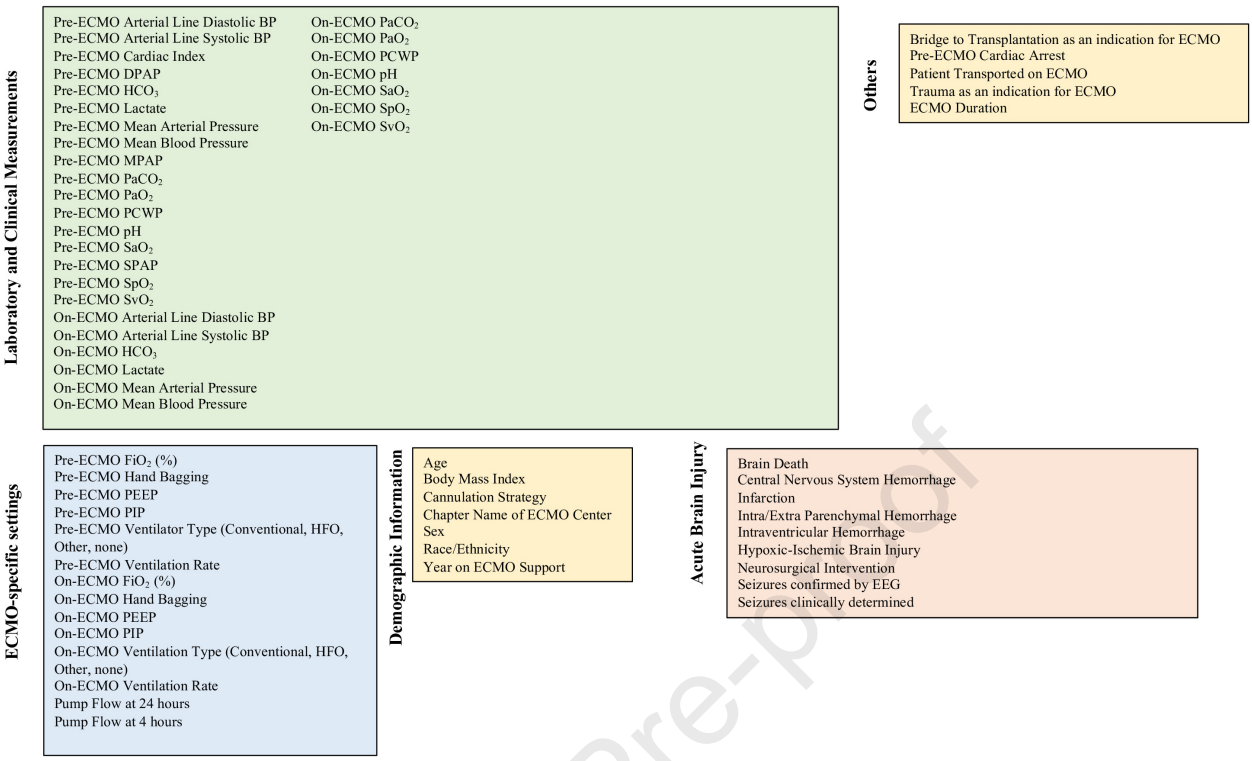
Figure 1. All 65 variables incorporated into our machine learning models including laboratory values, ECMO settings, demographics, other variables, and our primary outcome (acute brain injury).

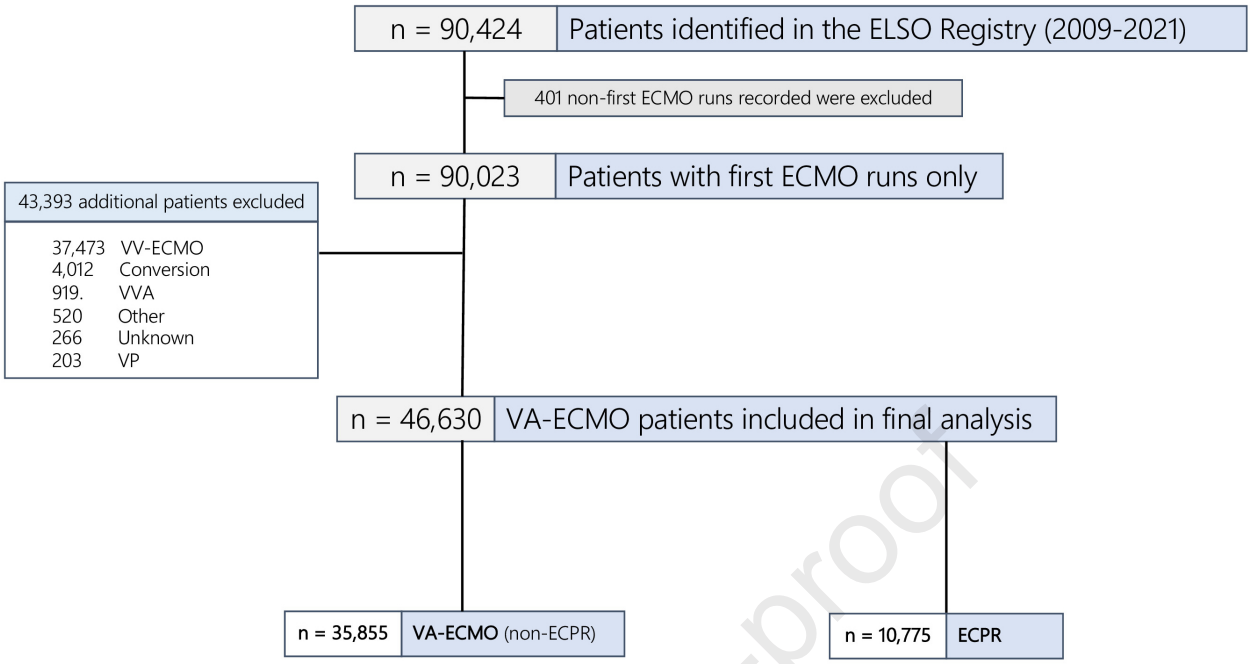
Figure 2. Flowchart of study cohort (VA-ECMO and ECPR patients) from the ELSO Registry in 2009-2020. ECMO = extracorporeal membrane oxygenation, VA = venoarterial, VV = venovenous, Conversion = VA→VV or VV→VA, ECPR = extracorporeal cardiopulmonary resuscitation, VVA = venovenoarterial, Other = mode not defined, VP = venopulmonary.

Figure 3. Receiver-operating characteristic curves for predicting **A)** acute brain injury (ABI), **B)** central nervous system (CNS) ischemia, and **C)** intracranial hemorrhage (ICH) in venoarterial extracorporeal membrane oxygenation (VA-ECMO) patients.

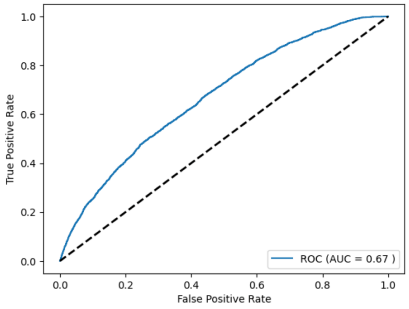
Figure 4. Feature importance in increasing importance (ascending) for each neurological outcome: **A)** acute brain injury, **B)** central nervous system ischemia, and **C)** intracranial hemorrhage in VA-ECMO patients.

Figure 5. Summary of key study findings. Machine learning identified longer ECMO duration (in days) and higher 24 hour ECMO pump flow rates as the most important risk factors for acute brain injury in VA-ECMO patients. Better standardized neurological monitoring is required to detect the true prevalence across ELSO centers.

