Using machine learning to predict neurologic injury in venovenous extracorporeal membrane oxygenation recipients: An ELSO Registry analysis

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ABSTRACT

Background: Venovenous extracorporeal membrane oxygenation (VV-ECMO) is associated with acute brain injury (ABI), including central nervous system (CNS) ischemia (defined as ischemic stroke or hypoxic-ischemic brain injury [HIBI]) and intracranial hemorrhage (ICH). Data on prediction models for neurologic outcomes in VV-ECMO are limited.

Methods: We analyzed adult (age ≥18 years) VV-ECMO patients in the Extracorporeal Life Support Organization (ELSO) Registry (2009-2021) from 676 centers. ABI was defined as CNS ischemia, ICH, brain death, and seizures. Data on 67 variables were extracted, including clinical characteristics and pre-ECMO/on-ECMO variables. Random forest, CatBoost, LightGBM, and XGBoost machine learning (ML) algorithms (10-fold leave-one-out cross-validation) were used to predict ABI. Feature importance scores were used to pinpoint the most important variables for predicting ABI.

Results: Of 37,473 VV-ECMO patients (median age, 48.1 years; 63% male), 2644 (7.1%) experienced ABI, including 610 (2%) with CNS ischemia and 1591 (4%) with ICH. The areas under the receiver operating characteristic curve for predicting ABI, CNS ischemia, and ICH were 0.70, 0.68, and 0.70, respectively. The accuracy, positive predictive value, and negative predictive value for ABI were 85%, 19%, and 95%, respectively. ML identified higher center volume, pre-ECMO cardiac arrest, higher ECMO pump flow, and elevated on-ECMO serum lactate level as the most important risk factors for ABI and its subtypes.

Conclusions: This is the largest study of VV-ECMO patients to use ML to predict ABI reported to date. Performance was suboptimal, likely due to lack of standardization of neuromonitoring/imaging protocols and data granularity in the ELSO Registry. Standardized neurologic monitoring and imaging are needed across ELSO centers to detect the true prevalence of ABI. (JTCVS Open 2024;21:140-67)
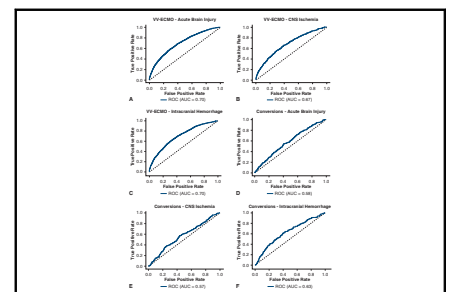
Machine learning performance to predict ABI in VV-ECMO patients using the ELSO Registry.

CENTRAL MESSAGE

Using the largest global database of extracorporeal membrane oxygenation (ECMO) patients, machine learning performed suboptimally in predicting acute brain injury in venovenous-ECMO patients, likely due to lack of data granularity.

PERSPECTIVE

Using machine learning, we demonstrated suboptimal prediction of neurologic complications such as acute brain injury (ABI) in the Extracorporeal Life Support Organization (ELSO) Registry. This performance may be attributable to the lack of data granularity in the Registry. Given the low prevalence of ABI in the ELSO Registry, standardized neurologic monitoring protocols across ELSO centers are imminent.

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Abbreviations and Acronyms

ABG	=	arterial blood gas
ABI	=	acute brain injury
AUC-ROC	=	area under the receiver-operating characteristic curve
CNS	=	central nervous system
ECMO	=	extracorporeal membrane oxygenation
ELSO	=	Extracorporeal Life Support Organization
HIBI	=	hypoxic-ischemic brain injury
ICH	=	intracranial hemorrhage
IQR	=	interquartile range
LOOCV	=	leave-one-out-cross-validation
ML	=	machine learning
NPV	=	negative predictive value
$PaCO_2$	=	partial pressure of carbon dioxide
PaO_2	=	partial pressure of oxygen
PPV	=	positive predictive value
SHAP	=	Shapley additive explanations
VA	=	venoarterial
VV	=	venovenous

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory support method for patients with respiratory failure.[1] VV-ECMO is associated with poor neurologic outcomes,[2] including acute brain injury (ABI), with central nervous system (CNS) ischemia (ischemic stroke and hypoxic-ischemic brain injury [HIBI]) and intracranial hemorrhage (ICH), and occurs in approximately 5% of VV-ECMO patients.[3] The overall mortality risk in VV-ECMO patients is 36%; however, the mortality risk in those with ischemic stroke (68% mortality) and ICH (72% mortality) is even higher.[3] Identifying risk factors may help minimize their occurrence. Prior analyses of the Extracorporeal Life Support Organization (ELSO) Registry, the largest international database of ECMO patients with more than 200,000 cases, using logistic regression showed that acidosis, hypoxemia, and coagulation disturbances immediately before cannulation were independently associated with ABI in VV-ECMO patients.[3]

Machine learning (ML) may be able to ascertain modifiable risk factors associated with ABI that might have been undetected in prior multivariable logistic regression models by unveiling relationships not visible using traditional regression.[4,5] Specifically, ML may be superior to traditional regression[6-9] because it can ascertain both linear and noncomplex nonlinear relationships,[10] use more information in a single model (eg, traditional regression is limited to one covariate per 10 observations), and better optimize and fine-tune parameters that ultimately lead to improved model performance and validation.[8,11] Data mining, the concept of extracting patterns and rules from large datasets, is central to ML, as it allows for the models to learn and trains them to future datasets.[12,13] This predictive analysis feature, which allows for risk factor identification through feature selection, is perhaps the most important feature distinguishing it from traditional regression. Furthermore, the ELSO Registry provides a theoretical advantage in using ML to predict ABI owing to its large sample size across the numerous ECMO centers worldwide and various clinical parameters for fine-tuning, enhancing its generalizability compared to previous studies that were conducted in single centers and focused on a specific ECMO indication.[14,15] A previous ELSO Registry study (n = 23,182) with venoarterial (VA)-ECMO patients using ML to predict in-hospital mortality demonstrated good performance (area under the receiver operating characteristic curve [AUC-ROC], 0.80).[7] However, currently there is a dearth of studies aimed at predicting neurologic outcomes, such as ABI, in VV-ECMO patients using ML. Here we aimed to use ML to predict ABI and to identify associated risk factors using the largest ELSO database of adult VV-ECMO patients.

MATERIALS AND METHODS
Study Design and Population

This retrospective study was approved by the Johns Hopkins Hospital Institutional Review Board with a waiver of informed consent (IRB00216321; approved October 22, 2019). The ELSO Registry is an international multicenter registry collecting data from 676 ECMO centers (2009-2021) across the world.[16] The Registry collects demographic information, baseline comorbidities, hemodynamic and arterial blood gas (ABG) data before and during ECMO support, neurologic and systemic on-ECMO complications, and clinical outcomes, including in-hospital mortality.[17] Comorbidities were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes.

Inclusion criteria. Patients who were age ≥18 years and supported with VV-ECMO between 2009 and 2021 were included. An exploratory analysis of "conversion" ECMO patients—those who were converted

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from VA-ECMO to VV-ECMO or from VV-ECMO to VA-ECMO—was performed.

Exclusion criteria. Repeat ECMO runs within the same patient were excluded. Patients on VA-ECMO support were excluded.

Data Collection

Figure 1 depicts the 67 features collected for the ML pipeline. The ELSO Registry gathers ABG and hemodynamic information before and after ECMO cannulation, defined as "pre-ECMO" and "on-ECMO" variables. Within 6 hours of ECMO cannulation, pre-ECMO ABGs were drawn and the pre-ECMO ventilator settings were recorded. The pre-ECMO ABG closest to the start of ECMO cannulation was used if multiple ABGs were available within the 6-hour period. The on-ECMO ABGs and hemodynamic variables nearest to 24 hours, determined at 18 to 30 hours postcannulation, were used as postcannulation values. A trained ELSO data manager from each ELSO center abstracted data points that were meant to be collected concurrently, such as oxygen saturation measured by pulse oximetry versus ABG analysis. All pre-ECMO support codes—including cardiac arrest, mechanical cardiac support, vasopressor and inotrope infusions, bridge to transplant as an ECMO indication, patient transported

to another ELSO center—represented conditions present within 24 hours of ECMO initiation.

Definitions

ABI includes CNS ischemia, defined as infarction (ischemic stroke) and/or diffuse ischemia (HIBI); intraparenchymal/extraparenchymal hemorrhage; intraventricular hemorrhage; seizures determined by electroencephalography or clinically; and neurosurgical intervention (eg, intracranial pressure monitor, external ventricular drain, craniotomy). Ischemic stroke was determined by computed tomography (CT) scan, ultrasound, or magnetic resonance imaging. HIBI was determined by CT scan. ICH was determined by CT scan and was defined as intraparenchymal/extraparenchymal hemorrhage and/or intraventricular hemorrhage. Brain death was captured by one of the following methods: (1) neurologic determination of death according to the Canadian Neurocritical Care Guideline; (2) ancillary tests, including cerebral angiography and radionuclide angiography, that demonstrate the absence of intracerebral blood flow; and (3) apnea test on ECMO. The definitions for demographics, pre-ECMO support, hemodynamics, ABGs, and systemic complications are provided in the Appendix E1. We calculated the RESPscore as a marker of survival based on prior literature.[18]
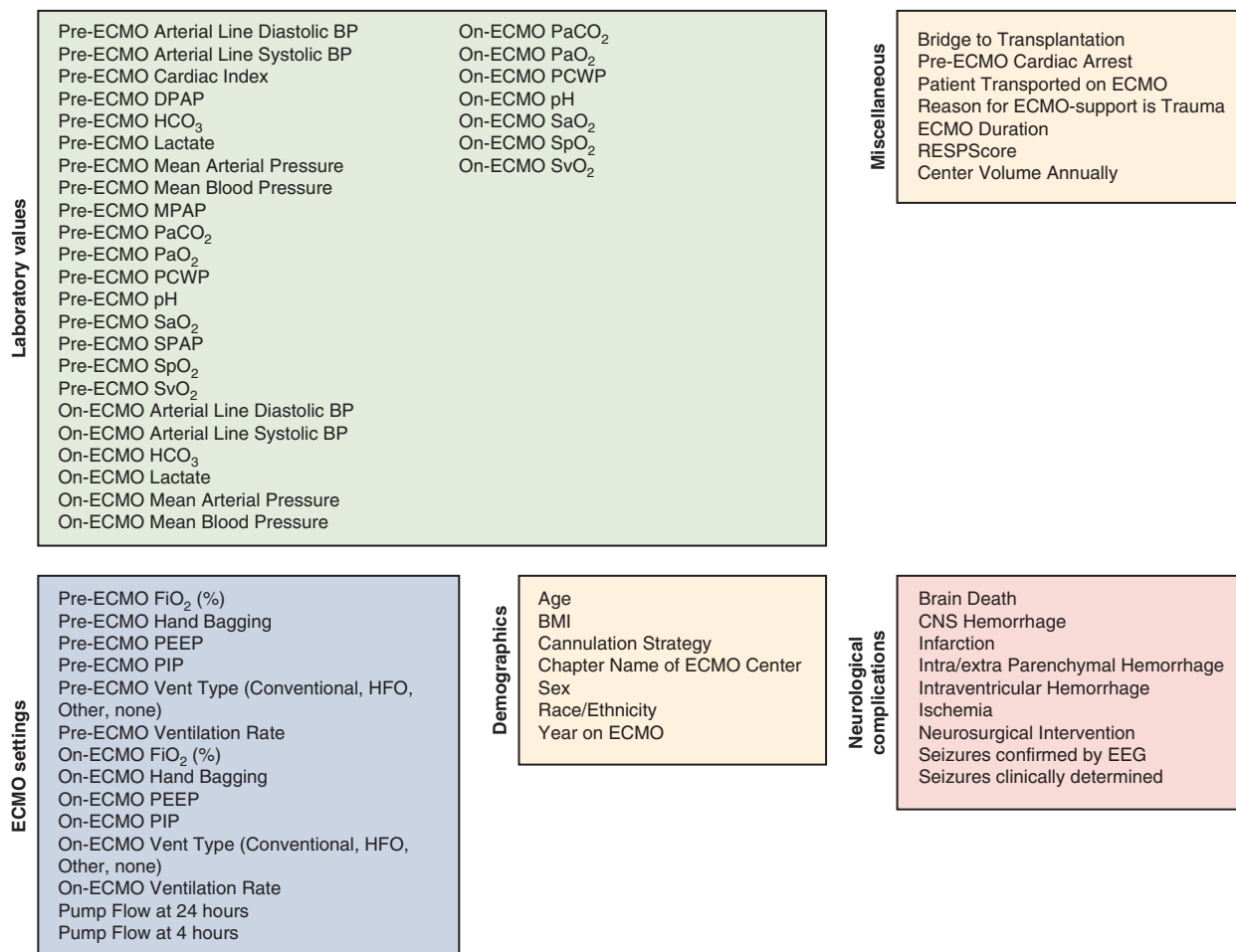
FIGURE 1. Variables used in our machine learning pipeline to predict ABI, ranging from demographics to on-ECMO laboratory values. *ECMO,* Extracorporeal membrane oxygenation; *BP,* blood pressure; *PaCO$_2$,* partial pressure of carbon dioxide; *PaO$_2$,* partial pressure of oxygen; *PCWP,* pulmonary capillary wedge pressure; *DPAP,* diastolic pulmonary arterial pressure; *SaO$_2$,* arterial blood gas oxygen saturation; *SpO$_2$,* peripheral oxygen saturation; *SvO$_2$,* mixed venous oxygen saturation; *MPAP,* mean pulmonary arterial pressure; *FiO$_2$,* fraction of inspired oxygen; *PEEP,* positive-end expiratory pressure; *PIP,* peak inspiratory pressure; *EEG,* electroencephalogram.

