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Original Article

Risk factors for bleeding and thrombotic complications during extracorporeal membrane oxygenation support in adults based on the MIMIC-IV database

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Abstract: Objective: To identify risk factors for bleeding and thrombotic complications during extracorporeal membrane oxygenation (ECMO) support in adults and to develop a predictive model based on these factors. Method: Data from 323 adult patients treated with ECMO in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database were retrospectively analyzed. Demographic information, clinical characteristics, and laboratory test results were collected. Kaplan-Meier (K-M) and Cox regression analyses were used to identify risk factors for bleeding and thrombotic complications and construct a predictive model. Results: Bleeding and thrombotic complications was noted in 84 (26.0%) patients, with a median onset time of 13 days after ECMO. Univariate analysis identified age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, ECMO indication, ECMO withdrawal, extracorporeal cardiopulmonary resuscitation (ECPR), and coagulation function as potential risk factors (all $P < 0.05$). Multivariate analysis revealed that ECMO withdrawal and platelet count (PLT) were independent protective factors, while D-dimer was an independent risk factor ($P < 0.05$). A predictive model was developed based on ECMO withdrawal, D-dimer, and PLT, with areas under the curves (AUCs) of 0.932, 0.931, and 0.941 for predicting bleeding complications at 6, 9, and 12 days after ECMO treatment, respectively. Conclusion: The incidence of ECMO-related bleeding and thrombotic complications is high. ECMO withdrawal, PLT, and D-dimer are independent influencing factors. This predictive model can assist in early identification of high-risk patients and guide clinical decision-making.

Keywords: ECMO, bleeding and thrombotic complications, risk factors, predictive model, MIMIC-IV database

Introduction

Extracorporeal membrane oxygenation (ECMO) is an important life support technique commonly used for treating severe cardiopulmonary failure. However, ECMO therapy is frequently associated with bleeding and thrombotic complications, which significantly affect patient prognosis [1]. Previous studies have reported that the incidence of bleeding in ECMO-treated patients ranges from 29% to 33%, with the incidence of intracranial hemorrhage ranging from 2% to 21%, and major hemorrhage from 5% to 22% [2, 3]. These complications not only increase mortality rates but also prolong ICU stays and overall hospitalization, thereby raising healthcare costs [4]. Therefore, identifying risk factors for bleeding and thrombotic complications during ECMO therapy is crucial for early identification of high-risk patients and the implementation of targeted preventive measures.

Two studies have explored several bleeding-related risk factors, including age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, ECMO indication, ECMO withdrawal, extracorporeal cardiopulmonary resuscitation (ECPR), and coagulation function [5, 6]. However, the conclusions of these studies have varied, and the sample sizes have limited the robustness of the evidence [7-9]. Therefore, high-quality studies with large sample sizes were urgently needed to more precisely define the risk factors for bleeding and thrombotic complications in patients on ECMO.

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The Medical Information Mart for Intensive Care IV (MIMIC-IV) is a large, multicenter, high-quality database containing abundant data on demographic and clinical characteristics, laboratory test results, treatments, and prognostic factors. It provides valuable data support for ECMO-related studies. Using the MIMIC-IV database, this study retrospectively analyzed the data of 323 adult patients treated by ECMO to identify risk factors for bleeding and thrombotic complications during ECMO support and develop a predictive model. The goal was to provide a reference for clinical decision-making, ultimately enhancing the safety and efficacy of ECMO treatment.