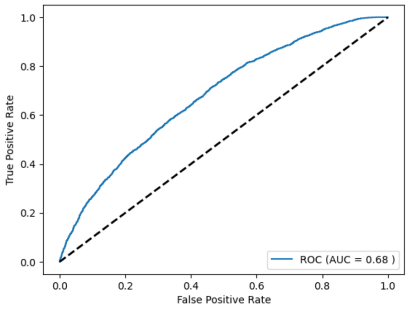




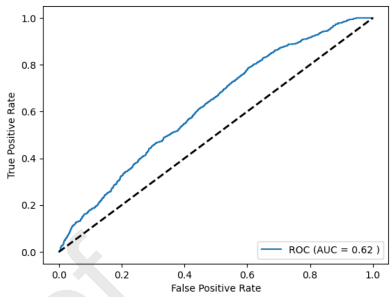
A VA-ECMO (non-ECPR) - ABI

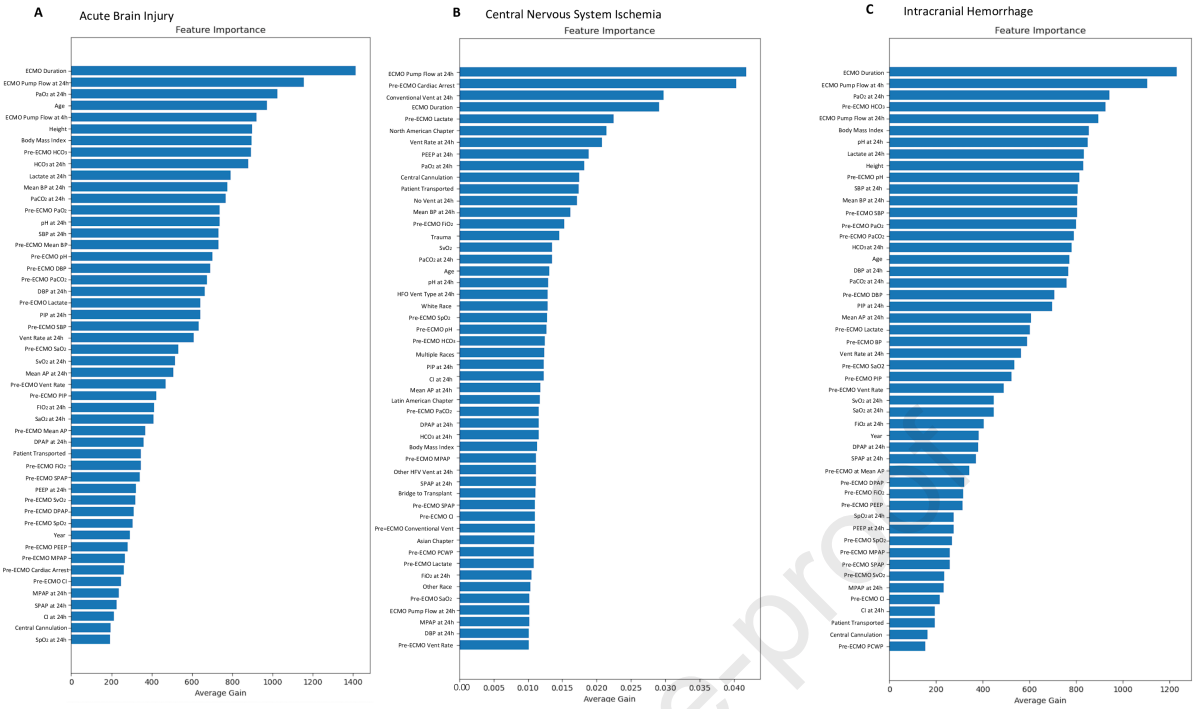


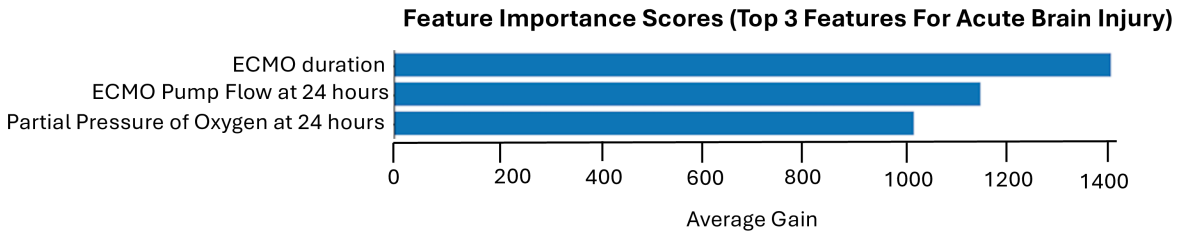
B VA-ECMO (non-ECPR) – CNS Ischemia

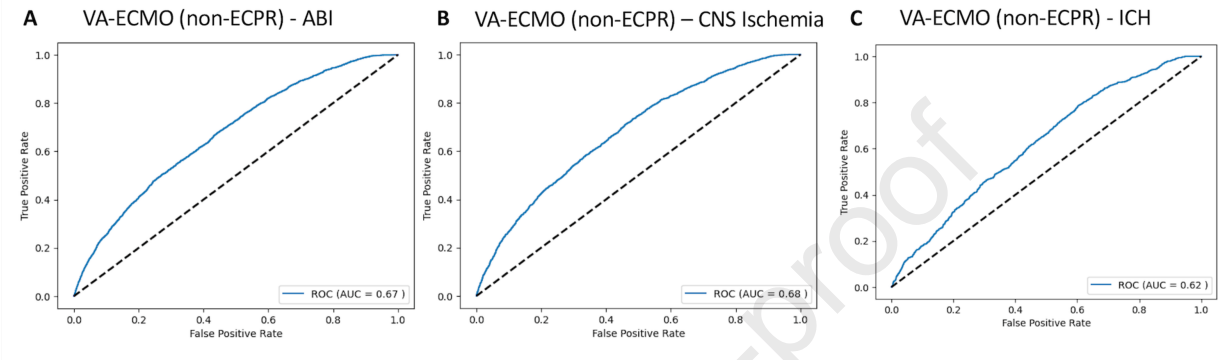


C VA-ECMO (non-ECPR) - ICH









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Acute Brain Injury Risk Prediction Models in Venoarterial Extracorporeal Membrane Oxygenation Patients with Tree-Based Machine Learning: An ELSO Registry Analysis

STUDY POPULATION

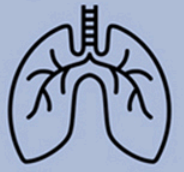
Adult VA-ECMO and ECPR patients (first-runs only) from the **ELSO Registry**

35,855 ***VA-ECMO*** *patients:* ***2,769 (7.7%) with*** acute brain injury

10,775 ***ECPR*** *patients:* ***1,787 (16.5%)*** *with acute brain injury*

Most important risk factors for acute brain injury identified by machine learning in VA-ECMO patients:

1) ***Longer duration of ECMO support***
2) ***Higher ECMO pump flow rate (at 24 hours)***
3) ***Higher on-ECMO partial pressure of oxygen***



Most important risk factors for acute brain injury identified by machine learning in ECPR patients:

1) ***Longer duration of ECMO support***
2) ***Older age***
3) ***Higher ECMO pump flow rate (at 24 hours)***

Despite a low prevalence of acute brain injury in the ELSO Registry, machine learning still identified both longer duration of ECMO support and higher ECMO pump flow rates as the most important risk factors for acute brain injury in VA-ECMO and ECPR patients. Standardized neurological monitoring and imaging protocols are important to better detect acute brain injury across ELSO centers.

ECPR: extracorporeal cardiopulmonary resuscitation; ELSO: Extracorporeal Life Support Organization; VA-ECMO: venoarterial extracorporeal membrane oxygenation.

Online Supplemental Content

Supplemental Methods

Supplemental Results

Supplemental Table 1. Variables with missingness in ELSO Registry for all adult ECMO patients from 2009-2021.

Supplemental Table 2. Baseline characteristics and clinical variables of venoarterial extracorporeal membrane oxygenation patients stratified by presence of ABI.

Supplemental Figure 1. SHAP value plots for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in VA-ECMO patients.

Supplemental Table 3. Comparisons between the top 3 most important features for ABI in VA-ECMO patients.

Supplemental Table 4. Comparisons between the top 3 most important features for CNS ischemia in VA-ECMO patients.

Supplemental Table 5. Comparisons between the top 3 most important features for ICH in VA-ECMO patients.