Outcomes

The primary outcome was ABI at any time point while on ECMO support. Secondary outcomes were CNS ischemia and ICH (subgroups of ABI).

Statistical Analysis

Continuous variables were recorded as median and interquartile range (IQR); categorical variables, as frequencies. The Wilcoxon rank-sum and Pearson χ^2 tests were used to compare continuous and categorical variables, respectively. $P < .05$ was considered to indicate statistical significance.

Data preprocessing. Categorical features were one hot–encoded before running the ML algorithms. The default imputation method—multiple imputation—for each algorithm for Python packages such as XGBoost and CatBoost was used for missing data (maximum <30% missing data). All missing data are conveyed in Table E1.

ML algorithm and pipeline. We analyzed the appropriateness of 4 different ML algorithms to predict ABI from the ELSO Registry: Random Forest, CatBoost, LightGBM, and XGBoost. Bayesian optimization was used to split the dataset at random into a training set (70%) and a test set (30%) based on prior literature.[19] Hyperparameters were fine-tuned for all 4 algorithms. Using the fine-tuned hyperparameters, each of the 4 ML models was fitted onto the training set and then assessed on the test set. The top-performing model was chosen for further optimization.

We used random oversampling of patients with ABI in the training set at varying occurrences. For each oversampling frequency, we evaluated the model with a 10-fold cross-validation approach. Once we identified the most ideal oversampling rate, we used the best-performing model on the entire cohort, using a leave-one-out cross-validation (LOOCV) method. This method functions by using all observations in the training set except for 1 individual observation that is reserved for use in the test set. This LOOCV stepwise technique was repeated across the entire cohort. Each observation was used as the test set. This method correspondingly produced N number of models that were subsequently trained and then tested on the holdout N observations. In the end, all observations were pooled to yield a combined N number of observations. We ensured the reproducibility of our results by using this LOOCV approach, which reduces the risk of bias by testing the ML algorithm on the whole cohort. We then computed the AUC-ROC, the area under the precision recall curve, and Brier scores to measure the predictive performance of each model. We also chose a cutoff that optimized the F1 score. Finally, we calculated corresponding sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

Important Features in ML Algorithms

To provide better interpretability to the ML models, we determined which variables were most essential for correctly predicting ABI through feature importance scores and Shapley additive explanations (SHAP) values. We analyzed the hierarchical feature importance in each model, which depicts the contribution of each feature in the boosted decision trees. The interpretation of SHAP values is described in the Appendix E1. Feature importance scores and SHAP values allowed us to identify the most relevant clinical features associated with each outcome. All statistical analyses were conducted using R Studio (R 4.1.2, www.r-project.org) and Python.

RESULTS

Of the total cohort of 37,473 VV-ECMO patients, 2644 (7.1%) experienced ABI (Figure 2). The median age of the cohort was 48.1 years (IQR, 35.9-58.5 years), and 63% (n = 23,649) were male. The median duration of ECMO support was 9.9 days (IQR, 4.0-20.3 days).

Compared to those without ABI, VV-ECMO patients with ABI were more likely to be Asian or Hispanic, more likely to have had pre-ECMO vasopressor infusions, and had higher ECMO pump flow rates at 4 and 24 hours of ECMO support (Table 1). Asian and Hispanic VV-ECMO patients with higher pump flow rates (ie, exceeding the median of 4 L/min) had higher bicarbonate levels at 24 hours of cannulation compared to those with lower pump flow rates (27.0 mEq/L vs 25.5 mEq/L; $P < .001$). This is important, because metabolic alkalosis and higher bicarbonate levels are associated with more severe disease in patients with acute respiratory failure.[20]

Model Performance in VV-ECMO

The model obtained an AUC-ROC of 0.70 for predicting ABI (Table 2, Figure 3), with an accuracy of 85%. The true positive rate, true negative rate, false positive rate, and false negative rate were 34%, 89%, 11%, and 66%, respectively. The PPV and NPV were 19% and 95%, respectively. The precision, recall, and F1 values were 0.19, 0.34, and 0.24, respectively, and the Brier score was 0.17.

For CNS ischemia, the model obtained an AUC-ROC of 0.67 (Table 2, Figure 3) with an accuracy of 95%, a true positive rate of 15%, true negative rate of 96%, false positive rate of 4%, and false negative rate of 85%. The PPV and NPV were 7% and 99%, respectively. The precision, recall, and F1 values were 0.066, 0.15, and 0.09, respectively, and the Brier score was 0.14.

For ICH, the model obtained an AUC-ROC of 0.70 (Table 2, Figure 3) with an accuracy of 89%. The true positive rate, true negative rate, false positive rate, and false negative rate were 32%, 91%, 9%, and 68%, respectively. The PPV and NPV were 14% and 97%, respectively. The precision, recall, and F1 values were 0.14, 0.33, and 0.19, respectively, and the Brier score was 0.20.

Feature Importance Scores in VV-ECMO

We identified the 3 most important features by calculating average gains in feature importance scores and presented the other significant variables (Figure 4). The top 3 features for ABI prediction were duration of ECMO, annual center volume, and body mass index (Figure 4, A and Figure E1, A). The median duration of ECMO for patients with ABI was shorter versus those without ABI (9.2 days vs 9.9 days; $P = .01$). The median annual center volume was higher for patients with ABI compared to those without ABI, although the difference did not reach statistical significance (45.67 cases/year vs 43.60 cases/year; $P = .6$). The median body mass index for patients with ABI was slightly higher versus those without ABI, although this difference did not reach statistical significance (30.43 kg/m^2 vs 30.11 kg/m^2; $P = .06$). Other important modifiable risk factors for ABI identified by feature importance scores included higher pre-ECMO systolic blood pressure, higher
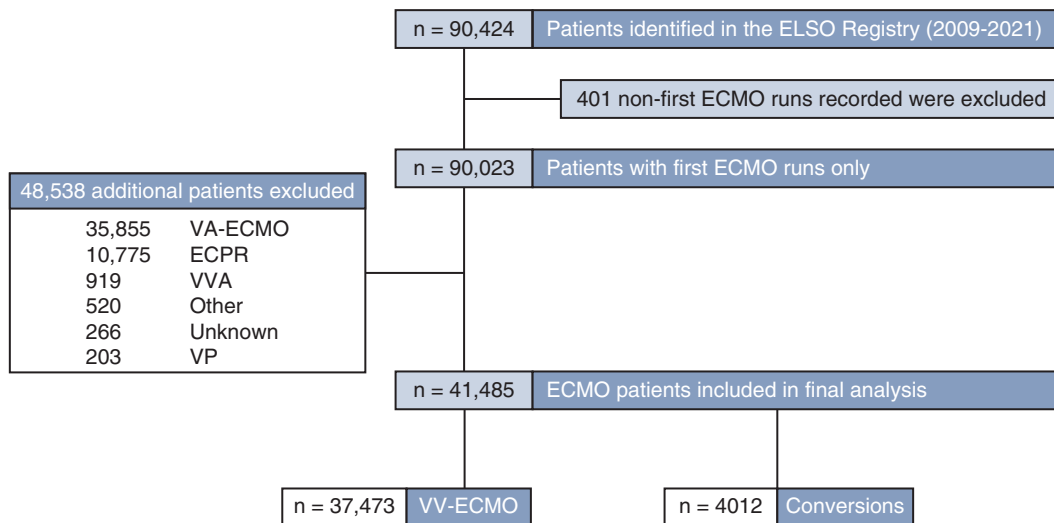
FIGURE 2. Flow diagram for creation of the cohort study. *ECMO*, Extracorporeal membrane oxygenation; *VA*, venoarterial; *VV*, venovenous; *Conversions*, VA→VV or VV→VA; *ECPR*, extracorporeal cardiopulmonary resuscitation; *VVA*, venovenoarterial; *Other*, mode not defined; *VP*, venopulmonary.

on-ECMO partial pressure of oxygen (PaO_2), and lower on-ECMO pH (all within the top-10 most important risk factors). For predicting CNS ischemia, the top-3 features were pre-ECMO cardiac arrest, being supported on ECMO at an Asian Pacific ELSO center, and on-ECMO serum lactate level (Figure 4, *B* and Figure E1, *B*). The prevalence of CNS ischemia was higher in patients who experienced cardiac arrest before ECMO compared to those without pre-ECMO cardiac arrest (4.4% vs 1.4%; $P < .001$). The prevalence of CNS ischemia was lower in patients supported on ECMO at an Asian Pacific ELSO Center compared to those not supported on ECMO at a North American ELSO center (1% vs 2%; $P = .002$). The median on-ECMO serum lactate level was higher in patients with CNS ischemia compared to those without CNS ischemia (3.235 mmol/L vs 2.463 mmol/L; $P < .001$). The top 3 variables for predicting ICH were duration of ECMO, annual center volume, and ECMO pump flow at 24 hours (Figure 4, *C* and Figure E1, *C*). The median duration of ECMO was longer in patients with ICH versus those without ICH (10.6 days vs 9.9 days; $P = .026$). The median annual center volume was higher in those with ICH versus those without ICH, although this difference did not reach statistical significance (45.67 cases/year vs 43.60 cases/year; $P = .29$). The median ECMO pump flow rate at 24 hours was higher in those with ICH versus those without ICH (4.220 vs 4.100; $P < .001$).

Sensitivity Analysis by Time Period

In sensitivity analysis of earlier years of the study period (2009-2018; n = 16,832), the model obtained an AUC-ROC of 0.67. In such an analysis of later years of the study period (2019-2021; n = 20,641), the model obtained an AUC-ROC of 0.65.

Exploratory Analysis: ML to Predict Mortality in Patients With ABI

An additional ML model was run to predict mortality in the subset of patients who experienced ABI. The AUC-ROC was 0.70, and the model identified older age, lower on-ECMO 24-hour systolic blood pressure, later year of ECMO cannulation, and lower pre-ECMO diastolic blood pressure as the most important risk factors for mortality in patients with ABI.

Exploratory Analysis: Factors Associated With Pre-ECMO Cardiac Arrest

Given that pre-ECMO cardiac arrest was the most important modifiable risk factor for CNS ischemia, we ran univariable analyses to identify factors associated with pre-ECMO cardiac arrest (Table E2). Notably, patients who experienced cardiac arrest had greater use of additional temporary mechanical circulatory support, vasopressor and inotropic infusions, and pre-ECMO metabolic acidosis, hypoxia/hypoxemia, hypercarbia, greater magnitude in change of partial pressure of carbon dioxide ($PaCO_2$) from before to after cannulation, and lower pump flow rates compared to patients without cardiac arrest.

Supplementary Analysis of ECMO Patients Undergoing Modality Change

Among 4012 patients who were converted from one ECMO modality to another (ie, conversions), 466 (11.6%) experienced ABI (Figure E2). In this cohort, 2335 patients were converted from VA-ECMO to VV-ECMO, and 1677 were converted from VV-ECMO to VA-ECMO. The median age of this cohort of patients who were converted from one modality to another was 53 years (IQR, 39.2-62.4 years), and 65% (n = 2618)
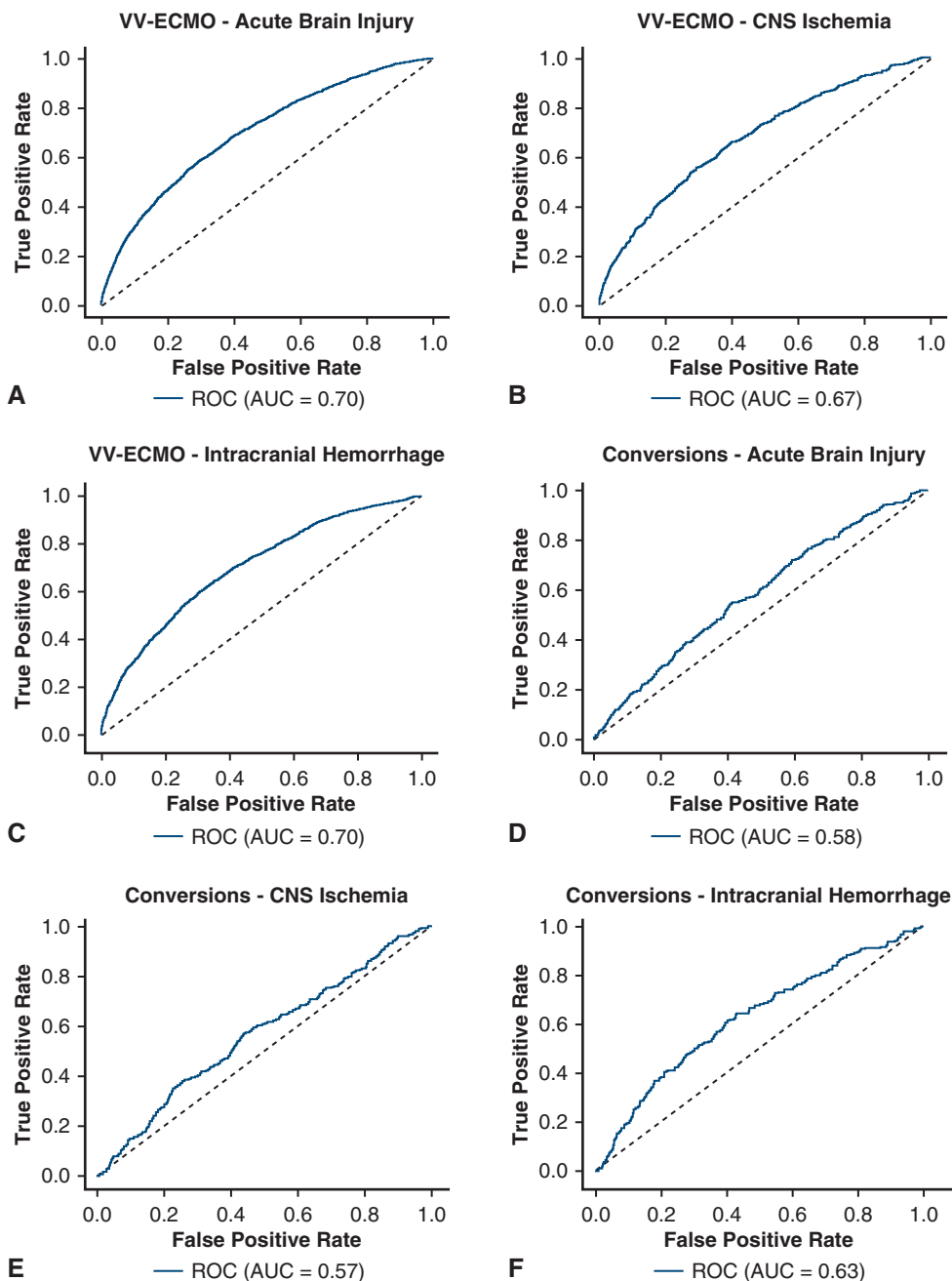
FIGURE 3. Receiver-operating characteristic curves (ROC) for predicting area under the receiver-operating characteristic curves (AUC) (A) acute brain injury, (B) central nervous system (CNS) ischemia, and (C) intracranial hemorrhage in venovenous extracorporeal membrane oxygenation (VV-ECMO) and for predicting (D) acute brain injury, (E) CNS ischemia, and (F) intracranial hemorrhage in "Conversion" patients.

were male. The median duration of ECMO support was 9.9 days (4.9-20.3, days). Among ECMO patients who were converted from one modality to another, those with ABI were younger, were cannulated for longer, and had lower pre-ECMO pH and $PaCO_2$ compared to those without ABI (Table E3).