Methods

MIMIC-IV data collection

Data from the MIMIC-IV database, developed by the Massachusetts Institute of Technology, were retrospectively analyzed. The MIMIC-IV database is a large, publicly accessible critical care database containing deidentified health data from approximately 250,000 ICU patients between 2008 and 2019. Using Structured Query Language (SQL), we screened 323 adult patients who were treated with ECMO and whose critical data were contained in the database. Inclusion criteria: 1) aged ≥ 18 years; 2) received ECMO treatment; and 3) had complete data records, including demographic characteristics, ECMO indications, ECMO withdrawal, ECPR status, and coagulation-related laboratory test markers. Exclusion criteria: 1) aged < 18 years; 2) no ECMO treatment; and 3) incomplete data record. A total of 323 patients were ultimately selected, of whom 84 experienced bleeding complications during ECMO therapy and 239 did not. The collected information included age, sex, APACHE II score, indications for ECMO (pulmonary, cardiac), ECMO withdrawal status, ECPR status, and laboratory tests such as fibrinogen (FIB), prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer testing, and platelet count (PLT).

This study was approved by the Institutional Review Board and Ethics Committee of our Changde City, Hunan Province People's Hospital, China (Ethics No. YX-2023-188-01). Since the study used de-identified patient data, which presented no potential harm or impact on the patients, the requirement for informed consent was waived. This waiver was granted by the Institutional Review Board and Ethics Committee in compliance with the regulatory and ethical standards for retrospective studies.

MIMIC-IV data extraction and cleaning

Relevant data were extracted from the MIMIC-IV database and then cleaned and organized. First, adult patients receiving ECMO treatment were screened using SQL. Data on their demographic and clinical characteristics and laboratory test results were extracted. Continuous variables were recorded as numeric values, while categorical variables were classified by category. The extracted data were then reviewed to exclude records with missing or outlier values, ensuring data integrity and accuracy.

Collection of indicators

The following relevant indicators were extracted from the MIMIC-IV database for patients receiving ECMO: (1) Demographic characteristics: age and sex; (2) Clinical characteristics: APACHE II score, indication for ECMO (pulmonary, cardiac), ECMO withdrawal status, ECPR status; (3) Laboratory findings: FIB, PT, aPTT, D-dimer, and PLT.

Statistical analysis

Data were analyzed using SPSS 29.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical data were presented as [n (%)], and differences between groups were assessed using Chi-square tests, denoted as χ^2. Continuous variables were first tested for normal distribution using the Shapiro-Wilk method. Continuous variables following a normal distribution were presented as ($\bar{x} \pm s$) and were analyzed using the t-test. Non-normally distributed data were presented as [median (25% quantile, 75% quantile)] and analyzed using the Wilcoxon rank-sum test. A P value < 0.05 was considered statistically significant.

Construction and validation of a predictive model

Cox regression and machine learning algorithms were used to develop a prognostic pre-

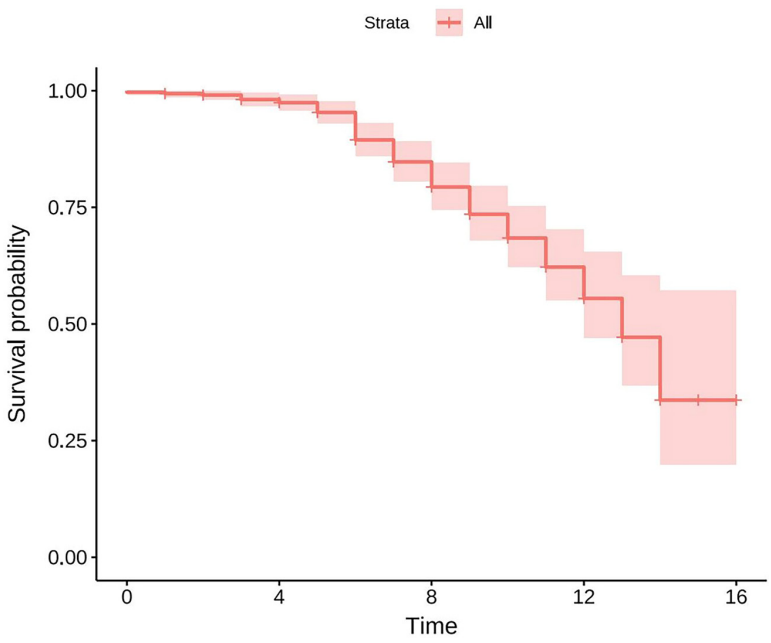

Figure 1. K-M curve of patients treated with ECMO who developed bleeding complications. K-M: Kaplan-Meier; ECMO: Extracorporeal Membrane Oxygenation.