Supplemental Table 6. Baseline characteristics and clinical variables extracorporeal cardiopulmonary resuscitation patients stratified by presence of ABI.

Supplemental Figure 2. Receiver-operating characteristic curves for predicting A) acute brain injury (ABI), B) central nervous system (CNS) ischemia, and C) intracranial hemorrhage (ICH) in extracorporeal cardiopulmonary resuscitation (ECPR) patients**.**

Supplemental Figure 3. Feature Importance Scores for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in ECPR patients.

Supplemental Figure 4. SHAP value plots for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in ECPR patients.

Supplemental Table 7. Model performance in extracorporeal cardiopulmonary resuscitation patients for predicting acute brain injury, central nervous system ischemia, and intracranial hemorrhage.

Supplemental Table 8. Comparisons between the top 3 most important features for ABI in ECPR patients.

Supplemental Table 9. Comparisons between the top 3 most important features for CNS ischemia in ECPR patients.

Supplemental Table 10. Comparisons between the top 3 most important features for ICH in ECPR patients.

Supplemental Methods

Definitions

On-ECMO PP was computed as "systolic blood pressure at 24 hours" – "diastolic blood pressure at 24 hours". Pre-ECMO and on-ECMO ventilator settings included conventional ventilation, high-frequency oscillatory ventilation, other high frequency ventilation (e.g., high frequency jet ventilation or percussive ventilation), other ventilation (not specified), and absence of ventilation. Pre-ECMO additional temporary mechanical circulatory support (tMCS) was defined as the intra-aortic balloon pump, Impella®, and left and right ventricular assist devices. Pre-ECMO cardiac arrest was defined as an episode that necessitated the use of cardiopulmonary resuscitation and performance of external cardiac massage within 24 hours of ECMO support. Central cannulation was outlined as the placement of cannula in the aorta. Peripheral cannulation was outlined as the placement of cannula in the peripheral vessels. Bridge to transplant was defined as a patient being placed on ECMO for "bridging" the patient to heart or lung transplant. Trauma was defined as a patient undergoing ECMO because of traumatic injury. Chapter name included the location of the ELSO center: Asia-Pacific, Europe, Latin America, North America, and South and West Asia. ECMO duration was defined as the number of hours patients received ECMO once cannulated.

Machine Learning Algorithm and Pipeline

With the fine-tuned hyperparameters, each of the 4 selected models were fitted onto the training dataset and evaluated on the test set with the best performing model being selected for further optimization. Given the low prevalence of ABI in our dataset, random

oversampling of patients with ABI in the training set was performed at different frequencies; for each oversampling frequency, the model was evaluated with a 10-CV approach. Upon identification of the optimal oversampling rate, we applied our best performing model to the entirety of the cohort with a leave-one-out-cross-validation (LOOCV) approach. The LOOCV works by including all observations in the training set except one singular observation to be used in the test set. The LOOCV step wise approach was repeated for the entire dataset. Each observation was used as the test set at one point, producing a total of "*N"* models that were trained and then tested on the holdout "*N"* observations. These observations were then combined to form one singular test set of size "*N"* observations. This LOOCV approach mitigates the risk of bias by testing the ML algorithm on the entire cohort and ensuring reproducibility of these results. Our tree-based ML models have built-in mechanisms to account binary features and non-binary features in our training set and modeling. At nodes at a branch point, for continuous variables, it is arbitrarily discretized into less than vs. greater than at a particular number and it does this until each bin/leaf is optimized.

Subsequently, we calculated the area under the receiver-operating characteristic curve (AUC-ROC), area under the precision recall curve, and a Brier score on these observations to assess the predictive performance of our models. After choosing a threshold that maximizes the F1 score, further model metrics including accuracy, true positive rate, true negative rate, false positive rate, false negative rate, positive predictive value (PPV), negative predictive value (NPV), precision, and recall were calculated. The accuracy represents how often the ML model correctly predicted the outcome of interest (number of correct predictions/total number of predictions); clinically, this represents the quality of the model in predicting ABI. Precision calculates how often the model correctly predicts the positive class (true positives/true positive + false positives); clinically, this metric tells us how often ABIs that are captured by the model

are truly ABIs (this is important as a false positive measurement of ABI may be unnecessarily treated and lead to increased resource utilization for the hospital and patient). Recall determines how often the model correctly identifies all true positives that are indeed actual positives (true positives/true positives + false negatives); this metric is important clinically when it is important to not miss any positive outcome as an undetected ABI can be devastating and lead to mortality. The F1 score represents the harmonic mean of both the precision and recall of the model (2*precision*recall/precision + recall). A higher F1 score represents a well-balanced performance by the model and can thus achieve both high precision and high recall, accurately identifying true ABIs and not under detecting any ABIs. The true positive rate represents the proportion of positive instances that were correctly predicted by the ML model (true positives/true positives + false negatives) and has similar clinical implications as recall. The false positive rate represents the proportion of negative instances that are incorrectly classified by the ML model (false positives/false positives + true negatives) and his similar clinical implications as precision. The true negative rate represents the specificity of the model, determining the probability that a true negative sample will actually test negative (true negatives/true negatives + false positives). Clinically, this is important in "ruling in" ABIs, with similar implications to precision and the false positive rate. The false negative rate ("miss rate") is the probability that a true positive sample will indeed be missed by the model (false negatives/false negatives + true positives). This has similar clinical implications as recall and the true positive rate. The positive predictive value is the probability that if a sample is recognized as a positive result, then the sample truly has the disease (true positives/true positives + false positives) whereas the negative predictive value is the probability that if a sample is recognized as a negative result, then the sample truly does not have the disease (true negatives/true negatives + false negatives).

Feature Importance Scores in ML

The Feature Importance Scores show the relative contribution of each feature ranked from highest (top bar) to lowest (bottom bar). In the SHAP plot, red values denoted features of high importance vs. blue values denoted features of low importance. Each dot represents the feature attribution value of each patient and is plotted as a SHAP value on the x-axis. SHAP values quantify the predictive impact of each feature. SHAP values greater than zero represent a greater likelihood of having ABI.

Supplemental Results

Feature importance in VA-ECMO

The median ECMO duration was higher in patients with ABI versus patients without ABI (4.8 versus 4.3 days, p<0.001). The median ECMO pump flow rate at 24 hours was higher in patients with ABI versus patients without ABI (4 versus 3.95 liters per minute, p<0.001). The median on-ECMO PaO_2 was higher in patients with ABI versus patients without ABI (162 versus 141 mmHg, p<0.001). The median ECMO pump flow rate at 24 hours was higher in patients with CNS ischemia versus patients without CNS ischemia (4 versus 3.95 liters per minute, p<0.001). The prevalence of CNS ischemia in patients with pre-ECMO cardiac arrest was higher than patients without cardiac arrest (5.8% versus 3.3%, p<0.001). The prevalence of CNS ischemia in patients with conventional venting at 24 hours of ECMO support was higher than patients without conventional venting at 24 hours of ECMO support (8.6% versus 2.7%, p<0.001). The median ECMO duration was higher in patients with ICH versus patients without ICH (6 versus 4.3 days, p<0.001). The median ECMO pump flow rate at 4 hours was higher in patients with ICH versus patients without ICH (3.98 versus 3.82 liters per minute, p<0.001). The median on-ECMO PaO_2 was similar between patients with ICH versus patients without ICH (151 versus 142 mmHg, p=0.27).

Exploratory analysis – Hyperoxia in VA-ECMO

VA-ECMO patients with ABI were more likely to have hyperoxia (>120 mm Hg at 24 hours of cannulation, n=1,475, 53%) than those patients without ABI (n=14,822, 45%, p<0.001). The median MAP was slightly lower in ABI patients with hyperoxia (12 mm Hg) vs. the median MAP in ABI patients without hyperoxia (13 mm Hg, p=0.003).

