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Ryo Esumi[1] MD, PhD; Hiroki Funao[2] MSc; Eiji Kawamoto[1] MD, PhD; Ryota Sakamoto[3] PhD; Asami Ito-Masui[1] MD, PhD; Fumito Okuno[4] MD; Toru Shinkai[4] MD, PhD; Atsuya Hane[4] MD; Kaoru Ikejiri[4] MD; Yuichi Akama[1] MD, PhD; Arong Gaowa[1] PhD; Eun Jeong Park[1] PhD; Ryo Momosaki[5] MD, PhD; Ryuji Kaku[6] MD, PhD; Motomu Shimaoka[1] MD, PhD

[1]Department of Molecular Pathobiology and Cell Adhesion Biology, Mie University Graduate School of Medicine Tsu city JP
[2]Department of Practical Nursing Mie University Graduate School of Medicine Tsu city JP
[3]Department of Medical Informatics Mie University Hospital Tsu city JP
[4]Department of Emergency and Critical Care Center Mie University Hospital Tsu city JP
[5]Department of Rehabilitation Medicine Mie University Graduate School of Medicine Tsu city JP
[6]Department of Anesthesiology Mie University Hospital Tsu city JP

Corresponding Author:
Eiji Kawamoto MD, PhD
Department of Molecular Pathobiology and Cell Adhesion Biology, Mie University Graduate School of Medicine
Edobashi 2-174
Tsu city
JP

Abstract

Background: The incidence of delirium in patients with burns receiving treatment in the intensive care unit (ICU) is high, reaching up to 77%, and has been associated with increased mortality rates. Therefore, early identification of patients at high risk of delirium onset is essential for improving treatment strategies.

Objective: This study aimed to create a machine learning model for predicting delirium in patients with burns during their ICU stay using patient data from the first day of ICU admission and to identify predictive factors for ICU delirium in patients with burns.

Methods: This study focused on 82 patients with burns aged ?18 years admitted to the ICU at Mie University Hospital for 24 h or more between January 2015 and June 2023. Seventy variables were measured in patients upon ICU admission and used as explanatory variables in the ICU delirium prediction model. Delirium was assessed using the Intensive Care Delirium Screening Checklist every 8 h after ICU admission. Ten different machine-learning methods were employed to predict ICU delirium. Multiple receiver operating characteristic curves were plotted for various machine learning models, and the area under each curve (AUC) was compared. Additionally, Shapley Additive exPlanations (SHAP) analysis was used to identify the top 15 risk factors contributing to delirium onset in each model.

Results: In this study, ICU delirium occurred in 32 out of 82 patients, representing 39% of the cohort. Key factors associated with the development of ICU delirium in burn patients include advanced age (77.0 years vs. 60.5 years; P<0.001), a higher intubation rate (1.0 vs. 0.0; P<0.001), larger burn area (16.0% vs. 8.0%; P=0.007), increased white blood cell count (13,380 cells/?L vs. 8,910 cells/?L; P=0.003), and significantly decreased daily urine output (412.5 mL vs. 1493.0 mL; P<0.001). These findings highlight the importance of these factors in predicting and managing ICU delirium among burn patients. Among the ten machine learning models tested, AdaBoost (AUC: 0.83), gradient boosting machine (AUC: 0.82), support vector machine (AUC: 0.79), logistic regression (AUC: 0.79), and random forest (AUC: 0.79) demonstrated high accuracy in predicting ICU delirium.

Conclusions: The 24-hour urine output (from ICU admission to 24 hours), SaO2 (oxygen saturation), burn area, total bilirubin level, and intubation upon ICU admission were identified as the major risk factors for the onset of delirium. Additionally, variables, such as the proportion of white blood cell fractions, including monocytes, methemoglobin concentration, and respiratory rate, were identified as important risk factors for ICU delirium. Clinical Trial: Not applicable

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Original Paper

Prediction of Delirium in Patients with Burns in the ICU and Identification of Risk Factors Using Machine Learning

Running title: Predicting Delirium in Patients with Burns

Ryo Esumi[1,2†], Hiroki Funao[3†], Eiji Kawamoto[1,4*], Ryota Sakamoto[5], Asami Ito-Masui[1,6], Fumito Okuno[6], Toru Shinkai[6], Atsuya Hane[6], Kaoru Ikejiri[6], Yuichi Akama[1], Arong Gaowa[1], Eun Jeong Park[1], Ryo Momosaki[7], Ryuji Kaku[8], Motomu Shimaoka[1]