dictive model for patients receiving ECMO. The data were randomly divided into training and validation sets at a ratio of 7:3. Model training was performed on the training set, with feature selection and parameter tuning to identify the optimal model. Tenfold cross-validation and the bootstrapping replication method of sampling were used to assess the discrimination and calibration capabilities of the model. Receiver operating characteristic (ROC) curves were plotted, and the areas under the curve (AUC) were calculated to assess the predictive performance of the model. These calculations were performed using the R software, with a significance level set at 0.05.

Results

MIMIC-IV database screening and univariate analysis

Patient screening was performed using the MIMIC-IV database. A total of 323 patients treated with ECMO, whose critical data were included in the database, were selected. Among them, 84 patients experienced bleeding during ECMO treatment, which included 46 cases of hemorrhage at the ECMO cannula site, 24 cases of gastrointestinal hemorrhage, 10 cases of psoas major muscle hemorrhage, and 4 cases of cerebral hemorrhage. K-M curve analysis demonstrated that the median time to onset of bleeding complications during ECMO treatment was 13 days after commencing ECMO treatment (95% CI: 12 days-NE [Not Estimable]) (**Figure 1**). No bleeding complications were observed in the remaining 239 patients. A comparison of baseline data between the two groups showed significant differences in age (years), sex, smoking status, hypertension, diabetes, hyperlipidemia, APACHE II score, ECMO indications, ECMO withdrawal status, and ECPR status (all $P < 0.05$) (**Tables 1**, **2**). Laboratory results for hematological parameters and coagulation markers showed significant differences in FIB, PT, aPTT, D-dimer, and PLT between the two groups (all $P < 0.05$) (**Tables 3**, **4**).

Univariate analysis of bleeding complications in ECMO patients

Subsequently, univariate Cox regression analysis was performed to examine potential risk factors for bleeding complications and the time of onset. The results, presented in **Table 5** and **Figure 2**, indicated that APACHE II score, ECMO indications, ECMO withdrawal status, ECPR status, FIB, PT, aPTT, D-dimer, and PLT were identified as potential risk factors (all $P < 0.05$).

Multivariate analysis of bleeding complications in ECMO patients

Based on the results of univariate Cox regression analysis, potential risk factors were further assessed using multivariate Cox regression analysis. The results, presented in **Table 6** and **Figure 3**, indicated that ECMO withdrawal and PT were independent protective factors against bleeding complications in patients on ECMO ($P < 0.05$), while D-dimer was an independent risk factor ($P < 0.05$).

Table 1. Comparison of demographic data between patients in the two groups

	All patients	Did not develop bleeding complications	Developed bleeding complications	*P* value
	N = 323	*N = 239*	*N = 84*	
Age	55.8 ± 11.0	54.6 ± 11.8	59.3 ± 7.47	< 0.001
Sex				0.526
Female	113 (35.0%)	86 (36.0%)	27 (32.1%)	
Male	210 (65.0%)	153 (64.0%)	57 (67.9%)	
Current smoker				0.172
No	291 (90.09%)	222 (92.89%)	74 (88.1%)	
Yes	32 (9.91%)	17 (7.11%)	10 (11.9%)	
Hypertension				0.562
No	194 (60.06%)	148 (61.92%)	49 (58.33%)	
Yes	129 (39.94%)	91 (38.08%)	35 (41.67%)	
Diabetes				0.632
No	287 (88.85%)	215 (89.96%)	74 (88.1%)	
Yes	36 (11.15%)	24 (10.04%)	10 (11.9%)	
Hyperlipidemia				0.541
No	246 (76.16%)	187 (78.24%)	63 (75%)	
Yes	77 (23.84%)	52 (21.76%)	21 (25%)	