Feature Importance in ECPR

The median ECMO duration was higher in patients with ABI versus patients without ABI (3.1 versus 2.5 days, p<0.001). Patients with ABI were younger versus patients without ABI (median age=54.4 versus 57.7 years, p<0.001). The median ECMO pump flow rate at 24 hours of ECMO support was higher in patients with ABI versus patients without ABI (3.8 versus 3.6 liters per minute, p<0.001). The top 3 variables for predicting CNS ischemia were duration of ECMO support, serum bicarbonate level at 24 hours of ECMO support, and BMI (**Supplemental Figure 2B, Supplemental Figure 3B, Supplemental Table 8)**. The median ECMO duration was higher in patients with CNS ischemia versus those without CNS ischemia (3.3 versus 2.5 days, p<0.001). Patients with CNS ischemia had similar levels of serum bicarbonate at 24 hours of ECMO support as patients without CNS ischemia (23 versus 23 milliequivalents per liter, p=0.47). Patients with CNS ischemia had a higher median BMI than patients without CNS ischemia (29.1 versus 27.6 kilograms/meters squared, p<0.001). The top 3 variables for predicting ICH were being supported on ECMO at a North American ELSO center, positive-end expiratory pressure at 24 hours of ECMO support and being supported on ECMO at a European ELSO center (**Supplemental Figure 2C, Supplemental Figure 3C, Supplemental Table 9)**. The prevalence of ICH was higher in patients supported on ECMO at a North American ELSO Center versus those not supported on ECMO at a North American ELSO Center (3.3% versus 1.7%, p<0.001). The

median positive-end expiratory pressure at 24 hours of ECMO support for patients with ICH was not different than that of patients without ICH (8 versus 8 mmHg, p=0.25). The prevalence of ICH was lower in patients supported on ECMO at a European ELSO Center versus those not supported on ECMO at a European ELSO Center (1.2% versus 3%, p<0.001).

Supplemental Table 1. Variables with missingness in ELSO Registry for all adult ECMO patients from 2009-2021.

Variable	Missing	X (%)
Pulmonary Capillary Wedge Pressure at 24h	87017	99
Pre-ECMO Pulmonary Capillary Wedge Pressure	86774	98
Pre-ECMO Cardiac Index	82670	94
Cardiac Index at 24h	81750	93
Pre-ECMO Mean Pulmonary Arterial Pressure	80178	91
Pre-ECMO Mixed Venous Oxygen Saturation	79730	90
Pre-ECMO Diastolic Pulmonary Arterial Pressure	78978	90
Pre-ECMO Systolic Pulmonary Arterial Pressure	78845	89
Mixed Venous Oxygen Saturation at 24h	76111	86
Diastolic Pulmonary Arterial Pressure at 24h	75479	86
Systolic Pulmonary Arterial Pressure at 24h	75388	86
Mixed Venous Oxygen Saturation at 24h	66204	75
Pre-ECMO Peripheral Oxyhemoglobin Saturation	65314	74
Peripheral Oxyhemoglobin Saturation at 24h	60599	69
Pre-ECMO Mean Airway Pressure	56242	64
Pre-ECMO Lactate	53670	61

Lactate at 24h	48005	54
Time to Extubation	47511	54
Pre-ECMO Peak Inspiratory Pressure	45232	51
Mean Airway Pressure at 24h	43657	50
Pre-ECMO Positive End-Expiratory Pressure	34613	39
Pre-ECMO Mean Blood Pressure	34500	39
Pre-ECMO Ventilation Rate	34263	39
Peak Inspiratory Pressure at 24h	32346	37
Pre-ECMO Arterial Oxyhemoglobin Saturation	32126	36
Patient Being Transported to ELSO Center	31678	36
Pre-ECMO Percentage of Inspired Oxygen	28816	33
Height	26604	30
Pre-ECMO Diastolic Blood Pressure	26570	30
Pre-ECMO Systolic Blood Pressure	26270	30
Arterial Oxyhemoglobin Saturation at 24h	24642	28
Mean Blood Pressure at 24h	24149	27
Pre-ECMO Serum Bicarbonate	23588	27
Pre-ECMO Partial Pressure of Oxygen	22914	26
Pre-ECMO Partial Pressure of Çarbon Dioxide	22713	26
Ventilation Rate at 24h	22255	25
Positive End-Expiratory Pressure at 24h	21837	25

Diastolic Blood Pressure at 24h	20687	23
Pre-ECMO pH	20641	23
Systolic Blood Pressure at 24h	20582	23
Percentage of Inspired Oxygen at 24h	20430	23
Partial Pressure of Oxygen at 24h	17543	20
Partial Pressure of Çarbon Dioxide at 24h	17432	20
Serum Bicarbonate at 24h	16402	19
ECMO Pump Flow Rate at 24h	15935	18
pH at 24h	15283	17
Time to Intubation	14839	17
ECMO Pump Flow Rate at 4h	11937	14
Weight	3116	4
ECMO Duration	78	0
Patient ID	0	0
Run ID	0	0
Run Number	0	0
Sex	0	0
Race/Ethnicity	0	0
Age	0	0
Primary Diagnosis by ICD 10	0	0
Primary Diagnosis by ICD9	0	0
ECMO Modality	0	0
Support Type	0	0
Discontinuation of ECMO	0	0
Discharged Alive off of ECMO	0	0
Discharge Location	0	0
Year on ECMO	0	0
Pre-ECMO Ventilation Type	0	0
Pre-ECMO Handbagging	0	0
Vent Type at 24h	0	0

Handbagging at 24h	0		0
Pre-ECMO Cardiac Arrest	0		0
Bridged to Transplant as Indication for ECMO	0		0
ID of ELSO Center	0		0
Continent of Chapter Name	0		0
Trauma as Indication for ECMO	0		0
Placement of Artificial Airway During ECMO	0		0

Supplemental Table 2. Baseline characteristics and clinical variables of venoarterial extracorporeal membrane oxygenation patients stratified by presence of ABI.

	Total VA-ECMO (no ECPR) (n=35,855)	**ABI (n=2,769, 8%)**	**No ABI (n=33,086, 92%)**	**P-value**
Demographics				
Age (years)	57.80 (45.9-66.4)	56.1 (43.2-64.8)	57.9 (46.1-66.6)	***<0.001***
Male sex	23,542 (66%)	1,726 (62%)	21,817 (66%)	***<0.001***
Body Mass Index, kg/m^2	27.8 (24.1-32.6)	28.4 (24.5-33.1)	27.8 (24 1-32.5)	***<0.001***
Race/ethnicity				***<0.001***
Asian	4,763 (13%)	319 (12%)	4,445 (13%)	
Black	3,560 (10%)	327 (12%)	3,234 (10%)	
Hispanic	1,941 (5%)	160 (6%)	1,782 (5%)	
White	20,133 (56%)	1,605 (58%)	18,529 (56%)	
Others	5,458 (15%)	358 (13%)	5,096 (15%)	
Year ECLS				***<0.001***
2009	319 (1%)	283 (10%)	36 (1%)	
2010	448 (1%)	398 (14%)	50 (1%)	
2011	646 (2%)	578 (21%)	68 (1%)	
2012	1,093 (3%)	991 (36%)	102 (1%)	
2013	1,339 (4%)	129 (5%)	1,210 (4%)	
2014	1,796 (5%)	166 (6%)	1,630 (5%)	
2015	2,483 (7%)	212 (8%)	2,271 (7%)	
2016	3,090 (9%)	242 (9%)	2,848 (9%)	
2017	4,128 (12%)	259 (9%)	3,869 (12%)	
2018	4,651 (13%)	325 (12%)	4,326 (13%)	
2019	5,581 (16%)	404 (15%)	5,177 (16%)	
2020	5,189 (14%)	387 (14%)	4,802 (15%)	
2021	5,092 (14%)	389 (14%)	4,703 (14%)	
Past medical history				