The model obtained an AUC-ROC of 0.58 with an accuracy of 58% for ABI, an AUC-ROC was 0.57 with an accuracy of

75% for CNS ischemia, and an AUC-ROC of 0.63 with an accuracy of 80% for ICH (Table E3). The most important features for predicting ABI, CNS ischemia, and ICH in conversion patients are shown in Figures E2 and E3.

DISCUSSION

This is the first study to apply tree-based ML to predict ABI in adult respiratory failure VV-ECMO patients using

TABLE 1. Baseline characteristics and clinical variables of VV-ECMO patients stratified by presence of ABI

Characteristic/variable	Total VV-ECMO (N = 37,473)	ABI (N = 2,644, 7%)	No ABI (N = 34,829, 93%)	P value
Demographics				
Age, y, median (IQR)	48.1 (35.9-58.5)	48.1 (35.8-58.5)	48.7 (32.3-57.8)	.43
Male sex, n (%)	23,649 (63)	1671 (63)	21,978 (63)	.98
Body mass index, kg/m^2, median (IQR)	30.1 (25.6-36.1)	30.4 (26.3-35.8)	30.1 (25.5-36.2)	.06
Race/ethnicity, n (%)				<.001
Asian	3925 (10)	318 (12)	3607 (10)	
Black	4150 (11)	246 (9)	3904 (11)	
Hispanic	4035 (11)	363 (14)	3672 (11)	
White	19,811 (53)	1320 (50)	18,491 (53)	
Others	5552 (15)	397 (15)	5155 (15)	
Year of ECLS, n (%)				
2009	357 (1)	29 (1)	328 (1)	<.001
2010	410 (1)	22 (1)	388 (1)	
2011	557 (1)	43 (2)	514 (1)	
2012	836 (2)	54 (2)	782 (2)	
2013	1304 (3)	86 (3)	1218 (3)	
2014	1777 (5)	138 (5)	1639 (5)	
2015	2019 (5)	140 (5)	1879 (5)	
2016	2773 (7)	178 (7)	2595 (7)	
2017	3106 (8)	150 (6)	2956 (8)	
2018	3693 (10)	246 (9)	3447 (10)	
2019	4447 (12)	267 (10)	4180 (12)	
2020	7716 (21)	611 (23)	7105 (20)	
2021	8478 (23)	680 (21)	7798 (22)	
Past medical history, n (%)				
Diabetes	2738 (7)	208 (8)	2530 (7)	.09
Hypertension	3415 (9)	277 (10)	3138 (9)	.09
Atrial fibrillation	1581 (4)	115 (4)	1466 (4)	.94
Cardiomyopathy	461 (1)	29 (1)	432 (1)	.64
Chronic obstructive pumonary disease	1583 (4)	111 (4)	1472 (4)	.74
Pre-ECMO support, n (%)				
Additional temporary mechanical circulatory support	899 (2)	57 (2)	842 (2)	.40
Vasopressor infusions	19,439 (52)	1619 (61)	17,820 (51)	<.001
Inotrope infusions	2203 (6)	158 (6)	2045 (6)	.83
Pre-ECMO cardiac arrest, n (%)	2770 (7)	368 (14)	2402 (7)	<.001
Pre-ECMO blood pressure variables, median (IQR)				
Systolic blood pressure, mm Hg	110 (95-128)	110 (70-127)	110 (95-128)	.27
Diastolic blood pressure, mm Hg	60 (51-70)	59 (50-68)	60 (51-70)	<.001
Mean blood pressure, mm Hg	75 (65-86)	75 (65-85)	75 (65-86)	.03
Pulse pressure, mm Hg	50 (39-63)	50 (40-64)	50 (39-63)	.16
Mean arterial pressure, mm Hg	22 (18-26)	22 (19-26)	22 (18-26)	.002
Pre-ECMO ABG, median (IQR)				
pH	7.26 (7.17-7.35)	7.23 (7.13-7.32)	7.27 (7.17-7.35)	<.001
HCO$_3$-, mEq/L	25.9 0 (21.6-31)	26 (21.1-31)	25.9 (21.6 -30.9)	.91
PaO$_2$, mm Hg	65 (53-81)	63 (51-78)	65 (53-82)	<.001
PaCO$_2$, mm Hg	58.5 (33.80-74.5)	62.2 (49.5-80)	58 (46.6-74)	<.001

(Continued)

TABLE 1. Continued

Characteristic/variable	Total VV-ECMO (N = 37,473)	ABI (N = 2,644, 7%)	No ABI (N = 34,829, 93%)	P value
Lactate, mmol/L	1.2 (1.8-3.1)	2 (1.3-4)	1.8 (1.2-3.1)	**<.001**
SpO₂, %	90 (85-95)	90 (83-94)	90 (85-95)	**.002**
SaO₂, %	90 (83-94)	89 (81-94)	90 (83-94)	**<.001**
On-ECMO blood pressure variables, median (IQR)				
Systolic blood pressure, mm Hg	115 (103-129)	115 (103-129)	115 (103-128)	.38
Diastolic blood pressure, mm Hg	60 (53-68)	60 (53-68)	60 (53-67)	.59
Mean blood pressure, mm Hg	76 (70-85)	76 (69-86)	76 (70-85)	.64
Pulse pressure, mm Hg	55 (45-66)	55 (45-67)	55 (45-66)	.14
Mean arterial pressure, mm Hg	15 (12-18)	15 (13-19)	15 (12-18)	.13
On-ECMO ABG, median (IQR)				
pH	7.4 (7.36-7.44)	7.4 (7.35-7.44)	7.4 (7.36-7.44)	**.03**
HCO₃, mEq/L	26 (23-30)	26 (22.5-30)	26 (23-30)	.28
PaO₂, mm Hg	78 (64.5-103)	75 (62-99)	78 (65-103)	**<.001**
PaCO₂, mm Hg	42.3 (37-48.2)	42 (37-48.5)	42.3 (37.1-48.1)	.38
Lactate, mmol/L	1.5 (1.1-2.3)	1.6 (1.2-2.5)	1.5 (1.1-2.3)	**<.001**
SpO₂, %	96 (92-98)	95 (92-98)	96 (92-98)	**.006**
SaO₂, %	95 (92-98)	95 (92-97)	95 (92-98)	**.007**
ΔPaCO₂	−15 (−30 to −4)	−19 (−35.2 to −6.25)	−15 (−30 to −4)	**<.001**
Pump flow rate at 4 h, L/min, median (IQR)	4.05 (3.5-4.6)	4.05 (3.5-4.6)	4.05 (3.5-4.6)	**<.001**
Pump flow rate at 24 h, L/min, median (IQR)	4.1 (3.5-4.7)	4.17 (3.63-4.8)	4.1 (3.5-4.7)	**<.001**
Days on ECMO support, median (IQR)	9.92 (4.88-20.3)	9.17 (3.83-21.6)	9.92 (4.92-20.2)	**.01**
Neurologic complications on-ECMO				
Composite ABI, n (%)				
Composite ischemia	610 (2)	610 (23)	0 (0)	**<.001**
Hypoxic-ischemic brain injury	139 (1)	139 (5)	0 (0)	**<.001**
Ischemic stroke	478 (1)	478 (18)	0 (0)	**<.001**
Composite ICH	1591 (4)	1591 (60)	0 (0)	**<.001**
Intra/extraparenchymal hemorrhage	745 (2)	745 (28)	0 (0)	**<.001**
Intraventricular hemorrhage	306 (1)	306 (12)	0 (0)	**<.001**
Brain death	462 (1)	462 (17)	0 (0)	**<.001**
Neurosurgical intervention	37 (1)	37 (1)	0 (0)	**<.001**
Seizures confirmed by EEG	107 (1)	107 (4)	0 (0)	**<.001**
Seizures clinically determined	249 (1)	249 (9)	0 (0)	**<.001**
Other complications on-ECMO, n (%)				
ECMO circuit mechanical failure	8724 (23)	660 (25)	8064 (23)	**.03**
Renal replacement therapy	9215 (25)	933 (35)	8282 (24)	**<.001**
Hemolysis	1772 (5)	188 (7)	1584 (5)	**<.001**
Cardiac arrhythmia	2778 (7)	281 (11)	2497 (7)	**<.001**
Gastrointestinal hemorrhage	1954 (5)	189 (7)	1765 (5)	**<.001**
Outcomes, n (%)				
In-hospital mortality	15,074 (40)	2088 (79)	12,986 (37)	**<.001**

Bold type indicates significance. *VV-ECMO*, Venovenous extracorporeal membrane oxygenation; *ABI*, acute brain injury; *IQR*, interquartile range; *ECLS*, extracorporeal life support; *ABG*, arterial blood gas; *ICH*, intracranial hemorrhage; *EEG*, electroencephalography.

TABLE 2. Model performance in VV-ECMO patients for predicting ABI, CNS ischemia, and ICH

Complication	AUC-ROC	Acc, %	TPR, %	TNR, %	FPR, %	FNR, %	PPV, %	NPV, %	Precision	Recall	F1	Brier score
ABI	0.70	85	34	89	11	66	19	95	0.19	0.34	0.24	0.17
CNS ischemia	0.67	95	15	96	4	85	7	99	0.066	0.15	0.09	0.14
ICH	0.70	89	32	91	9	68	14	97	0.14	0.33	0.19	0.20

VV-ECMO, Venovenous extracorporeal membrane oxygenation; *ABI*, acute brain injury; *CNS*, central nervous system; *ICH*, intracranial hemorrhage; *AUC-ROC*, area under the receiver-operating characteristic curve; *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.

a large, international multicenter database (the ELSO Registry) over a substantial period encompassing 2 respiratory virus pandemics (2009-2021). ML predicted ABI with an AUC-ROC of 0.70 and we identified several important clinical risk factors for ABI and its subtypes, including center volume, pre-ECMO cardiac arrest, longer duration of ECMO, higher ECMO pump flow rate, and higher on-ECMO serum lactate level (Figure 5).

Novelty of ML and the ELSO Registry

Theoretically, ML allows for the appropriate analysis of exceedingly large datasets, improving the efficiency and accuracy of prediction as the model develops more experience.[4,5] ML also facilitates an environment for recognizing new patterns and integrating data in a fashion that humans may be unable to achieve.[4] These ML methods facilitate an innovative way to look at different outcomes in a statistical model. They are powerful and accurate and demonstrate some interpretability of the output through feature importance scores. There also are key differences among the various ML models the we used. For example, while gradient boosting (XGBoost, CatBoost, and LightGBM) works sequentially and uses intuition to make a strong predictive model,[21] Random Forest is constructed in a completely independent fashion by amalgamating multiple decision trees into one final uniform model.[22] Therefore, XGBoost takes a more rigid, fixed-order approach, while Random Forest has greater flexibility. Boosting methods also have certain key differences. For example, CatBoost produces models iteratively, suggesting that each decision tree improves based on the prior decision tree, while LightGBM splits observations into bins and is known to generate output at a much faster pace than CatBoost.

Our use of the ELSO Registry allows us to generalize our results to a global population across multiple continents (North America, Europe, Asia, Pacific Islands, Latin America, Southwest Asia, and Africa) with an eclectic cohort of respiratory failure patients receiving VV-ECMO support from various ELSO centers. This allowed us to improve on various studies in ECMO populations using ML that were from a single center, had a small sample size, and/or capture only one specific ECMO indication.[14,23,24] Our study captured patients from over a decade, which may

further contribute to the generalizability and real-world validity of our model. Furthermore, although a previous ELSO Registry study of 23,182 VA-ECMO patients demonstrated that ML was able to predict survival with an AUC-ROC of 0.80,[7] it should be noted that assessing mortality is a less complex outcome to discern than ABI, which requires central adjudication and standardization of clinical practice, a limitation of the ELSO Registry dataset. Accordingly, ABI likely is underestimated in the ELSO Registry.