Table 2. Comparison of baseline disease characteristics between patients in the two groups

	All patients	Did not develop bleeding complications	Developed bleeding complications	*P* value
	N = 323	*N = 239*	*N = 84*	
APACHE II	31.8 ± 7.58	30.5 ± 6.61	35.4 ± 8.93	< 0.001
ECMO indications				< 0.001
Cardiac	171 (52.9%)	110 (46.0%)	61 (72.6%)	
Pulmonary	152 (47.1%)	129 (54.0%)	23 (27.4%)	
ECMO withdrawal				< 0.001
No	104 (32.2%)	64 (26.8%)	40 (47.6%)	
Yes	219 (67.8%)	175 (73.2%)	44 (52.4%)	
ECPR				0.003
No	223 (69.0%)	176 (73.6%)	47 (56.0%)	
Yes	100 (31.0%)	63 (26.4%)	37 (44.0%)	

Note: APACHE II: Acute Physiology and Chronic Health Evaluation II; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardiopulmonary Resuscitation.

Construction and validation of a predictive model of bleeding complications in ECMO patients

Building on the multivariate Cox regression results, a predictive model was developed incorporating ECMO withdrawal, D-dimer, and PLT. A nomogram was plotted based on these variables, as shown in **Figure 4A**. Subsequent ROC curves were plotted based on data obtained at 6, 9, and 12 days after ECMO treatment, yielding AUCs of 0.932, 0.931, and 0.941 for predicting the bleeding complications at these time points, respectively (**Figure 4B**).

Discussion

Based on the MIMIC-IV database, this study analyzed data from 323 patients treated with ECMO, of whom 84 (26.0%) experienced bleeding complications, including hemorrhage at the site of the ECMO cannula, gastrointestinal hemorrhage, psoas major muscle hemorrhage, and cerebral hemorrhage. These results were

Table 3. Comparison of hematological parameters between patients in the two groups

	All patients	Did not develop bleeding complications	Developed bleeding complications	*P* value
	N = 323	*N = 239*	*N = 84*	
Nucleated red blood cells (/μl)	35.57 ± 12.02	34.63 ± 11.85	36.27 ± 12.54	0.282
White blood cell count (/nl)	18.13 ± 5.83	18.83 ± 6.35	17.36 ± 5.28	0.058
Hemoglobin level (mg/dl)	10.46 ± 2.11	10.68 ± 2.28	10.25 ± 1.93	0.118

Table 4. Comparison of coagulation markers between patients in the two groups

	All patients	Did not develop bleeding complications	Developed bleeding complications	*P* value
	N = 323	*N = 239*	*N = 84*	
FIB	4.25 [1.20; 7.31]	4.67 [1.55; 7.31]	3.06 [1.20; 5.97]	< 0.001
PT	16.0 [7.28; 23.8]	15.2 [7.28; 23.8]	16.7 [13.2; 19.4]	< 0.001
aPTT	57.4 ± 14.5	55.1 ± 13.2	64.0 ± 16.2	< 0.001
D-dimers	4.51 [1.27; 14.4]	4.14 [1.27; 6.38]	11.6 [8.86; 14.4]	< 0.001
PLT	187 ± 63.4	196 ± 55.1	162 ± 77.8	< 0.001

Note: FIB: Fibrinogen; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; PLT: Platelet Count.