Diabetes	2,924 (8%)	252 (9%)	2,672 (8%)	0.06
Hypertension	4,205 (12%)	382 (14%)	3,823 (12%)	***<0.001***
Atrial fibrillation	3,083 (9%)	218 (8%)	2,865 (9%)	0.16
Cardiomyopathy	3413 (10%)	248 (9%)	3,165 (10%)	0.30
COPD	1083 (3%)	66 (2%)	1,017 (3%)	***0.04***
Pre-ECMO support				
Additional temporary mechanical circulatory support	11,730 (33%)	973 (35%)	10,757 (33%)	***0.005***
Vasopressor infusions	22,584 (63%)	1,876 (68%)	20,708 (63%)	**<0.001**
Inotrope infusions	11,503 (32%)	824 (30%)	10,679 (32%)	***0.006***
Pre-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	87 (72-104)	85 (70-103)	87 (72-104)	***<0.001***
Diastolic blood pressure (mm Hg)	54 (43-65)	52 (42-64)	54 (44-65)	***<0.001***
Mean blood pressure (mm Hg)	65 (54-76)	63 (53-75)	65 (54-76)	***0.001***
Pulse pressure (mm Hg)	32 (20-45)	31 (20-43)	32 (20-45)	0.053
Mean arterial pressure (mm Hg)	14 (10-18)	14 (11-19)	14 (10-18)	***0.03***
Pre-ECMO ABG				
pH	7.29 (7.18-7.38)	7.26 (7.14-7.35)	7.29 (7.19-7.38)	***<0.001***
HCO_3- (mEq/L)	20 (16-23.2)	19 (15.1-22.9)	20 (16-23.4)	***<0.001***
PaO_2 (mm Hg)	103 (68-217.5)	93.95 (62-212)	104 (68-218)	***<0.001***
$PaCO_2$ (mm Hg)	41 (33.80-50)	42.2 (34-54)	41 (33.7-50)	***<0.001***

Lactate (mmol/L)	6.1 (2.9-10.8)	6 (2.8-10.7)	8 (3.8-12)	***<0.001***
SpO_2 (%)	98 (92-100)	97 (89-100)	98 (93-100)	***<0.001***
SaO_2 (%)	97 (90-100)	96 (86-99)	97 (91-99)	***<0.001***
On-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	96 (84-110)	94 (81-108)	96 (84-110)	***<0.001***
Diastolic blood pressure (mm Hg)	64 (55-72)	64 (56-73)	64 (55-72)	***0.04***
Mean blood pressure (mm Hg)	74 (67-81)	73 (66-81)	74 (67-81)	***0.001***
Pulse pressure (mm Hg)	31 (18-46)	28 (15-44)	31 (18-46)	0.053
Mean arterial pressure (mm Hg)	12 (10-15)	13 (10-15)	12 (10-15)	***<0.001***
On-ECMO ABG				
pH	7.42 (7.37-7.46)	7.41 (7.36-7.46)	7.42 (7.37-7.47)	***0.005***
HCO_3- (mEq/L)	24.1 (21.7-27)	24 (21-27)	24.1 (21.8-27)	***0.02***
PaO_2 (mm Hg)	142 (91.8-250)	162 (94.1-297.57)	141 (91.5-244.2)	***<0.001***
$PaCO_2$ (mm Hg)	38 (33.3-42)	38 (33-42.5)	38 (33.3-42)	0.50
Lactate (mmol/L)	2.3 (1.4-4.4)	3.1 (1.8-5.7)	2.3 (1.4-4.2)	***<0.001***
SpO_2 (%)	99 (97-100)	99 (97-100)	99 (97-100)	0.30
SaO_2 (%)	98 (97-99)	99 (97-100)	98 (97-99)	***0.007***
$\Delta PaCO_2$	-3 (-12-4.7)	-4 (-16-3)	-2.9 (-12-5)	***<0.001***
Pump flow rate (4 hours, L/min)	3.83 (3.17-4.42)	3.9 (3.2-4.48)	3.82 (3.16-4.41)	***0.01***
Pump flow rate (24 hours, L/min)	3.24 (3.96-4.5)	4 (3.34-4.6)	3.95 (3.22-4.5)	***<0.001***
Days on ECMO support	4.33 (2-7.71)	4.83 (2.5-8.67)	4.29 (2-7.63)	***<0.001***

Neurological complications on-ECMO				
Composite ABI				
Composite Ischemia	1,459 (4%)	1,459 (53%)	0 (0%)	***<0.001***
Hypoxic-ischemic brain injury	280 (1%)	280 (10%)	0 (0%)	***<0.001***
Ischemic stroke	1,194 (3%)	1,194 (43%)	0 (0%)	***<0.001***
Composite ICH	792 (2%)	792 (29%)	0 (0%)	***<0.001***
Intra/extra parenchymal hemorrhage	269 (1%)	269 (10%)	0 (0%)	***<0.001***
Intraventricular hemorrhage	108 (1%)	108 (4%)	0 (0%)	***<0.001***
Brain death	659 (2%)	659 (24%)	0 (0%)	***<0.001***
Neurosurgical intervention	31 (1%)	31 (1%)	0 (0%)	***<0.001***
Seizures confirmed by EEG	31 (1%)	31 (1%)	0 (0%)	***<0.001***
Seizures clinically determined	188 (1%)	188 (7%)	0 (0%)	***<0.001***
Other complications on-ECMO				
ECMO circuit mechanical failure	4,413 (12%)	472 (17%)	3,941 (12%)	***<0.001***

Renal replacement theory	9,446 (26%)	1,092 (39%)	8,354 (25%)	***<0.001***
Hemolysis	1,303 (4%)	159 (6%)	1,144 (3%)	***<0.001***
Cardiac arrhythmia	4,152 (12%)	474 (17%)	3,678 (11%)	***<0.001***
Gastrointestinal hemorrhage	1,338 (4%)	174 (6%)	1,164 (4%)	***<0.001***
Outcomes				
In-hospital mortality	19,030 (53%)	2,320 (84%)	16,710 (51%)	***<0.001***

Δ = delta. ABG: arterial blood gases. ABI: acute brain injury. ICH: intracranial hemorrhage. VA-ECMO: venoarterial extracorporeal membrane oxygenation.

Supplemental Table 3. Baseline characteristics and clinical variables extracorporeal cardiopulmonary resuscitation patients stratified by presence of ABI.

	Total ECPR (n=10,775)	**ABI (n=1,787, 17%)**	**No ABI (n=8,988, 83%)**	**P-value**
Demographics				
Age (years)	57.1 (45.5-65.9)	57.70 (46.30-66.50)	54.40 (41.50-63.00)	***<0.001***
Male sex	7,388 (68%)	1,273 (71%)	6,116 (68%)	***0.008***
Body Mass Index, kg/m^2	27.68 (24.22-32.46)	28.29 (24.91-33.44)	27.55 (24.22-32.19)	***<0.001***
Race/ethnicity				***0.002***
Asian	2,093 (19%)	319 (18%)	1,775 (20%)	
Black	993 (9%)	197 (11%)	797 (9%)	
Hispanic	425 (4%)	89 (5%)	337 (4%)	
White	5,855 (54%)	956 (53%)	4,900 (55%)	
Others	1,409 (13%)	226 (13%)	1,179 (13%)	
Year ECLS				***<0.001***
2009	83 (1%)	27 (2%)	56 (1%)	
2010	102 (1%)	21 (1%)	81 (1%)	
2011	147 (1%)	38 (2%)	109 (1%)	
2012	241 (2%)	54 (3%)	187 (2%)	
2013	442 (4%)	85 (5%)	357 (4%)	
2014	497 (5%)	82 (5%)	415 (5%)	
2015	813 (8%)	143 (8%)	670 (7%)	
2016	927 (9%)	159 (9%)	768 (9%)	
2017	1,189 (11%)	158 (9%)	1,031 (11%)	
2018	1,443 (13%)	215 (12%)	1,228 (14%)	
2019	1,911 (18%)	301 (17%)	1,580 (18%)	
2020	1,580 (15%)	272 (15%)	1,308 (15%)	
2021	1,400 (13%)	232 (13%)	1,168 (13%)	
Past medical history				