VV-ECMO Risk Factors for ABI

We identified cardiac arrest occurring 6 hours before ECMO support as the most important risk factor for CNS ischemia. Longer duration of ECMO support was associated with a lower risk of ABI but a higher risk of its subtype ICH. Although cardiac arrest–related brain injury occurs hyperacutely, acute imaging and postarrest neurologic care remain critical for these patients. This includes conducting neurologic monitoring for secondary brain injury as recommended in a 2024 joint collaborative guideline of the American Heart Association and Neurocritical Care Society.[25]

Although cardiac arrest is a known risk factor,[26,27] the literature on the association between ECMO duration and ABI is lacking. The lower risk of ABI with shorter duration of ECMO may reflect selection bias of the subset of ECMO patients who underwent the decision to limit life-sustaining therapies in the setting of severe ABI or those patients who died directly from ABI and thus received a shorter duration of ECMO support. Finally, patients receiving ECMO at higher-volume centers were more likely to experience ABI and its subtypes, which may reflect a greater potential to cannulate sicker patients or an increased ability for these higher-volume centers to successfully detect ABI compared to ELSO centers across the world. This result also may reflect different practices for detecting ABI across different continents, which warrants further investigation.

Need for Standardized Neuromonitoring

The prevalence of ABI in both the VV-ECMO and conversion cohorts was relatively low in the ELSO Registry, which is in line with a previous ELSO Registry study of VA-ECMO patients that also used machine learning to predict ABI and observed poor model performance.[19] Notably,

Acute Brain Injury
Feature Importance

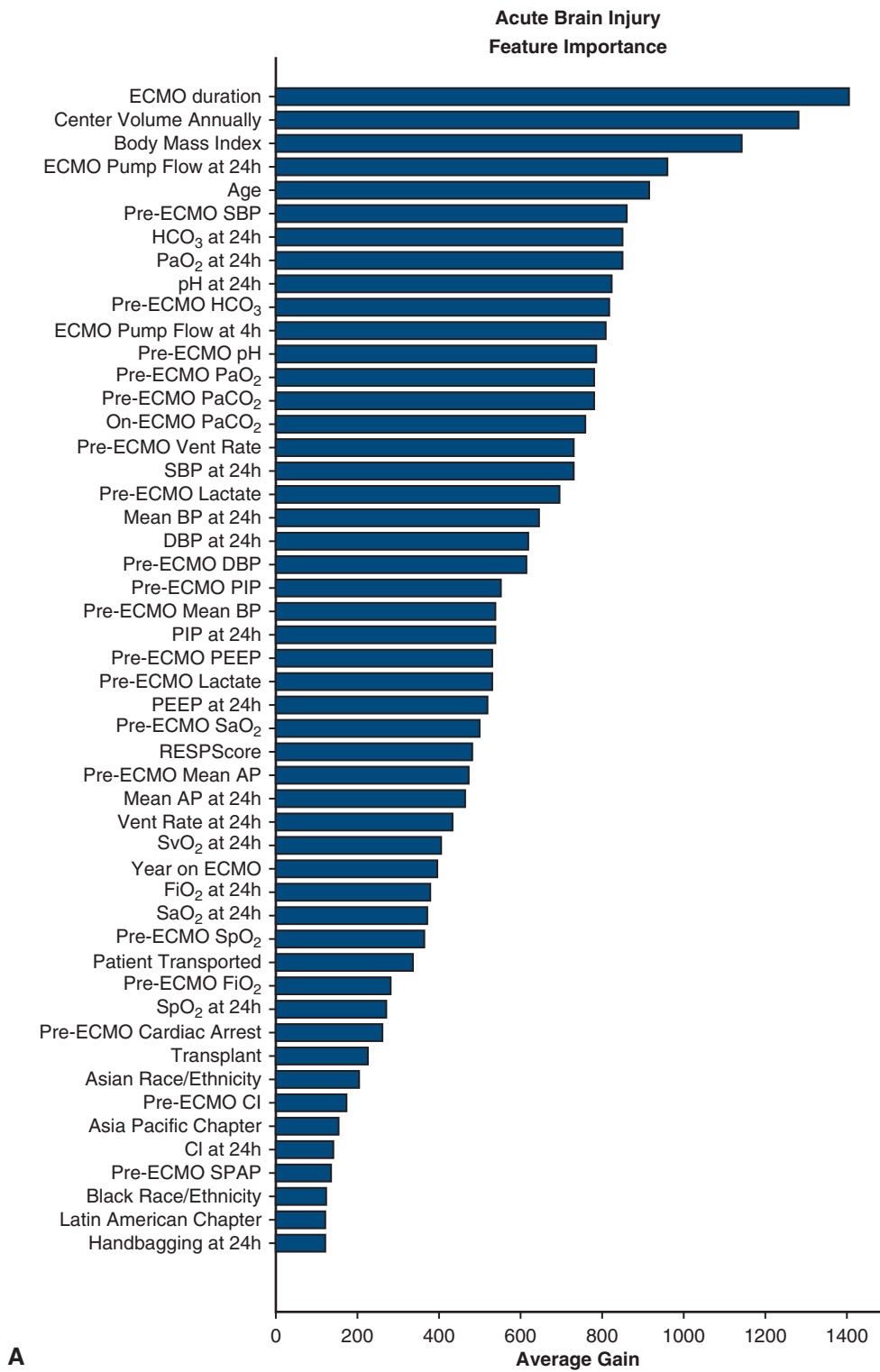| Feature	Average Gain
ECMO duration	~1400
Center Volume Annually	~1280
Body Mass Index	~1130
ECMO Pump Flow at 24h	~950
Age	~910
Pre-ECMO SBP	~860
HCO$_3$ at 24h	~850
PaO$_2$ at 24h	~850
pH at 24h	~830
Pre-ECMO HCO$_3$	~820
ECMO Pump Flow at 4h	~810
Pre-ECMO pH	~790
Pre-ECMO PaO$_2$	~780
Pre-ECMO PaCO$_2$	~780
On-ECMO PaCO$_2$	~760
Pre-ECMO Vent Rate	~730
SBP at 24h	~730
Pre-ECMO Lactate	~700
Mean BP at 24h	~650
DBP at 24h	~620
Pre-ECMO DBP	~620
Pre-ECMO PIP	~560
Pre-ECMO Mean BP	~540
PIP at 24h	~540
Pre-ECMO PEEP	~530
Pre-ECMO Lactate	~530
PEEP at 24h	~520
Pre-ECMO SaO$_2$	~500
RESPScore	~480
Pre-ECMO Mean AP	~470
Mean AP at 24h	~470
Vent Rate at 24h	~430
SvO$_2$ at 24h	~400
Year on ECMO	~400
FiO$_2$ at 24h	~380
SaO$_2$ at 24h	~375
Pre-ECMO SpO$_2$	~360
Patient Transported	~340
Pre-ECMO FiO$_2$	~280
SpO$_2$ at 24h	~270
Pre-ECMO Cardiac Arrest	~260
Transplant	~220
Asian Race/Ethnicity	~200
Pre-ECMO CI	~175
Asia Pacific Chapter	~155
CI at 24h	~145
Pre-ECMO SPAP	~140
Black Race/Ethnicity	~120
Latin American Chapter	~115
Handbagging at 24h	~120

A   Average Gain

FIGURE 4. Most important features for each neurological outcome: (A) acute brain injury, (B) central nervous system ischemia, and (C) intracranial hemorrhage in VV-ECMO patients. *ECMO*, Extracorporeal membrane oxygenation; *SBP*, systolic blood pressure; *PaO₂*, partial pressure of oxygen; *PaCO₂*, partial pressure of carbon dioxide; *BP*, blood pressure; *DBP*, diastolic blood pressure; *PIP*, peak inspiratory pressure; *PEEP*, positive-end expiratory pressure; *SaO₂*, arterial blood gas oxygen saturation; *SpO₂*, peripheral oxygen saturation; *CI*, cardiac index; *SPAP*, systolic pulmonary arterial pressure; *AP*, arterial pressure; Vent, ventilator; *BMI*, body mass index; *DPAP*, diastolic pulmonary arterial pressure.
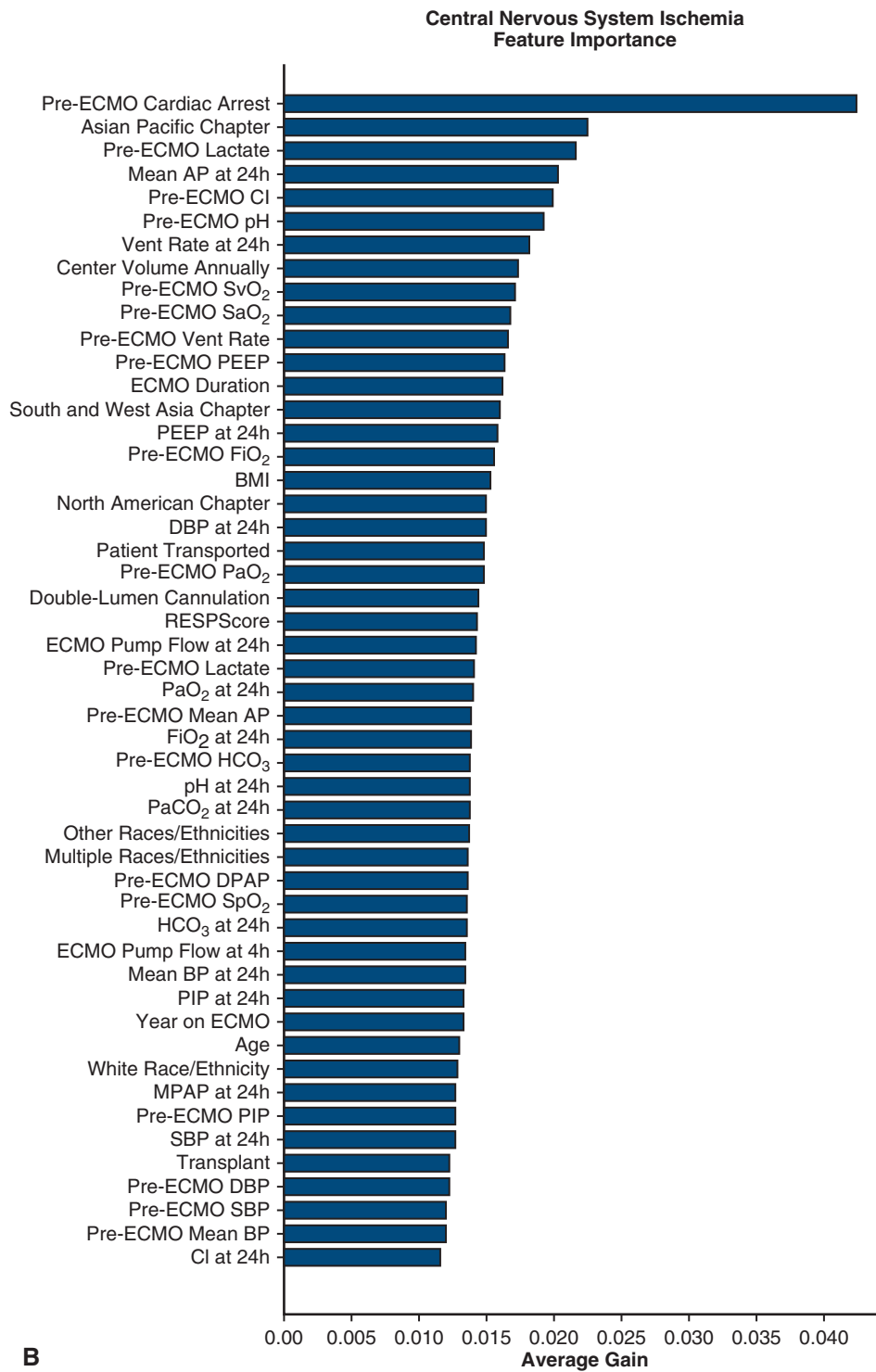
**Central Nervous System Ischemia
Feature Importance**

FIGURE 4. (*Continued*).