Table 5. Univariate analysis of bleeding complications in patients treated with ECMO

Variable	Coef	P	Exp.Coef.	Lower95	Upper95
Age	0.03	0.01	0.97	1.01	1.05
Sex	0.24	0.31	0.79	0.80	2.00
APACHE II	0.08	0.00	0.93	1.05	1.11
ECMO indications	-0.84	0.00	2.32	0.27	0.70
ECMO withdrawal	-0.75	0.00	2.12	0.31	0.72
ECPR	0.57	0.01	0.57	1.15	2.72
FIB	-0.73	0.00	2.07	0.40	0.58
PT	0.15	0.00	0.86	1.07	1.27
aPTT	0.04	0.00	0.96	1.02	1.05
D-dimer test	0.51	0.00	0.60	1.51	1.82
PLT	-0.01	0.00	1.01	0.99	1.00

Note: ECMO: Extracorporeal Membrane Oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; ECPR: Extracorporeal Cardiopulmonary Resuscitation; FIB: Fibrinogen; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; PLT: Platelet Count.

generally consistent with the reported incidence of ECMO-associated bleeding complications, which ranges from 29% to 33% in previous studies [10, 11]. K-M curve analysis showed that the median time to onset of bleeding complications was 13 days after ECMO initiation, suggesting that clinicians should closely monitor patients during the second week of ECMO treatment and implement heightened surveillance and preventive measures during this period. Univariate Cox regression analysis identified several significant markers associated with ECMO-related bleeding complications, including APACHE II score, indication for ECMO, ECMO withdrawal, ECPR, FIB, PT, aPTT, D-dimer, and PLT. Furthermore, multivariate Cox regression analysis showed that ECMO withdrawal and PLT were independent protective factors for bleeding complications, whereas D-dimer was an independent risk factor. These results align partially with previous findings. For instance, a meta-analysis including 3,157 patients from 10 studies demonstrated that reduced PLT was significantly associated with an increased risk of ECMO-associated bleeding [12]. Reduced PLT reflects impaired coagula-