Diabetes	872 (8%)	173 (10%)	699 (8%)	***0.007***
Hypertension	1,148 (11%)	234 (13%)	914 (10%)	***<0.001***
Atrial fibrillation	550 (5%)	93 (5%)	457 (5%)	0.83
Cardiomyopathy	518 (5%)	104 (6%)	414 (5%)	***0.03***
COPD	214 (2%)	42 (2%)	172 (2%)	0.23
Pre-ECMO support				
Additional temporary mechanical circulatory support	1,420 (13%)	231 (13%)	1,189 (13%)	0.73
Vasopressor infusions	6,393 (59%)	1,068 (60%)	5,325 (59%)	0.68
Inotrope infusions	1,371 (13%)	215 (12%)	1,156 (13%)	0.34
Pre-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	82 (60-108)	80 (57-109)	83 (60-108)	0.18
Diastolic blood pressure (mm Hg)	50 (33-66)	48 (30-67)	50 (33-66)	0.3695
Mean blood pressure (mm Hg)	82 (60-108)	82 (60-108)	82 (60-108)	***0.001***
Pulse pressure (mm Hg)	30 (19-47)	30 (19-44)	30 (19-47)	0.2177
Mean arterial pressure (mm Hg)	14 (11-18)	13 (10-18)	14 (11-18)	0.1473
Pre-ECMO ABG				
pH	7.16 (7.00-7.30)	7.090 (6.920-7.250)	7.170 (7-7.310)	***<0.001***
HCO_3- (mEq/L)	17.60 (13.00 - 22.00)	17.00 (12.95-21.35)	17.7 (13.0-22.0)	0.05333
PaO_2 (mm Hg)	76.0 (51.0-137.4)	67.7 (45.0-118.5)	77.2 (52.0-144)	***<0.001***
$PaCO_2$ (mm Hg)	49.00 (36.00-68.00)	55.00 (39.00-76.20)	48.00 (35.30-66.00)	***<0.001***

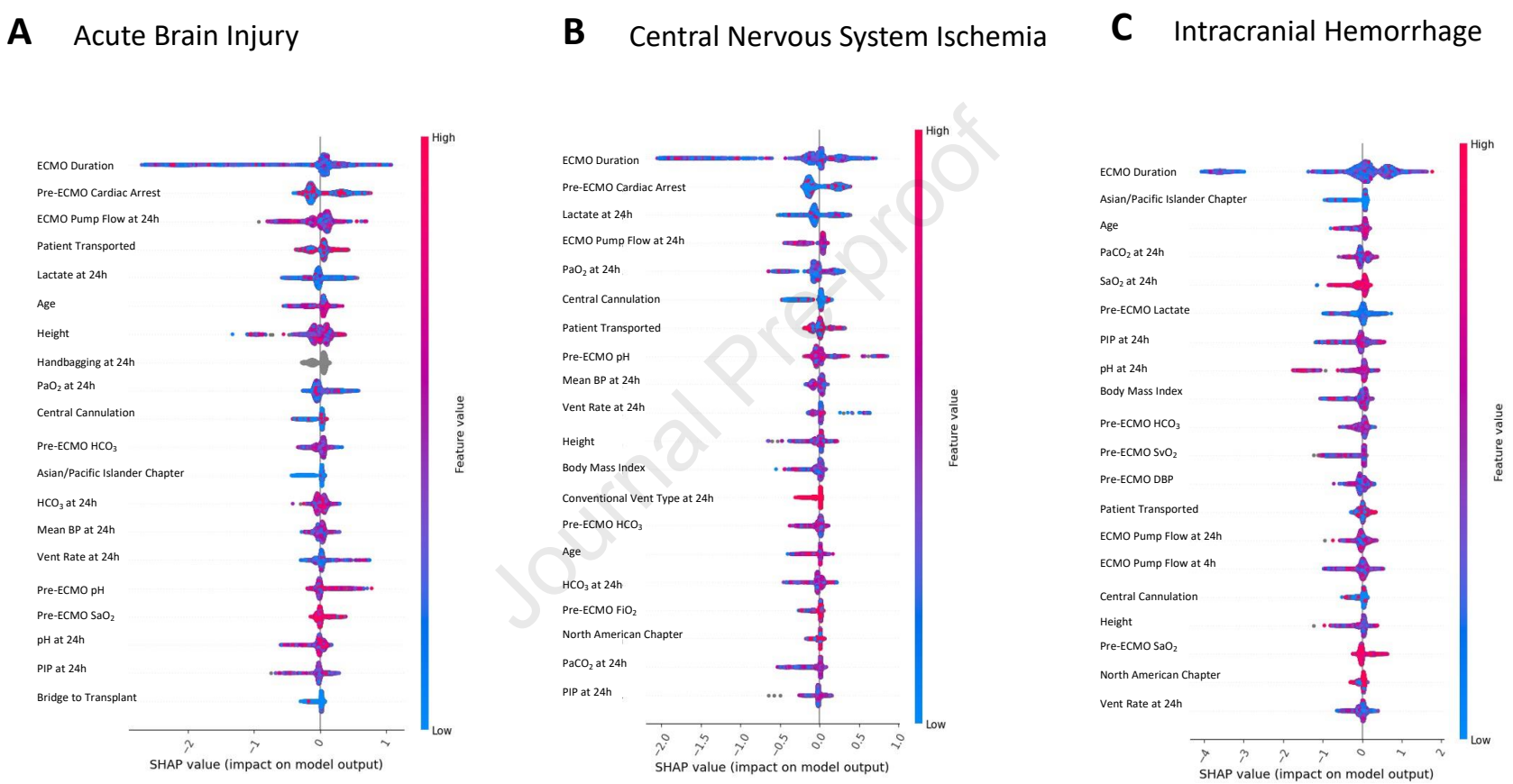
Lactate (mmol/L)	10.30 (5.00-14.60)	11.60 (7.425-15. 475)	10.00 (5.80-14.32)	***<0.001***
SpO_2 (%)	94 (81-99)	91 (77-99)	94 (82-99)	***0.02***
SaO_2 (%)	92 (76-98)	88 (67-97)	93 (78-98)	***<0.001***
On-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	94 (80-109.5)	91 (79-107)	95 (80-110)	***<0.001***
Diastolic blood pressure (mm Hg)	64 (56-73)	65 (55-74)	64 (56-73)	0.4142
Mean blood pressure (mm Hg)	72 (65-81)	73 (65-82)	72 (65-81)	***0.049***
Pulse pressure (mm Hg)	28 (14-44)	25 (12-41)	29 (15-44)	***<0.001***
Mean arterial pressure (mm Hg)	14 (11-18)	13 (10-18)	14 (11-18)	0.93
On-ECMO ABG				
pH	7.4 (7.34-7.46)	7.4 (7.34-7.45)	7.41 (7.34-7.46)	***0.042***
HCO_3- (mEq/L)	23 (20-26)	23 (19.7-26)	23 (20-26)	0.07
PaO_2 (mm Hg)	138.4 (95.65-290)	152 (95.65-290)	135 (87.3-258)	***<0.001***
$PaCO_2$ (mm Hg)	37 (32-42)	37 (32-42)	37 (32-42)	0.67
Lactate (mmol/L)	3.3 (1.8-7)	4 (2.25-7.4)	3.1 (1.8-6.8)	***<0.001***
SpO_2 (%)	99 (97-100)	99 (97-100)	99 (97-100)	0.48
SaO_2 (%)	98 (96-99)	98 (97-99)	98 (96-99)	0.08
$\Delta PaCO_2$	-11 (-29-1)	-15.65 (-38.20- -1)	-10 (-27-1.2)	***<0.001***
Pump flow rate (4 hours, L/min)	3.5 (2.9-4.1)	3.6 (3.0-4.2)	3.5 (2.86-4.1)	***<0.001***
Pump flow rate (24 hours, L/min)	3.6 (3.0-4.24)	3.8 (3.15-4.36)	3.6 (2.91-4.2)	***<0.001***
Cannulation strategy				