our models demonstrated low PPV but high NPV for ABI and its subtypes in both cohorts. Although the ELSO Registry includes the largest cohort of ECMO patients available, data gathered from hundreds of different ECMO centers resulted in a heterogeneous cohort, especially with the varied methodologies used to detect ABI across centers. In a prior study, noninvasive standardized neuromonitoring detected ABI in up to 33% of VA-ECMO patients,[28] but this
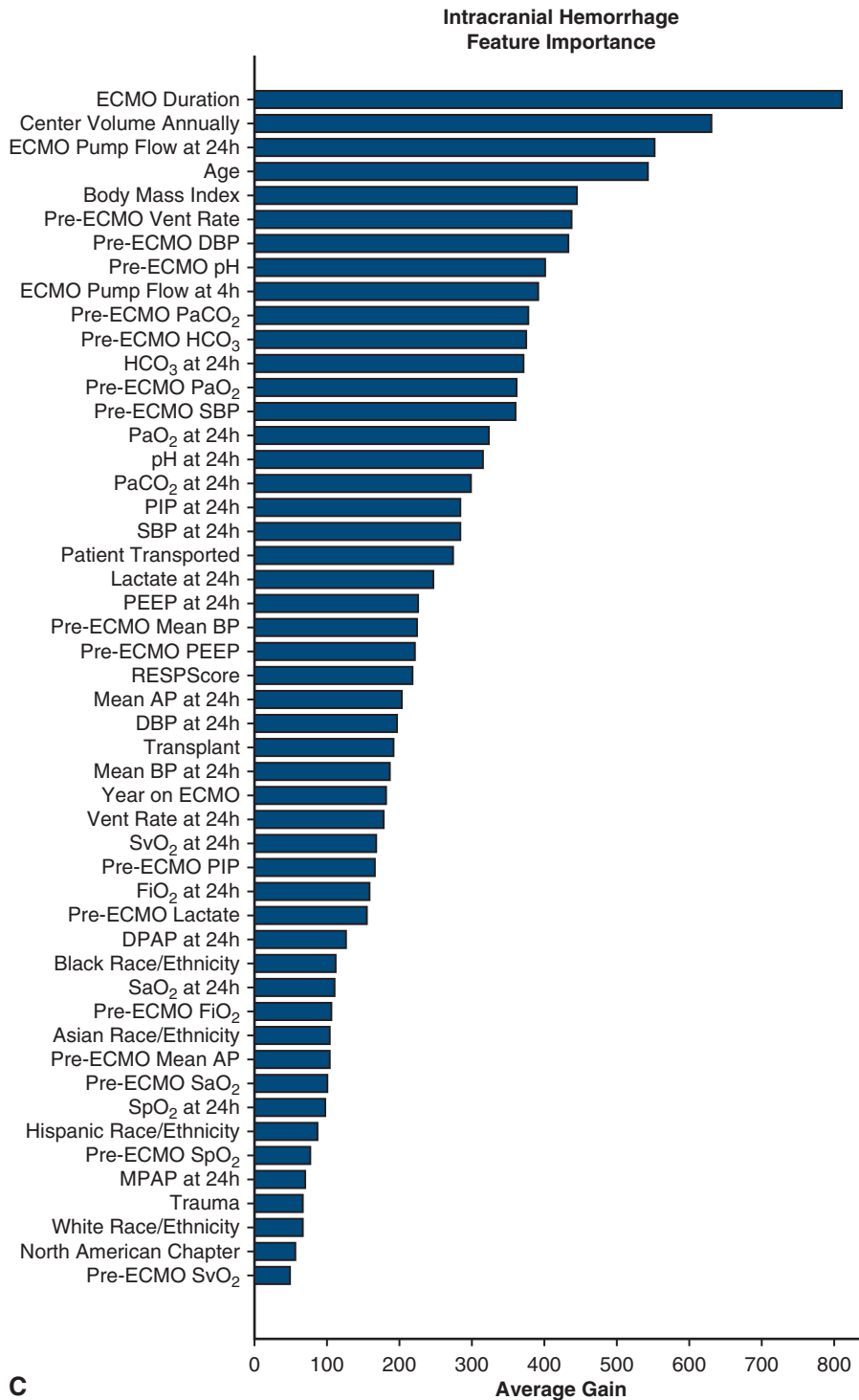
Intracranial Hemorrhage Feature Importance

FIGURE 4. (*Continued*).

methodology has not been implemented by all ECMO centers. Centers implementing standardized neuromonitoring have been shown to detect ABI at a higher prevalence, in 10%[29] and 16%[30] of VV-ECMO patients. This is supported by a single-center pediatric ECMO study of 68 VV-ECMO patients and 106 VA-ECMO patients that demonstrated a high prevalence of ABI (51%) when standardized neuromonitoring with neuroimaging protocol was implemented.[31] This study also used artificial intelligence to predict ABI primarily in VA-ECMO patients and
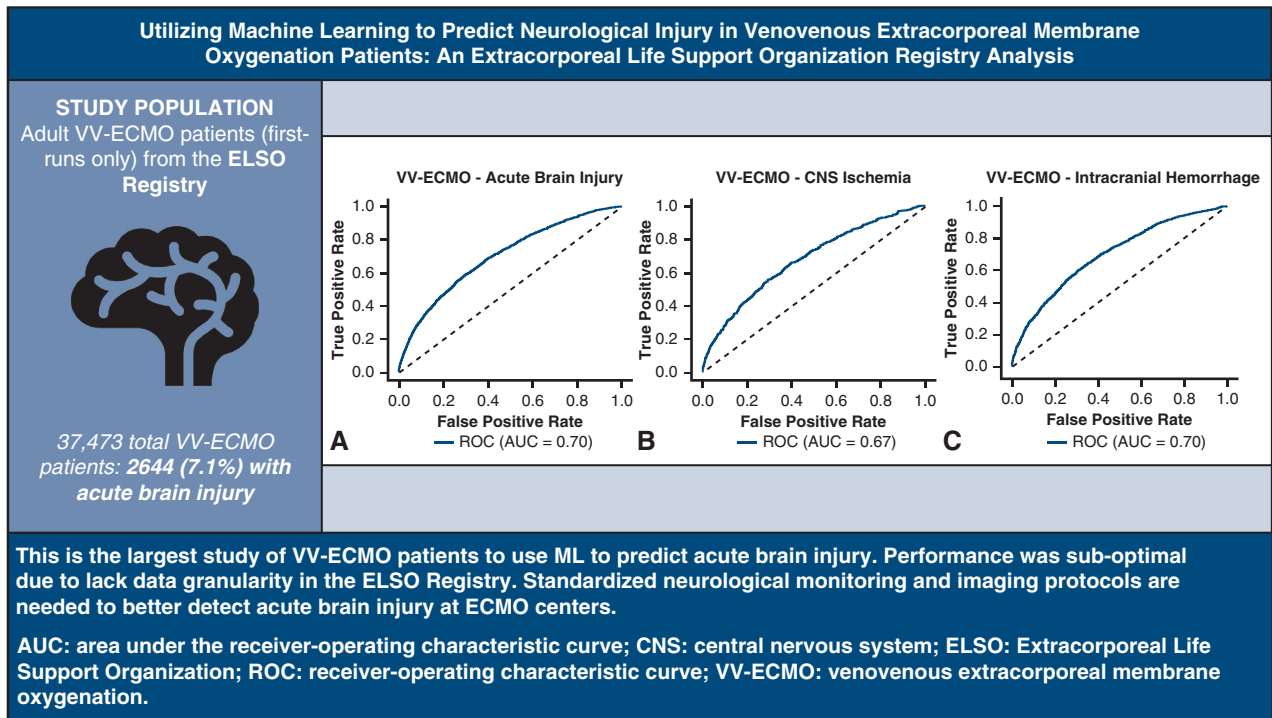
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JTCVS OPEN

Utilizing Machine Learning to Predict Neurological Injury in Venovenous Extracorporeal Membrane Oxygenation Patients: An Extracorporeal Life Support Organization Registry Analysis

STUDY POPULATION
Adult VV-ECMO patients (first-runs only) from the **ELSO Registry**

37,473 total VV-ECMO patients: 2644 (7.1%) with acute brain injury

VV-ECMO - Acute Brain Injury
— ROC (AUC = 0.70)

VV-ECMO - CNS Ischemia
— ROC (AUC = 0.67)

VV-ECMO - Intracranial Hemorrhage
— ROC (AUC = 0.70)

This is the largest study of VV-ECMO patients to use ML to predict acute brain injury. Performance was sub-optimal due to lack data granularity in the ELSO Registry. Standardized neurological monitoring and imaging protocols are needed to better detect acute brain injury at ECMO centers.

AUC: area under the receiver-operating characteristic curve; CNS: central nervous system; ELSO: Extracorporeal Life Support Organization; ROC: receiver-operating characteristic curve; VV-ECMO: venovenous extracorporeal membrane oxygenation.

FIGURE 5. Summary of our study's findings demonstrating the performance of machine learning to predict acute brain injury and its subtypes in patients receiving venovenous extracorporeal membrane oxygenation. Overall, the performance of the models was sub-optimal (area under the receiver-operating characteristic curve of 0.70, 0.67, and 0.70 for acute brain injury, central nervous system ischemia, and intracranial hemorrhage, respectively). Standardized neurological monitoring and imaging protocols are recommended to accurately diagnose acute brain injury across all Extracorporeal Life Support Organization centers.

demonstrated a better AUC-ROC (0.76)[31] versus our AUC-ROC with the ELSO Registry (0.70 in VV-ECMO patients).

Our model's performance in predicting ABI also was inferior to that of studies using ML to predict survival in single-center studies (AUC = 0.92,[14] 0.82,[32] and 0.85[33]) and the ELSO Registry (0.80),[7] likely because mortality is a less complex outcome to discern with ML. Notably, in the training set, the SAVE score developed using the ELSO Registry achieved an AUC of 0.65, which is much closer to our model's performance and may reflect the lack of granularity and great heterogeneity in data collection within the ELSO Registry, as external validation of the SAVE score in 161 patients from a single continent exhibited great accuracy (AUC = 0.90).[34] Similarly, the RESPscore for VV-ECMO patients demonstrated similar performance (AUC = 0.74 in the ELSO Registry and 0.92 in an independent test set of 140 patients).[18] Both studies suggest that our current ML models may perform better in smaller independent test sets and thus warrant external validation with the exact same variables used in the ELSO Registry.

If ABI were reliably predicted soon after VV-ECMO initiation, given the modifiable risk factors associated with pre-ECMO cardiac arrest, actionable steps for ECMO clinicians could include modifying vasopressor/inotrope[35,36] and left ventricle venting use,[37,38] enhancing pulsatile ECMO flow[39] to improve hemodynamic stability and decrease pulmonary blood flow, giving bicarbonate to reverse metabolic acidosis, giving supplemental oxygen (as hypoxemia is frequently documented in ECMO patients),[36,40,41] increasing ventilation rate or tidal volume to decrease $PaCO_2$, and fine-tuning ECMO settings such as ECMO pump flow rates. Overall, given the low detection rate of ABI across ELSO centers, standardized neuromonitoring is imminently needed to accurately detect this devastating and important outcome.

Limitations

Our study has several limitationst starting with its retrospective and observational nature, precluding assessment of causative effects. Second, the prevalence of ABI was low in the ELSO Registry, likely due to a lack of

standardized noninvasive neurologic monitoring protocols across all ECMO centers. Third, owing to high heterogeneity in the data, we limited our analysis to the variables that were most essential overall using feature importance scores. Nevertheless, we were able to identify novel and highly important features for ABI that prior regression modeling was unable to perceive in the ELSO Registry, and we determined the direction of these features by examining the prevalence of ABI in the raw data. Fourth, because pre-ECMO and on-ECMO hemodynamics and ABGs were collected only at a single time point, we were unable to assess multiple time points for these important laboratory values in our ML models. However, whether these laboratory values would change substantially throughout the ECMO run or in the hours prior to cannulation is unclear. Nevertheless, real-time continuous data entered into these ML models may serve as a more dynamic risk factor during events in the first 24, 48, and 72 hours and thus potentially could better predict outcomes. Fifth, anticoagulation is a known risk factor for ICH in VV-ECMO patients, but we could not capture this feature in the ELSO Registry. Sixth, other neurologic outcomes, such as Cerebral Performance Category score or other markers of neurocognitive dysfunction and delirium, were not captured by the ELSO Registry. Seventh, given the high statistical power of the ELSO Registry, the statistically significant associations between certain variables (eg, pre-ECMO PaO_2 was 63 mm Hg for VV-ECMO patients with ABI vs 65 mm Hg for VV-ECMO patients without ABI; $P < .001$) might not be clinically significant and require further investigation. Finally, we did not externally validate our findings with an independent dataset, which is warranted in the future with granular data.

CONCLUSIONS

This is the first study using ML to predict ABI in a large cohort of VV-ECMO patients. However, its performance was suboptimal, likely due to lack of data granularity in the ELSO Registry. We identified cardiac arrest at 6 hours before ECMO cannulation as the most important risk factor for ABI, while longer duration of ECMO support and ECMO as a bridge to transplantation as an indication for ECMO were associated with lower risk of ABI in VV-ECMO patients. Given the underestimated prevalence of ABI in the ELSO Registry, standardized neuromonitoring is important across ECMO centers to accurately detect this important neurological outcome.