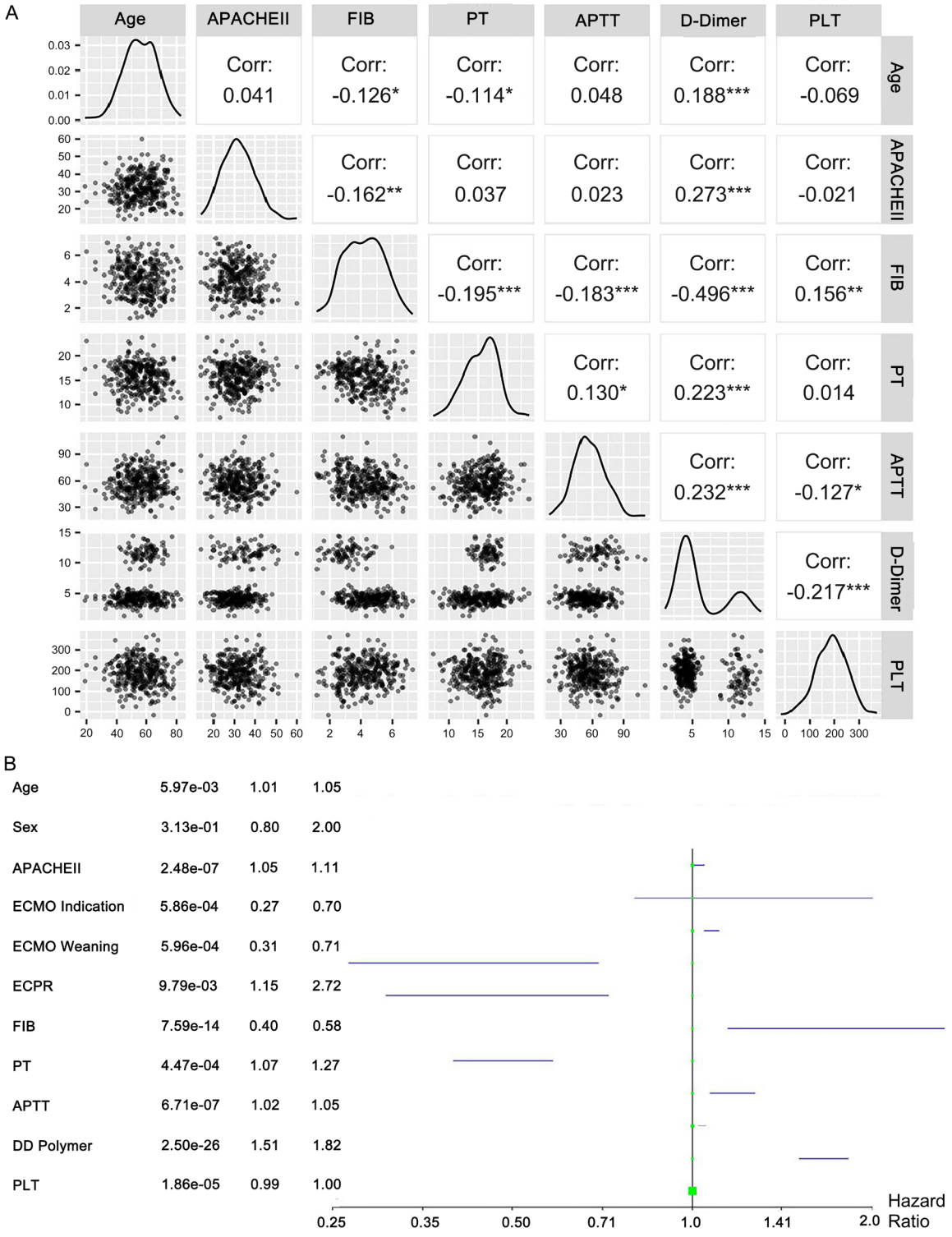

Figure 2. Univariate analysis of bleeding complications in patients treated with ECMO. A. Correlation Matrix; B. Forest Plot. ECMO: Extracorporeal Membrane Oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; ECPR: Extracorporeal Cardiopulmonary Resuscitation; FIB: Fibrinogen; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; DD: D-dimer; PLT: Platelet Count.

tion function, whereas platelet adhesion to the inner wall of the ECMO tube accelerates PLT depletion [13, 14]. Therefore, close monitoring of PLT levels and timely platelet transfusion are

Table 6. Multivariate analysis of bleeding complications in patients undergoing ECMO

Variable	Coef	P	Exp..Coef.	Lower95	Upper95
Age	-0.01	0.64	0.99	0.97	1.02
APACHE II	0.02	0.07	1.02	1.00	1.05
ECMO indications					
Pulmonary	-0.08	0.78	0.92	0.52	1.64
ECMO withdrawal					
Yes	-0.73	0.00	0.48	0.30	0.78
ECPR					
Yes	-0.11	0.65	0.90	0.55	1.44
FIB	-0.21	0.08	0.81	0.63	1.03
PT	-0.08	0.29	0.92	0.79	1.07
aPTT	0.01	0.39	1.01	0.99	1.02
D-dimers	0.51	< 0.01	1.67	1.49	1.87
PLT	0.00	0.03	1.00	0.99	1.00

Note: ECMO: Extracorporeal Membrane Oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; ECPR: Extracorporeal Cardiopulmonary Resuscitation; FIB: Fibrinogen; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; PLT: Platelet Count.

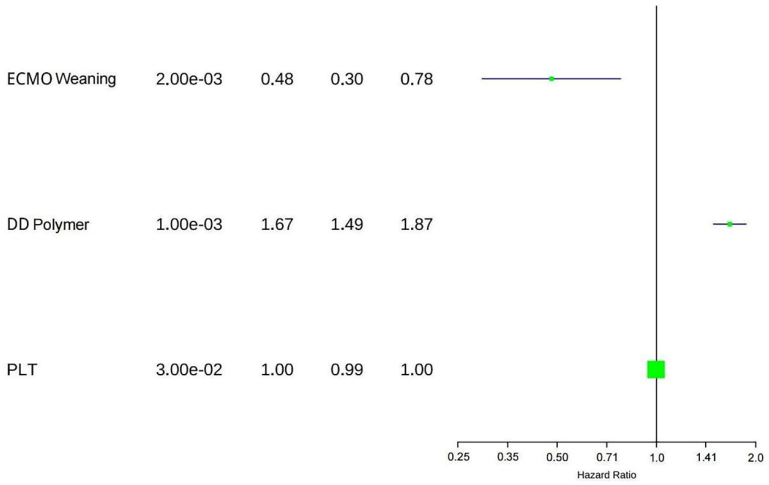

Figure 3. Multivariate analysis of bleeding complications in patients undergoing ECMO. ECMO: Extracorporeal Membrane Oxygenation; DD: D-dimer; PLT: Platelet Count.