Days on ECMO support	2.625 (0.875-5.333)	3.083 (1.583-5.625)	2.458 (0.6667-5.2917)	***<0.001***
Neurological complications on-ECMO				
Composite ABI				
Composite Ischemia	799 (7%)	799 (9%)	0 (0%)	***<0.001***
Hypoxic-ischemic brain injury	357 (3%)	357 (4%)	0 (0%)	***<0.001***
Ischemic stroke	462 (4%)	462 (5%)	0 (0%)	***<0.001***
Composite ICH	281 (3%)	281 (3%)	0 (0%)	***<0.001***
Intra/extra parenchymal hemorrhage	82 (1%)	82 (1%)	0 (0%)	***<0.001***
Intraventricular hemorrhage	39 (0%)	39 (1%)	0 (0%)	***<0.001***
Brain death	681 (6%)	681 (8%)	0 (0%)	***<0.001***
Neurosurgical intervention	13 (0%)	13 (1%)	0 (0%)	***<0.001***
Seizures confirmed by EEG	175 (2%)	175 (2%)	0 (0%)	***<0.001***
Seizures clinically determined	152 (1%)	152 (2%)	0 (0%)	***<0.001***
Other complications on-ECMO				

ECMO circuit mechanical failure	1,217 (11%)	222 (12%)	995 (11%)	0.10
Renal replacement theory	2,450 (23%)	606 (34%)	1,844 (21%)	***<0.001***
Hemolysis	319 (3%)	228 (13%)	91 (1%)	***<0.001***
Cardiac arrhythmia	1,384 (13%)	1,053 (59%)	331 (4%)	***<0.001***
Gastrointestinal hemorrhage	457 (4%)	348 (19%)	109 (1%)	***<0.001***
Outcomes				
In-hospital mortality	7,490 (70%)	1,579 (88%)	5,911 (66%)	***<0.001***

Δ = delta. ABG: arterial blood gases. ABI: acute brain injury. ICH: intracranial hemorrhage. ECPR: extracorporeal cardiopulmonary resuscitation.

Supplemental Figure 1. SHAP value plots for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in VA-ECMO patients.



Supplemental Table 3. Comparisons between the top 3 most important features for ABI in VA-ECMO patients.

	With ABI	**Without ABI**	p-value
Median ECMO duration	4.8 days	4.3 days	<0.001
Median ECMO pump flow rate at 24 hours	4 liters/minute	3.95 liters/minute	<0.001
Median on-ECMO PaO_2	162 mmHg	141 mmHg	<0.001

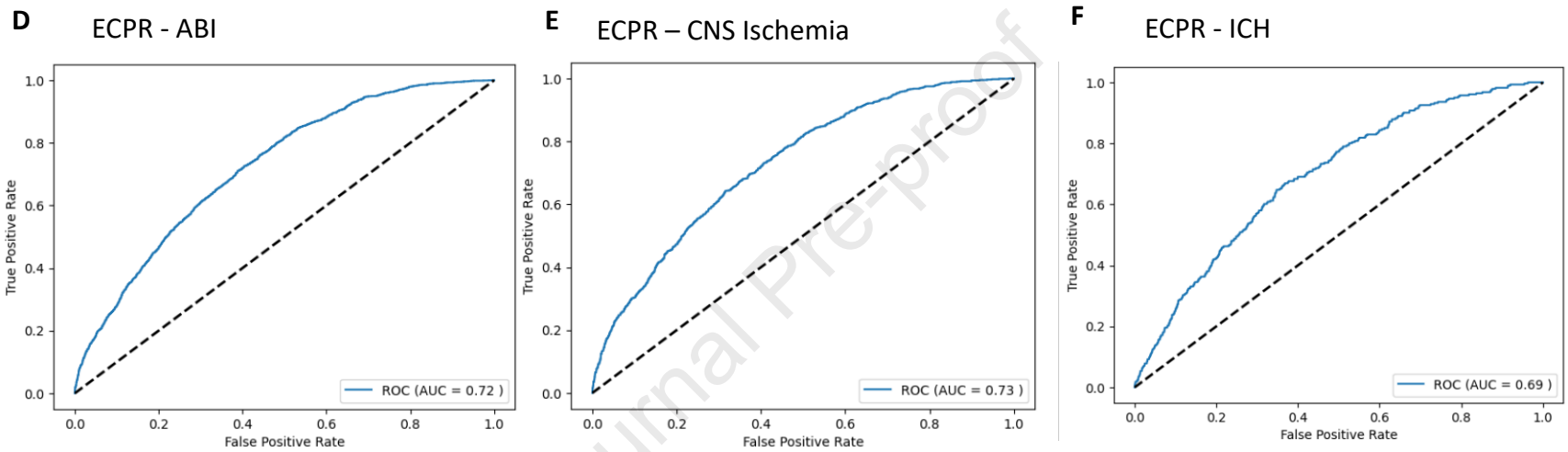
Supplemental Table 4. Comparisons between the top 3 most important features for CNS ischemia in VA-ECMO patients.

	With CNS ischemia	**Without CNS ischemia**	p-value
Median ECMO pump flow rate at 24 hours	4 liters/minute	3.95 liters/minute	<0.001
Pre-ECMO cardiac arrest	5.8% (n=633)	N/A	<0.001
Without pre-ECMO cardiac arrest	3.3% (n=796)	N/A	
With conventional venting at 24 hours	8.6% (n=2,342)	N/A	<0.001
Without conventional venting at 24 hours	2.7% (n=44)	N/A	

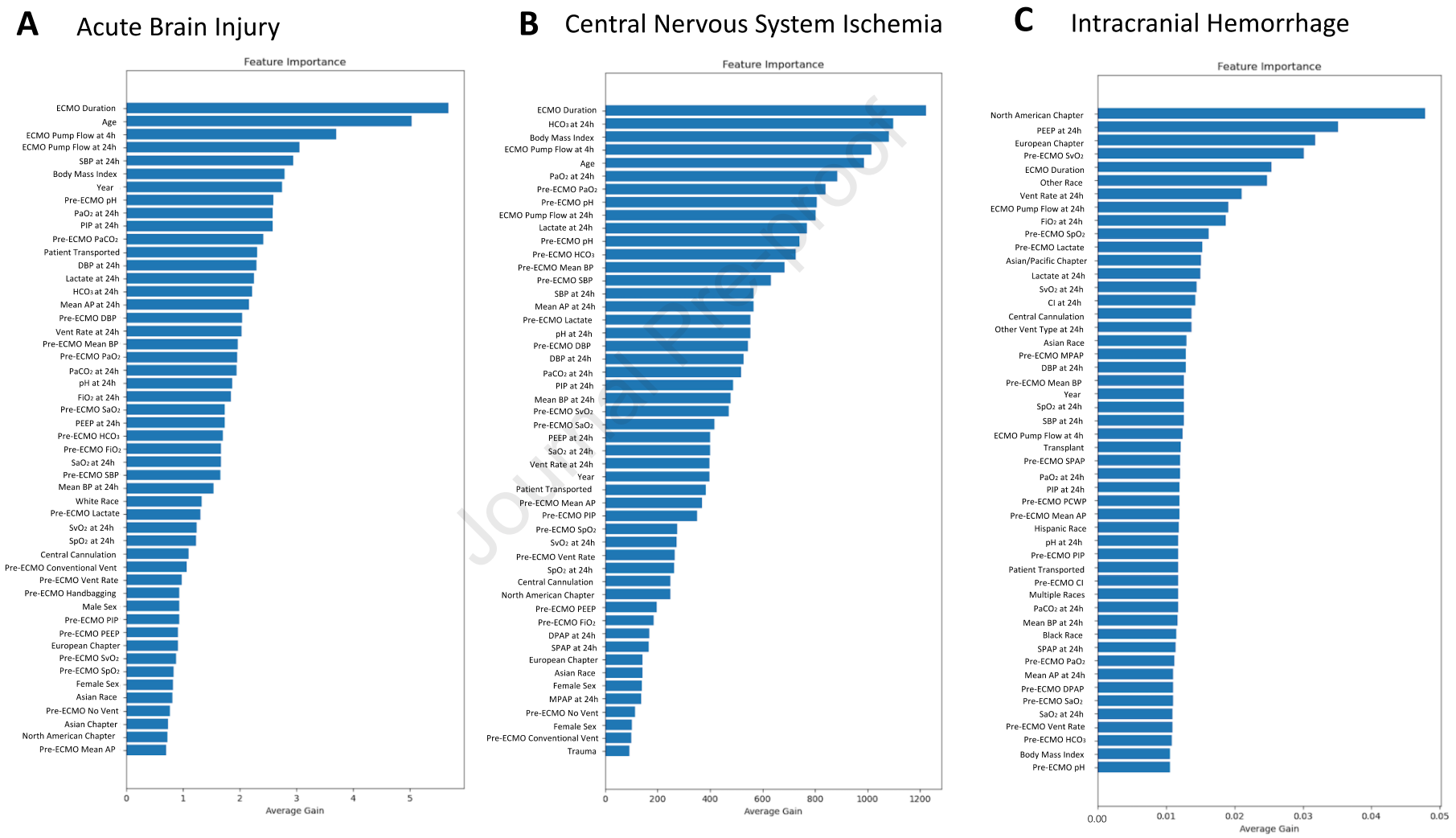
Supplemental Table 5. Comparisons between the top 3 most important features for ICH in VA-ECMO patients.