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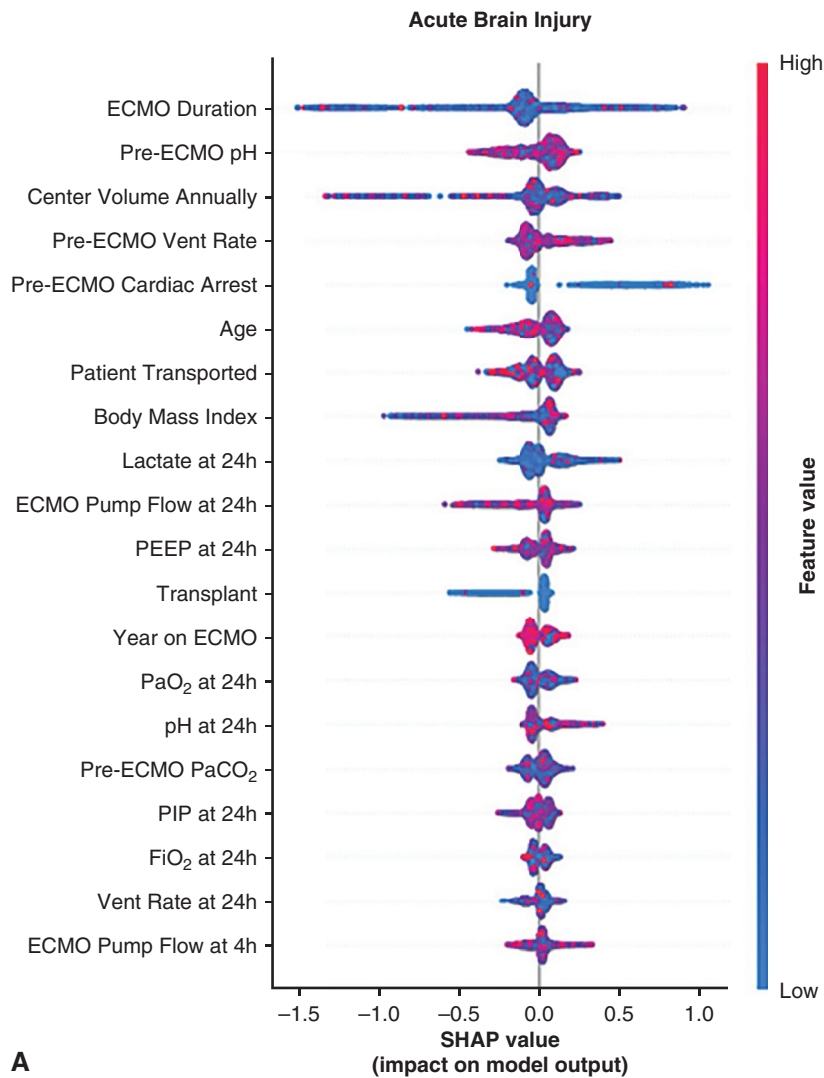
FIGURE E1. Shapley additive explanations (*SHAP*) value plots for acute brain injury (A), central nervous system ischemia (B), and intracranial hemorrhage in venovenous extracorporeal membrane oxygenation patients (C). *ECMO*, Extracorporeal membrane oxygenation; *PEEP*, positive-end expiratory pressure; *PaO₂*, partial pressure of oxygen; *PIP*, peak inspiratory pressure; *FiO₂*, fraction of inspired oxygen; *AP*, Arterial pressure; *SaO2*, arterial blood gas oxygen saturation; *DBP*, diastolic blood pressure; *Vent*, ventilator.
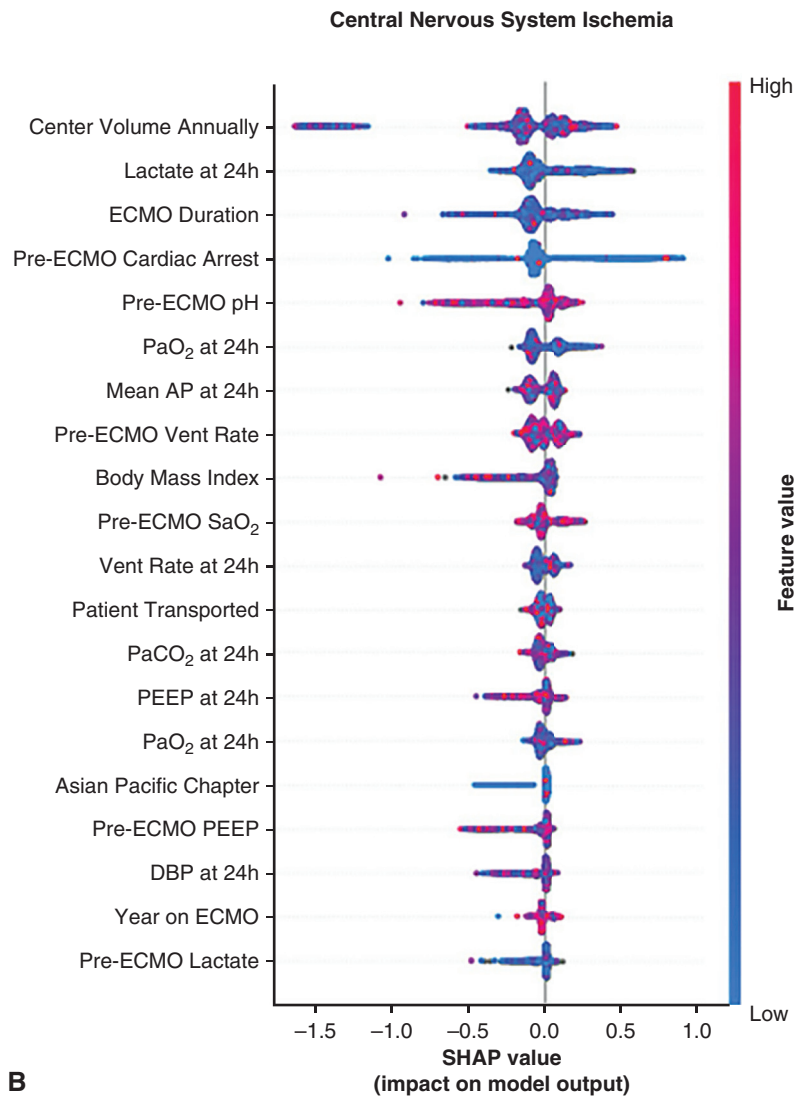
Central Nervous System Ischemia

B

FIGURE E1. (*Continued*).
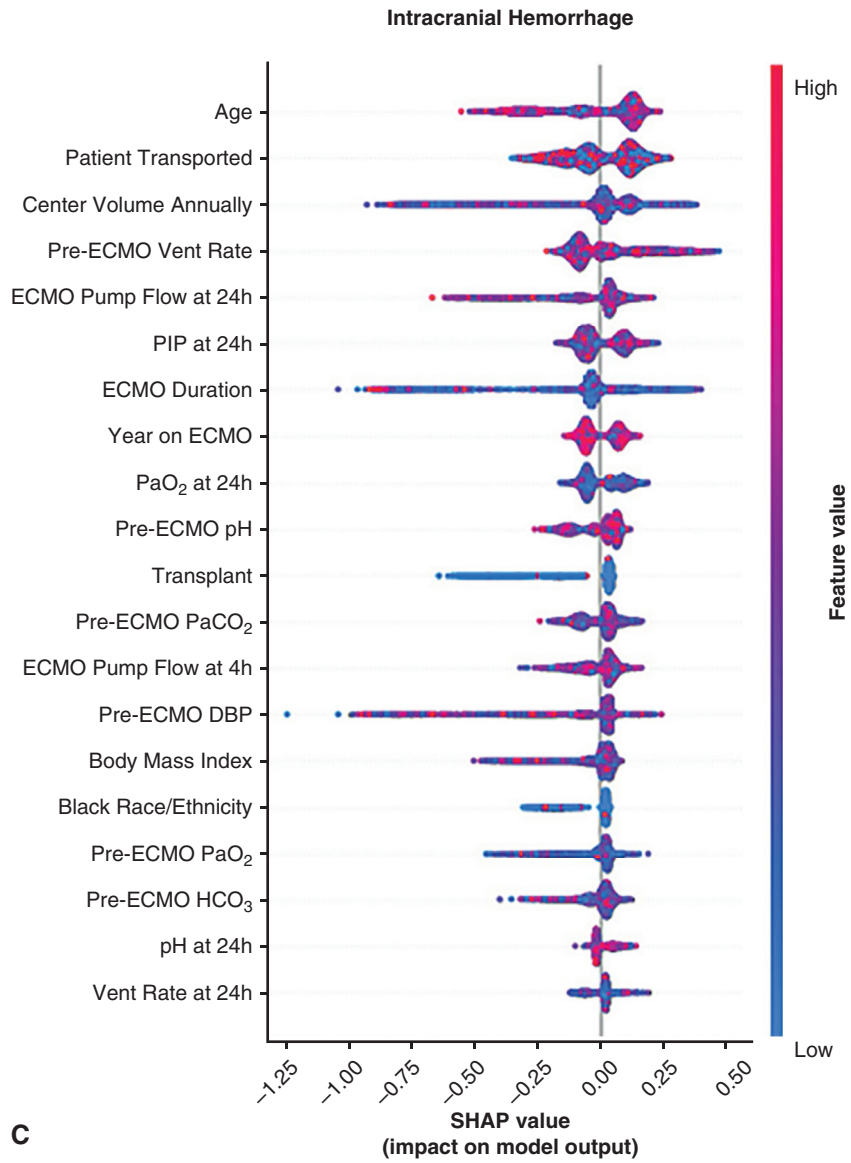
Intracranial Hemorrhage

FIGURE E1. (*Continued*).
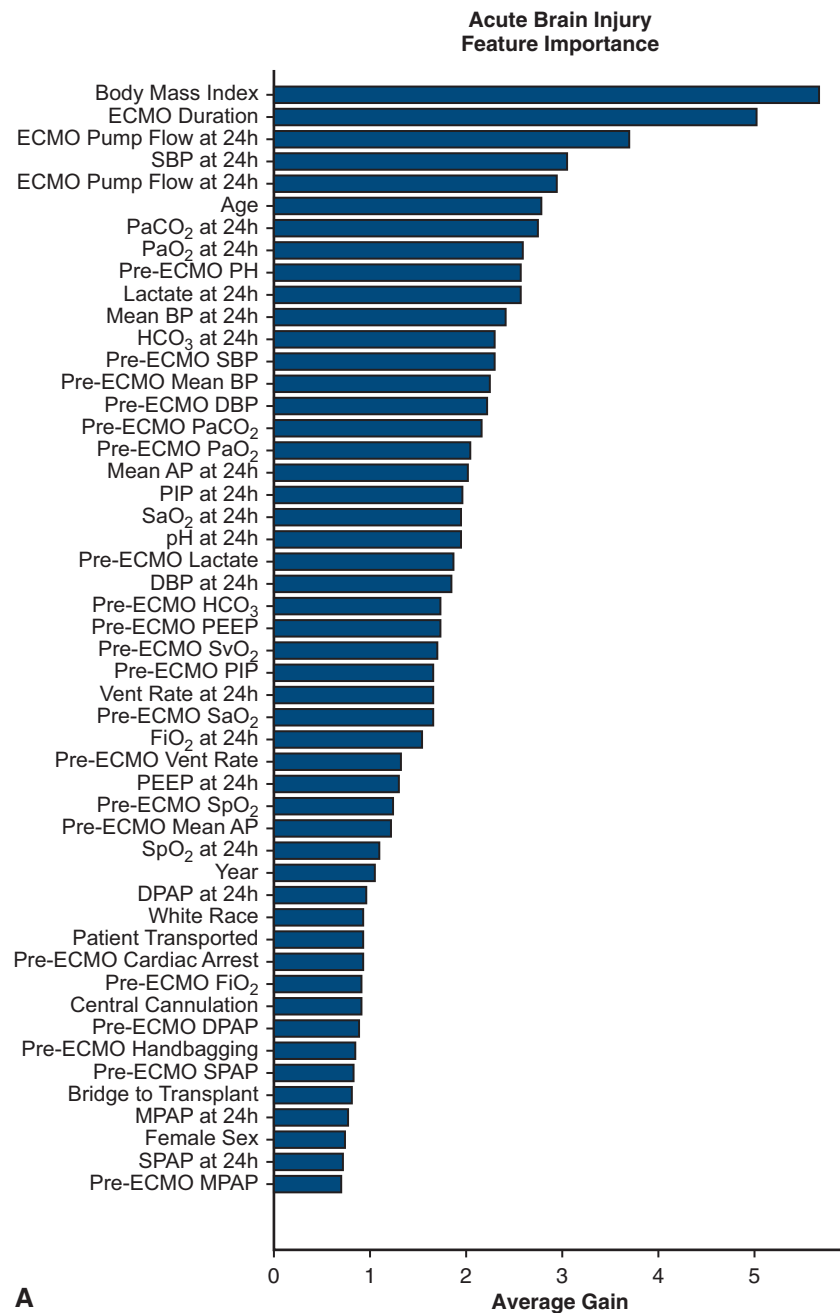
FIGURE E2. The most important features of each neurologic outcome. A, Acute brain injury. B, Central nervous system ischemia. C, Intracranial hemorrhage in conversion patients. *ECMO*, Extracorporeal membrane oxygenation; *PaCO₂*, partial pressure of carbon dioxide; *PaO₂*, partial pressure of oxygen; *BP*, blood pressure; *AP*, Arterial pressure; *PIP*, peak inspiratory pressure; *SaO₂*, arterial blood gas oxygen saturation; *PEEP*, positive-end expiratory pressure; *SvO₂*, mixed venous oxygen saturation; *Vent*, ventilator; *DPAP*, diastolic pulmonary arterial pressure; *FiO₂*, fraction of inspired oxygen; *SpO₂*, peripheral oxygen saturation; *SPAP*, systolic pulmonary arterial pressure; *MPAP*, mean pulmonary arterial pressure.

**Central Nervous System Ischemia
Feature Importance**

FIGURE E2. (*Continued*).