crucial for patients with progressive PLT reduction [15]. D-dimer, a marker of hyperfibrinolysis, is strongly associated with bleeding risks. Hussein et al. found that ECMO patients had significantly elevated D-dimer levels compared to healthy individuals, which can lead to a hypercoagulable state, secondary hyperfibrinolysis, and increased risk of bleeding [16]. Therefore, monitoring dynamic changes in D-dimer is important for assessing bleeding risks and guiding anticoagulation treatment.

Each of the indicators identified in our study plays a distinct role in the development of bleeding complications in ECMO patients. The APACHE II score, which assesses disease severity, was found to be associated with increased bleeding risk, likely due to more severe underlying conditions that predispose patients to coagulopathy [17]. ECMO indications, particularly the need for cardiac versus pulmonary support, also influenced bleeding risk; patients requiring ECMO for cardiac reasons had a higher incidence of bleeding, possibly due to more complex cardiovascular histories and longer durations of mechanical support [18]. ECMO withdrawal was identified as a protective factor, possibly because patients successfully weaned off ECMO tend to have better overall health and less exposure to the prothrombotic environment of the ECMO circuit [19]. ECPR, used in emergency situations, was linked to higher bleeding risk, possibly due to the rapid and intense physiological stress it imposes [20, 21]. Coagulation parameters such as FIB, PT, aPTT, and D-dimer reflect various aspects of the coagulation cascade [22, 23]. Elevated D-dimer levels indicate ongoing fibrinolysis and thrombosis, heightening the risk of both clot formation and subsequent bleeding. PLT