	With ICH	**Without ICH**	p-value
Median ECMO duration	6 days	4.3 days	<0.001
Median ECMO pump flow rate at 4 hours	3.98 liters/minute	3.82 liters/minute	<0.001
Median on-ECMO PaO_2	151 mmHg	142 mmHg	0.27

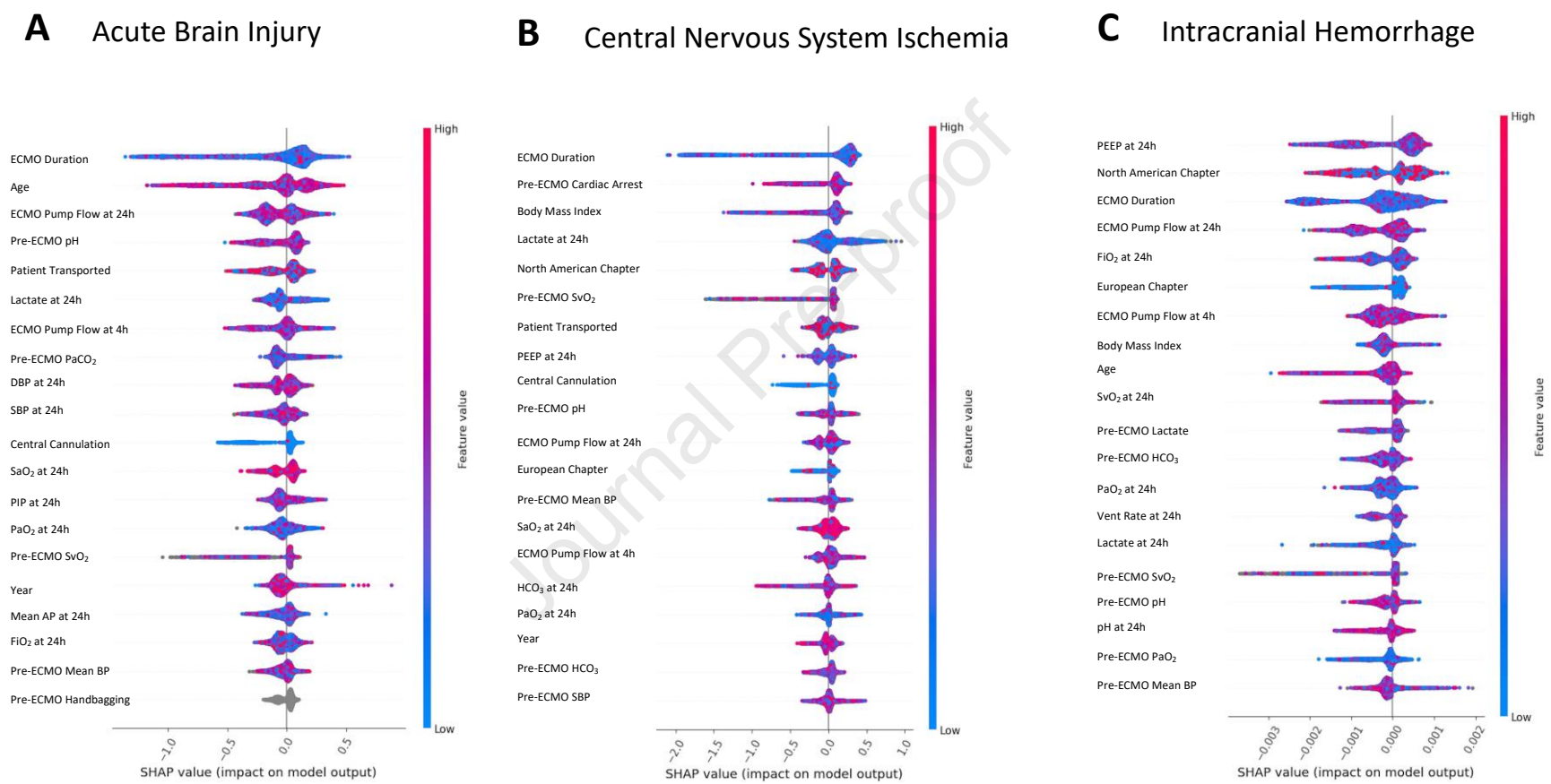
Supplemental Figure 2. Receiver-operating characteristic curves for predicting A) acute brain injury (ABI), B) central nervous system (CNS) ischemia, and C) intracranial hemorrhage (ICH) in extracorporeal cardiopulmonary resuscitation (ECPR) patients**.**



Supplemental Figure 3. Feature Importance Scores for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in ECPR patients.



Supplemental Figure 4. SHAP value plots for A) acute brain injury, B) central nervous system ischemia, and C) intracranial hemorrhage in ECPR patients.



Supplemental Table 7. Model performance in extracorporeal cardiopulmonary resuscitation patients for predicting acute brain injury, central nervous system ischemia, and intracranial hemorrhage.

	Acc	TPR	TNR	FPR	FNR	PPV	NPV
ABI	69%	61%	70%	30%	39%	29%	90%
CNS Ischemia	81%	41%	85%	15%	59%	18%	95%
ICH	88%	28%	89%	11%	72%	7%	98%

Acc: Accuracy. TPR: True Positive Rate. TNR: True Negative Rate. FPR: False Positive Rate. FNR: False Negative Rate. PPV: Positive Predictive Value. NPV: Negative Predictive Value. ABI: acute brain injury. CNS: central nervous system. ICH: intracranial hemorrhage.

Supplemental Table 8. Comparisons between the top 3 most important features for ABI in ECPR patients.

	With ABI	**Without ABI**	p-value
Median ECMO duration	3.1 days	2.5 days	<0.001
Age	57.7 years	54.4 years	<0.001
Median ECMO pump flow rate at 24 hours	3.8 liters/minute	3.6 liters/minute	<0.001

Supplemental Table 9. Comparisons between the top 3 most important features for CNS ischemia in ECPR patients.

	With CNS ischemia	**Without CNS ischemia**	p-value
Median ECMO duration	3.3 days	2.5 days	<0.001
Serum bicarbonate at 24 hours	23 milliequivalents/liter	23 milliequivalents/liter	0.47
Body mass index	29.1 kilograms/meters squared	27.6 kilograms/meters squared	<0.001

Supplemental Table 10. Comparisons between the top 3 most important features for ICH in ECPR patients.

	With ICH	**Without ICH**	p-value
Supported at North American ELSO center	3.3% (n=195)	N/A	<0.001
Not supported at North American ELSO center	1.7% (n=86)	N/A	
Median positive-end expiratory pressure at 24 hours	8 mmHg	8 mmHg	0.25
Supported at North American ELSO center	1.2% (n=29)	N/A	<0.001
Not supported at North American ELSO center	3% (n=252)	N/A	