**Intracranial Hemorrhage
Feature Importance**

C
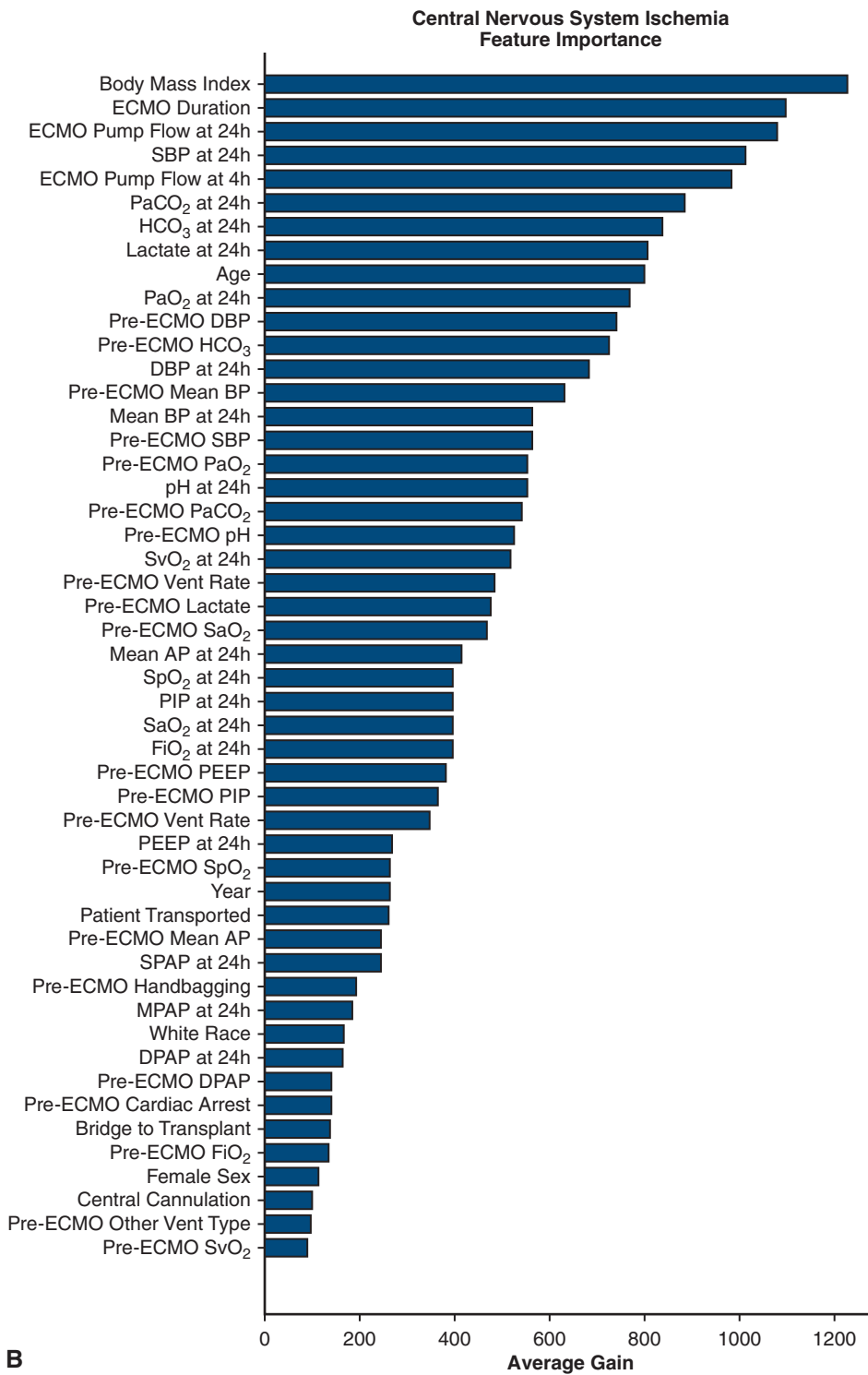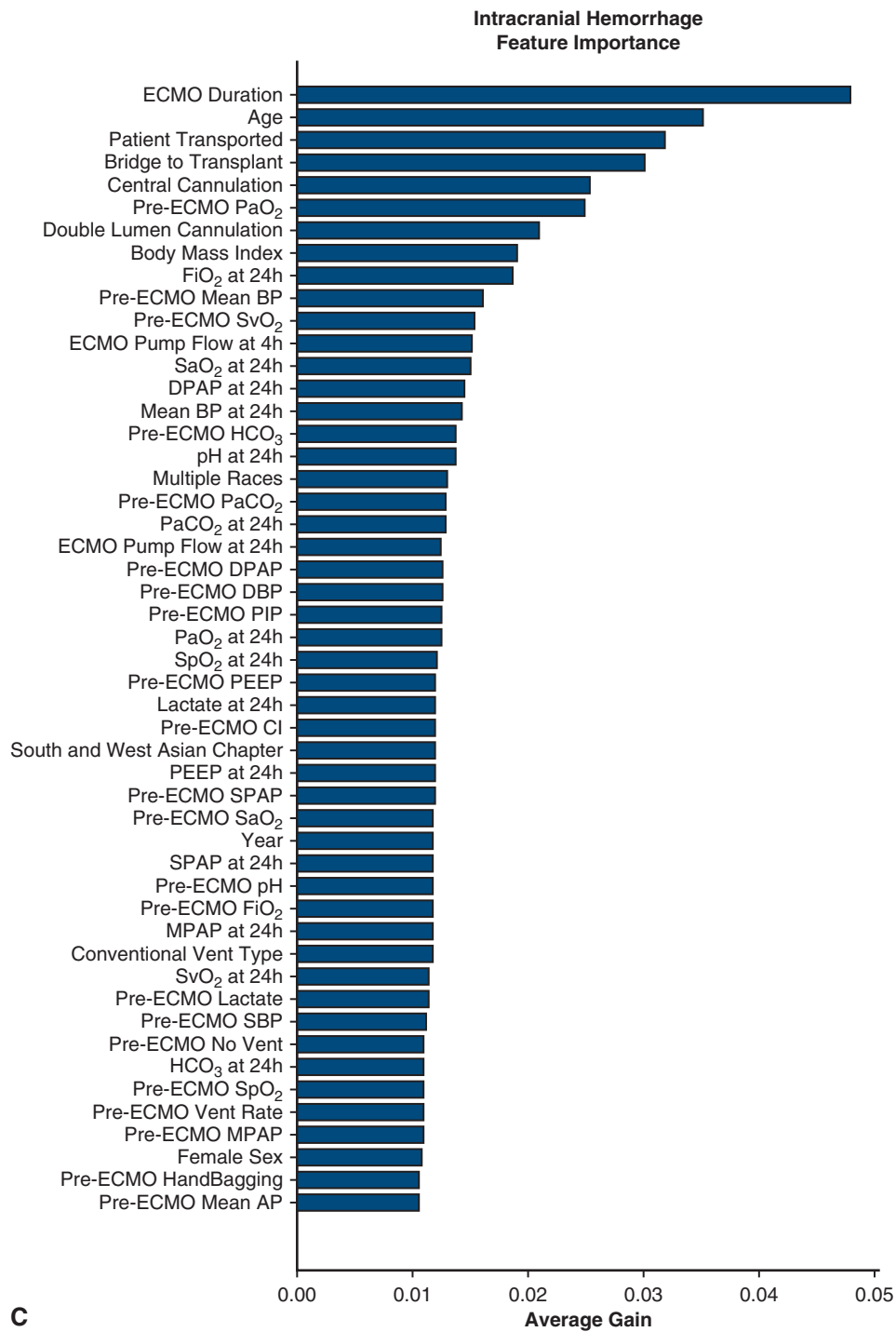
FIGURE E2. (*Continued*).
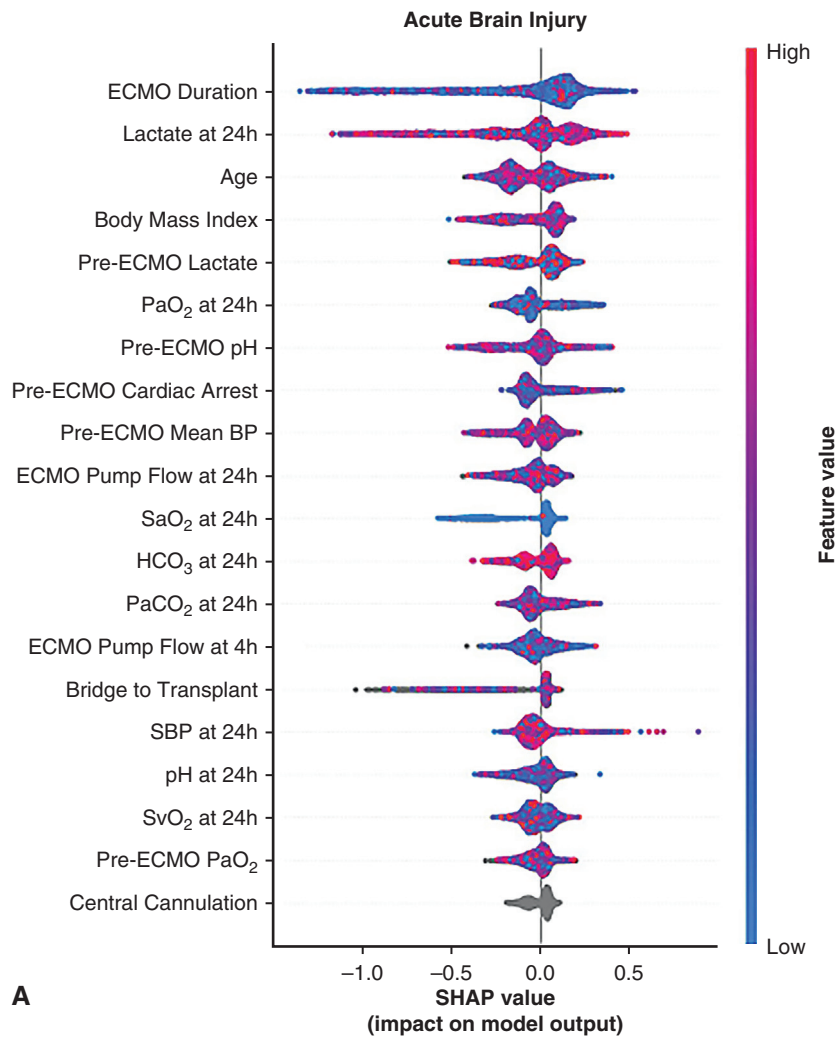
FIGURE E3. Shapley additive explanations (*SHAP*) value plots for acute brain injury (A), central nervous system ischemia (B), and intracranial hemorrhage (C) in conversion patients. *ECMO*, Extracorporeal membrane oxygenation; *PaO₂*, partial pressure of oxygen; *BP*, blood pressure; *SaO₂*, arterial blood gas oxygen saturation; *PaCO₂*, partial pressure of carbon dioxide; *SvO₂*, mixed venous oxygen saturation; *Vent*, ventilator; *DPAP*, diastolic pulmonary arterial pressure; *FiO₂*, fraction of inspired oxygen; *MPAP*, mean pulmonary arterial pressure.

FIGURE E3. (*Continued*).

Intracranial Hemorrhage

FIGURE E3. (*Continued*).

TABLE E1. Variables with missingness in the ELSO Registry for all adult ECMO patients between 2009 and 2021