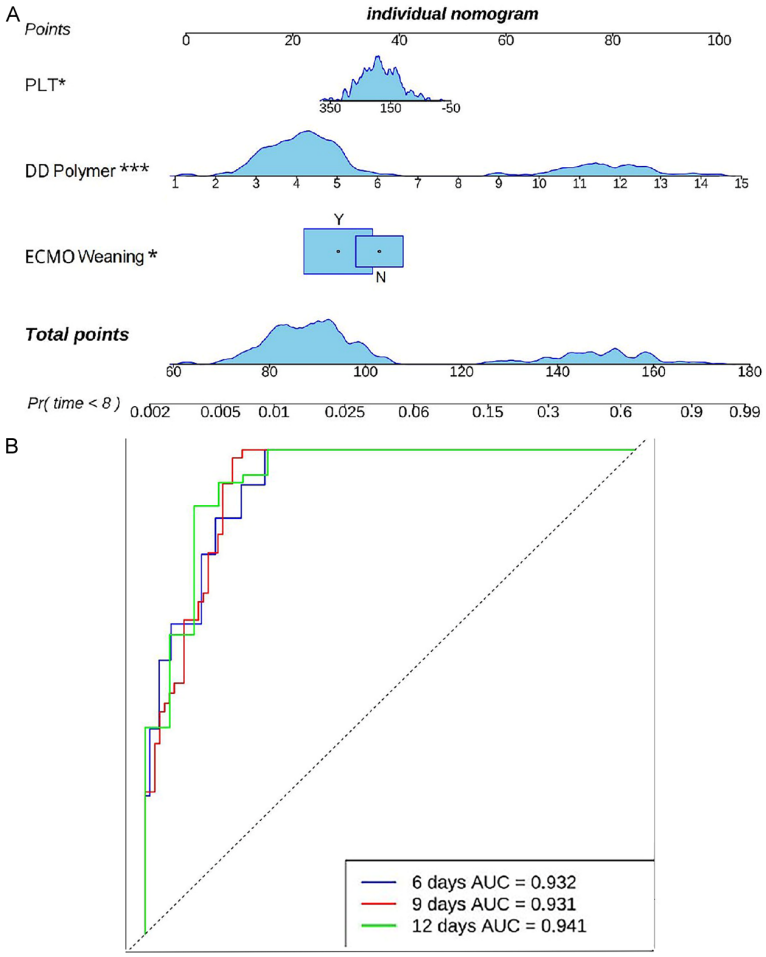

Figure 4. Construction and validation of a predictive model of bleeding complications in patients undergoing ECMO. A. Nomogram; B. Calibration Curve. ECMO: Extracorporeal Membrane Oxygenation; DD: D-dimer; PLT: Platelet Count; AUC: area under the curve.

plays a critical role in hemostasis; reduced PLT counts impair clot formation, making patients more susceptible to bleeding. Together, these indicators provide a comprehensive view of the complex interplay between patient characteristics and ECMO-induced bleeding complications.

To identify patients with a high bleeding risk from ECMO treatment at an early stage, we constructed a risk prediction model based on the results of multivariate Cox regression analysis. Three key markers, including ECMO withdrawal, D-dimer, and PLT, were selected for model construction. Nomograms were plotted to visualize the relationship between these indicators and risk of bleeding. ROC curves were generated for 6, 9, and 12 days after ECMO treatment, with AUCs calculated to be 0.932, 0.931, and 0.941, respectively. This suggests that the model has strong predictive performance, making it a useful tool for the early clinical identification of high-risk patients. Several studies have previously developed predictive models for ECMO-related bleeding complications, both in China and internationally [24, 25]. For instance, one study constructed a bleeding risk model based on age, blood creatinine, lactate, and hemoglobin, yielding an AUC of 0.72 [26]. Another study included PLT, aPTT, heparin dosage, and ECMO flow rate, in a logistic regression model, with an AUC of 0.77 [6]. However, these studies had relatively small sample sizes and lacked external validation, which limits the generalizability of their models. In contrast, our study includes a larger sample size and shows good predictive performance, though further external validation is needed to confirm its reliability for clinical application.

This study was one of the first to utilize MIMIC-IV database to explore risk factors for bleeding and thrombotic complications during ECMO support in adults. Unlike previous studies that often relied on smaller sample sizes and lacked external validation, our study benefits from a robust dataset containing comprehensive demographic, clinical, and laboratory data. By identifying ECMO withdrawal and PLT as independent protective factors and D-dimer as an independent risk factor, we have developed a predictive model with high accuracy (AUCs of 0.932, 0.931, and 0.941 at 6, 9, and 12 days post-ECMO treatment). This model not only provides a valuable tool for early identification of high-risk patients but also provides insights into potential preventive measures, such as timely platelet transfusion and monitoring of D-dimer levels. The use of advanced statistical methods, including Cox regression and machine learning algorithms, further en-

hances the reliability and generalizability of our findings.

However, this study has several limitations: First, as a retrospective observational study, it carries the risk of selection and confounding bias, necessitating validation in prospective studies. Second, the study sample was sourced from a single database which may limit its generalizability. Therefore, the predictive model needs to be validated in a multicenter study to confirm its external applicability. Third, some clinical data were missing, which may have affected the accuracy of the results.

Using data from the MIMIC-IV database, this study found that the incidence of bleeding complications during ECMO therapy in adults was 26.0%. ECMO withdrawal and PLT were identified as independent protective factors, whereas D-dimer was an independent risk factor. The predictive model developed from these three markers demonstrated strong predictive performance, enabling early identification of high-risk patients. This model can guide clinical decision-making and potentially improve patient prognosis. Future prospective studies are needed to further validate the predictive value of this model in clinical settings.

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Disclosure of conflict of interest

None.

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