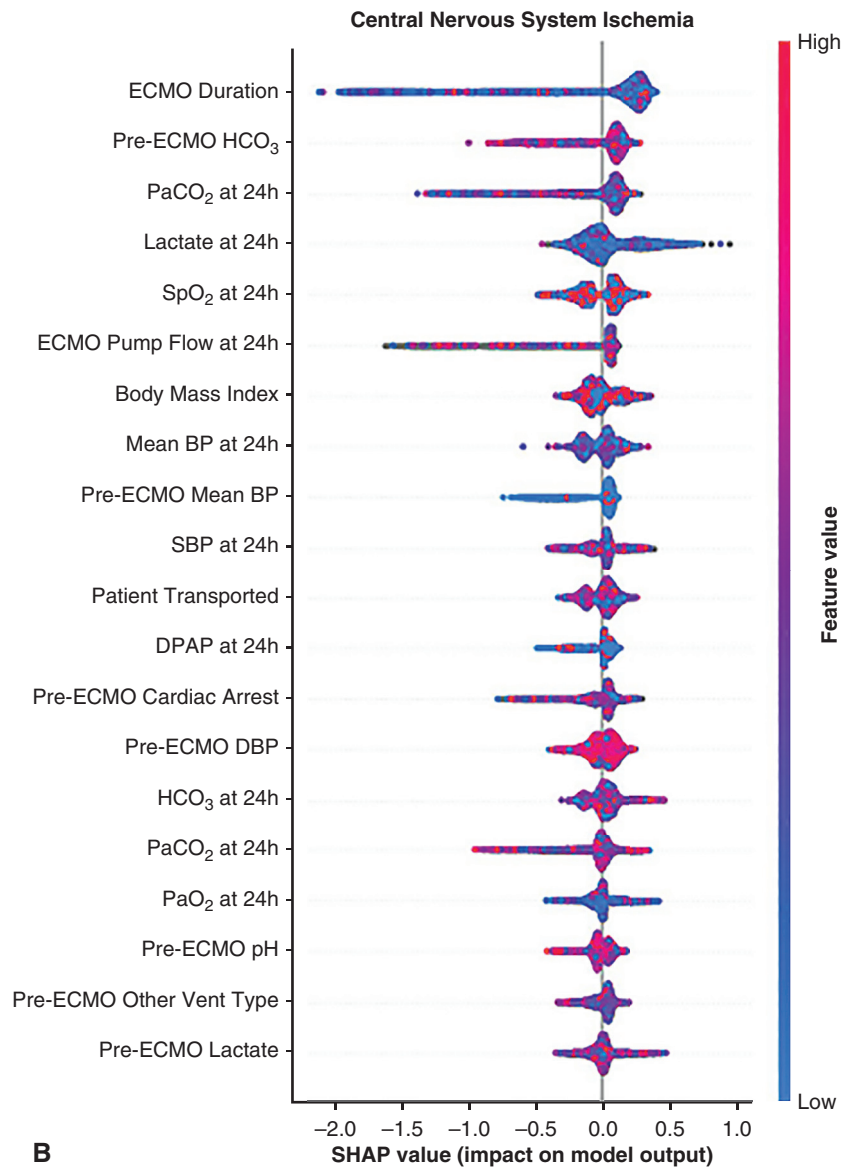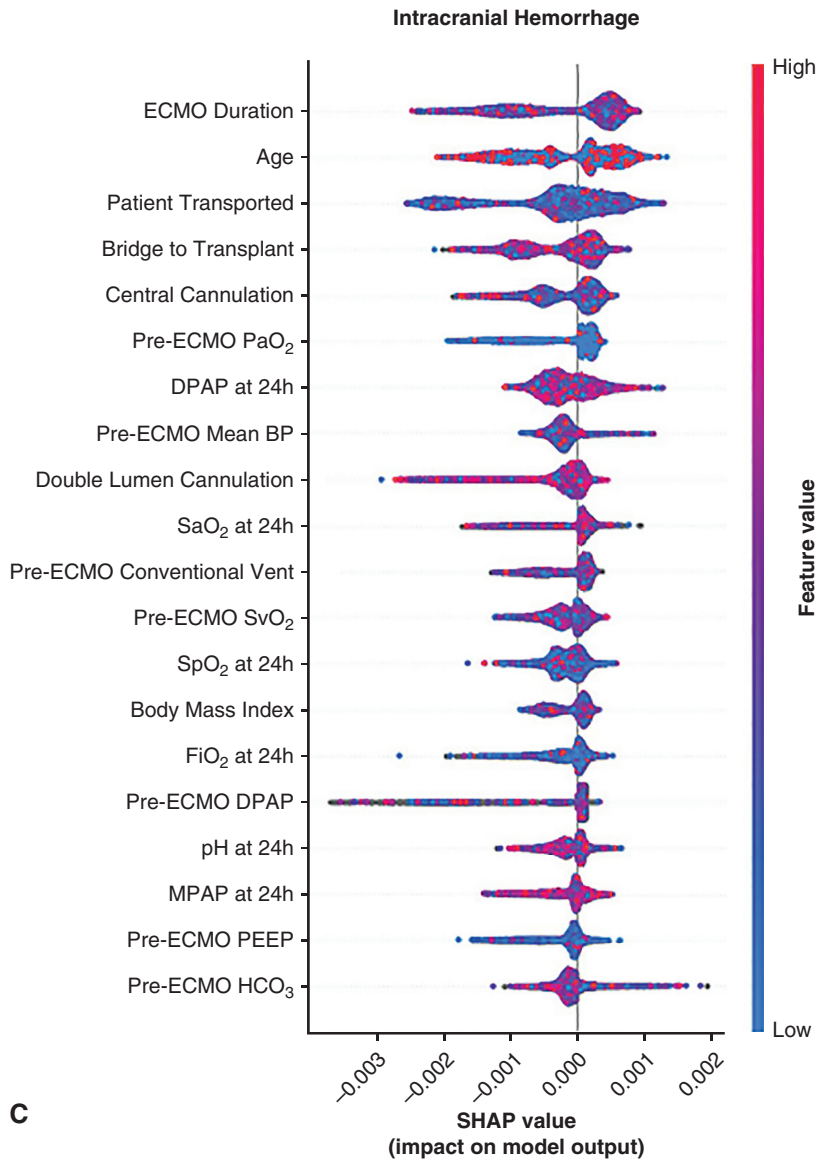| Variable	Missing	X, %
Pulmonary capillary wedge pressure at 24 h	87,017	99
Pre-ECMO pulmonary capillary wedge pressure	86,774	98
Pre-ECMO cardiac index	82,670	94
Cardiac index at 24 h	81,750	93
Pre-ECMO mean pulmonary arterial pressure	80,178	91
Pre-ECMO mixed venous oxygen saturation	79,730	90
Pre-ECMO diastolic pulmonary arterial pressure	78,978	90
Pre-ECMO systolic pulmonary arterial pressure	78,845	89
Mixed venous oxygen saturation at 24 h	76,111	86
Diastolic pulmonary arterial pressure at 24 h	75,479	86
Systolic pulmonary arterial pressure at 24 h	75,388	86
Mixed venous oxygen saturation at 24 h	66,204	75
Pre-ECMO peripheral oxyhemoglobin saturation	65,314	74
Peripheral oxyhemoglobin saturation at 24 h	60,599	69
Pre-ECMO mean airway pressure	56,242	64
Pre-ECMO lactate	53,670	61
Lactate at 24 h	48,005	54
Time to extubation	47,511	54
Pre-ECMO peak inspiratory pressure	45,232	51
Mean airway pressure at 24 h	43,657	50
Pre-ECMO positive end-expiratory pressure	34,613	39
Pre-ECMO mean blood pressure	34,500	39
Pre-ECMO ventilation rate	34,263	39
Peak inspiratory pressure at 24 h	32,346	37
Pre-ECMO arterial oxyhemoglobin saturation	32,126	36
Patient being transported to ELSO center	31,678	36
Pre-ECMO percentage of inspired oxygen	28,816	33
Height	26,604	30
Pre-ECMO diastolic blood pressure	26,570	30
Pre-ECMO systolic blood pressure	26,270	30
Arterial oxyhemoglobin saturation at 24 h	24,642	28
Mean blood pressure at 24 h	24,149	27
Pre-ECMO serum bicarbonate	23,588	27
Pre-ECMO partial pressure of oxygen	22,914	26
Pre-ECMO partial pressure of çarbon dioxide	22,713	26
Ventilation rate at 24 h	22,255	25
Positive end-expiratory pressure at 24 h	21,837	25
Diastolic blood pressure at 24 h	20,687	23
Pre-ECMO pH	20,641	23
Systolic blood pressure at 24 h	20,582	23
Percentage of inspired oxygen at 24 h	20,430	23
Partial pressure of oxygen at 24 h	17,543	20
Partial pressure of çarbon dioxide at 24 h	17,432	20
Serum bicarbonate at 24 h	16,402	19

(Continued)

TABLE E1. Continued

Variable	Missing	X, %
ECMO pump flow rate at 24 h	15,935	18
pH at 24 h	15,283	17
Time to intubation	14,839	17
ECMO pump flow rate at 4 h	11,937	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 ICD-9	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 24 h	0	0
Handbagging at 24 h	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

ELSO, Extracorporeal Life Support Organization; *ECMO*, extracorporeal membrane oxygenation; *ICD*, International Classification of Diseases.

TABLE E2. Baseline characteristics and clinical variables of conversion ECMO patients stratified by presence of ABI

Characteristic	Total conversions (N = 4012)	ABI (N = 466; 11%)	No ABI (N = 3546; 89%)	P value
Demographics				
Age, y, median (IQR)	53 (39.2-62.4)	50.4 (37-59.9)	53.3 (39.7-62.8)	**.001**
Male sex, n (%)	2619 (65)	290 (62)	2329 (66)	.14
Body mass index, kg/m^2, median (IQR)	29.3 (25.1-34.7)	29.9 (26.2-35)	29.3 (25-34.7)	.09
Race/ethnicity, n (%)				.93
Asian	358 (9)	42 (9)	316 (9)	
Black	459 (11)	55 (12)	404 (11)	
Hispanic	347 (9)	37 (8)	310 (9)	
White	2294 (57)	272 (58)	2022 (57)	
Others				
Year of ECLS, n (%)				.21
2009	42 (1)	5 (1)	37 (1)	
2010	40 (1)	8 (2)	32 (1)	
2011	40 (1)	6 (1)	34 (1)	
2012	49 (1)	11 (2)	38 (1)	
2013	67 (2)	6 (1)	61 (2)	
2014	112 (3)	13 (3)	99 (3)	
2015	131 (3)	10 (2)	121 (3)	
2016	132 (3)	14 (3)	118 (3)	
2017	320 (8)	41 (9)	279 (8)	
2018	571 (14)	61 (13)	510 (14)	
2019	875 (22)	99 (21)	776 (22)	
2020	753 (19)	77 (17)	676 (19)	
2021	880 (22)	115 (25)	765 (22)	
Past medical history, n (%)				
Diabetes	341 (8)	40 (9)	301 (8)	.95
Hypertension	472 (12)	50 (11)	422 (12)	.51
Atrial fibrillation	372 (9)	33 (7)	339 (10)	.12
Cardiomyopathy	254 (6)	24 (5)	230 (6)	.32
Chronic obstructive pulmonary disease	154 (4)	15 (3)	139 (4)	.51
Pre-ECMO support, n (%)				
Additional temporary mechanical circulatory support	744 (19)	75 (16)	669 (19)	.15
Vasopressor infusions	2474 (62)	279 (60)	2195 (62)	.4
Inotrope infusions	868 (22)	77 (17)	791 (22)	.004
Pre-ECMO blood pressure variables, median (IQR)				
Systolic blood pressure, mm Hg	96 (80-115)	96 (77.5-115)	96 (80-115)	.58
Diastolic blood pressure, mm Hg	57 (47-67)	57 (46-66)	57 (47-67)	.73
Mean blood pressure, mm Hg	69 (58-81)	68 (57-81)	70 (58.3-81)	.32
Pulse pressure, mm Hg	39 (26-54)	39 (25-53)	39 (27-54)	.93
Mean arterial pressure, mm Hg	18 (14-24)	18 (12.5-24)	18 (14-24)	.79
Pre-ECMO ABG values, median (IQR)				
pH	7.26 (7.15-7.35)	7.24 (7.11-7.33)	7.26 (7.16-7.35)	**.004**
HCO$_3$-,mEq/L	22 (18-26.1)	22 (17.2-26.4)	22 (18.1-26.1)	.14
PaO$_2$, mm Hg	71 (54-115)	66 (51-109.5)	72 (54-116)	**.01**
PaCO$_2$, mm Hg	50.8 (40-65)	52 (40.9-66)	50.3 (40-65)	.22
Lactate, mmol/L	2 (4.4-8.3)	2.2 (5.15-9.7)	1.9 (4.3-8.2)	.05
SpO$_2$, %	92 (84-98)	90 (83-96.5)	92 (84-98)	.21
SaO$_2$, %	91 (82-100)	89 (78-97)	91 (82-100)	.017
On-ECMO blood pressure variables, median (IQR)				
Systolic blood pressure, mm Hg	100 (87-116)	99 (85-116)	100 (87-116)	.29
Diastolic blood pressure, mm Hg	63 (56-71)	64 (56-70)	63 (56-71)	.91
Mean blood pressure, mm Hg	74 (68-82)	75 (68-81)	74 (68-83)	.41
Pulse pressure, mm Hg	38 (22-53)	36 (19-51)	38 (23-53)	.18

(Continued)

TABLE E2. Continued

Characteristic	Total conversions (N = 4012)	ABI (N = 466; 11%)	No ABI (N = 3546; 89%)	P value
Mean arterial pressure, mm Hg	14 (12-17)	14 (11-17.3)	14 (12-17)	.66
On-ECMO ABG values, median (IQR)				
pH	7.41 (7.36-7.45)	7.4 (7.36-7.45)	7.41 (7.37-7.46)	**.03**
HCO$_3$-, mEq/L	25 (22-28.2)	24.9 (21.9-28.4)	25 (22-28.2)	.47
PaO$_2$, mm Hg	104 (71-193)	105 (68.9-239)	104 (71-191)	.84
PaCO$_2$, mm Hg	39.8 (35-45)	40 (35-46)	39.8 (35-44.9)	.23
Lactate, mmol/L	2.3 (1.4-4.5)	2.8 (1.6-6.1)	2.3 (1.4-4.3)	**<.001**
SpO$_2$, %	98 (94-100)	98 (94-99)	98 (94-100)	.37
SaO$_2$, %	97 (94-99)	97 (93-99)	97 (94-99)	.51
ΔPaCO$_2$, median (IQR)	−10 (−24 to 0)	−10.65 (−24 to 0)	−10 (−24 to 0)	.77
Pump flow rate at 4 h, L/min, median (IQR)	4 (3.4-4.6)	4.1 (3.4-4.7)	4 (3.4-4.6)	.13
Pump flow rate at 24 h, L/min, median (IQR)	4.2 (3.6-4.8)	4.2 (3.5-4.9)	4.2 (3.6-4.8)	.64
Days on ECMO support	11.3 (6-20.8)	12.8 (6.12-24.6)	11.1 (6-20.3)	**.003**
Neurologic complications on-ECMO, n (%)				
Composite ABI, n (%)				
Composite Ischemia	210 (5)	210 (45)	0 (0)	**<.001**
Hypoxic-ischemic brain injury	54 (1)	54 (12)	0 (0)	**<.001**
Ischemic stroke	158 (4)	158 (34)	0 (0)	**<.001**
Composite ICH	204 (5)	204 (44)	0 (0)	**<.001**
Intra/extraparenchymal hemorrhage	100 (2)	100 (21)	0 (0)	**<.001**
Intraventricular hemorrhage	43 (1)	43 (9)	0 (0)	**<.001**
Brain death	71 (2)	71 (15)	0 (0)	**<.001**
Neurosurgical intervention	5 (1)	5 (1)	0 (0)	**<.001**
Seizures confirmed by EEG	19 (1)	19 (4)	0 (0)	**<.001**
Seizures clinically determined	37 (1)	37 (8)	0 (0)	**<.001**
Other complications on-ECMO, n (%)				
ECMO circuit mechanical failure	1271 (32)	187 (40)	1084 (31)	**<.001**
Renal replacement therapy	1771 (44)	236 (51)	1535 (43)	**.002**
Hemolysis	400 (10)	78 (17)	322 (9)	**<.001**
Cardiac arrhythmia	785 (20)	107 (23)	678 (19)	**.049**
Gastrointestinal hemorrhage	332 (8)	52 (11)	280 (8)	**.02**
Outcomes, n (%)				
In-hospital mortality	2328 (58)	364 (78)	1964 (55)	**<.001**

Conversions: ECMO modality changed from VA-ECMO to VV-ECMO or from VV-ECMO to VA-ECMO. Bold type indicates significance. *VV-ECMO*, Venovenous extracorporeal membrane oxygenation; *ABI*, acute brain injury; *IQR*, interquartile range; *ECLS*, extracorporeal life support; *ABG*, arterial blood gas; *ICH*, intracranial hemorrhage; *EEG*, electroencephalography; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation.

TABLE E3. Model performance in conversion patients for predicting ABI, CNS ischemia, and ICH

Complication	AUC-ROC	Acc, %	TPR, %	TNR, %	FPR, %	FNR, %	PPV, %	NPV, %	Precision	Recall	F1	Brier score
ABI	0.58	58	55	59	41	45	15	91	0.15	0.55	0.23	0.15
CNS ischemia	0.57	75	35	77	23	65	8	96	0.8	0.35	0.13	0.08
ICH	0.63	80	36	82	18	64	10	96	0.099	0.37	0.16	0.22

ABI, Acute brain injury; *CNS*, central nervous system; *ICH*, intracranial hemorrhage; *AUC-ROC*, area under the receiver-operating characteristic curve; *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.