[1]Department of Molecular Pathobiology and Cell Adhesion Biology, Mie University Graduate School of Medicine, Tsu, Japan
[2]Department of Emergency Medicine, National Hospital Organization Mie Chuo Medical Center, Tsu, Japan
[3]Department of Practical Nursing, Mie University Graduate School of Medicine, Tsu, Japan
[4]Department of Intensive Care Medicine, Mie University Hospital, Tsu, Japan
[5]Department of Medical Informatics, Mie University Hospital, Tsu, Japan
[6]Department of Emergency and Critical Care Center, Mie University Hospital, Tsu, Japan
[7]Department of Rehabilitation Medicine, Mie University Graduate School of Medicine, Tsu, Japan
[8]Department of Anesthesiology, Mie University Hospital, Tsu, Japan

*** Correspondence:**
Eiji Kawamoto, MD, PhD
a-2kawamoto@med.mie-u.ac.jp
[†]These authors contributed equally to this work.

Abstract

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Seventy variables were measured in patients upon ICU admission and used as explanatory variables in the ICU delirium prediction model. Delirium was assessed using the Intensive Care Delirium Screening Checklist every 8 h after ICU admission. Ten different machine-learning methods were employed to predict ICU delirium. Multiple receiver operating characteristic curves were plotted for various machine learning models, and the area under each curve (AUC) was compared. Additionally, Shapley Additive exPlanations (SHAP) analysis was used to identify the top 15 risk factors contributing to delirium onset in each model.

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Trial Registration: Not applicable

Keywords: burns; delirium; intensive care unit; machine learning; prediction model

Introduction

Delirium is a significant complication in patients in the intensive care unit (ICU) and is recognized as an urgent medical need requiring treatment and prevention. Delirium is defined as acute brain dysfunction associated with underlying conditions characterized by fluctuating bouts of impaired consciousness, attention, and cognition. This condition is frequently observed in patients admitted to the ICU, with delirium occurring in 10–50% of patients (1). Delirium is an independent predictor of poor outcomes, and there is currently no established specific treatment, making early diagnosis and prevention critically important (2). Particularly, the incidence of delirium in patients with burns can reach 77% (3), with reports indicating that 30% of patients who develop delirium respond effectively to prevention and treatment (4). These facts underscore the importance of identifying patients at high risk of delirium and implementing preventive measures.

In recent years, research on ICU delirium prediction using artificial intelligence technology has advanced, with a particular focus on the application of machine learning algorithms such as random forest (RF), support vector machine (SVM), and gradient boosting (5). These algorithms can identify relevant features associated with delirium from large volumes of patient data and conduct analyses with speed and accuracy beyond human capacity. However, research on the prediction of ICU delirium in patients with burns remains underdeveloped, and very few studies have been conducted in this field.

This study aimed to demonstrate whether it is possible to predict ICU delirium in patients with burns using machine learning. Specifically, we hypothesized that a machine learning model utilizing clinical data such as vital signs and blood test results could predict delirium in ICU patients. The null hypothesis was that these models would not be superior to random chance in predicting ICU

delirium.
While ICU delirium prediction potential for multiple machine learning models, as well as the model with the highest accuracy, was assessed, the second objective of this study was to identify risk factors for ICU delirium in patients with burns and contribute to the development of more effective prevention and treatment strategies.

This ICU delirium prediction approach using machine learning has the potential to support the early detection of ICU delirium in patients with burns and ultimately improve patient outcomes.

Methods

Patient Demographics and Data Collection

This study is a retrospective observational study focused on predicting delirium in patients with burns admitted to the ICU. This study included 82 patients with burns aged ≥18 years who were admitted to the Mie University ICU for 24 h or more between January 2015 and June 2023. The sample size of 82 patients was determined by including all burn patients admitted to the ICU within the study period.

Patients were retrospectively included following the inclusion criteria, ensuring comprehensive capture of all eligible cases during the study period. This approach minimizes selection bias and allows for a representative sample of the burn patient population in our ICU.

Physiological, biochemical, and clinical data collected from these patients upon ICU admission were used to extract 70 explanatory variables. This study aimed to develop a model using these 70 variables to predict delirium onset during ICU admission, assess its accuracy, and identify the risk factors contributing to each model.

The Definition, Diagnostic Criteria, and Standard Assessment of ICU Delirium

ICU delirium, also known as ICU psychosis, is an acute, fluctuating change in consciousness and cognition that occurs frequently in critically ill patients. ICU delirium is characterized by disturbances in attention, awareness, and cognitive function. These disturbances are often temporary and reversible but can lead to prolonged ICU stays, increased morbidity and mortality, and long-term cognitive impairments if not properly managed.

The standard assessment of ICU delirium involves the use of validated diagnostic tools to ensure accurate detection and timely intervention. Two widely recognized tools are the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC).

The CAM-ICU is a structured diagnostic tool specifically designed for use in the ICU setting. It is based on the Confusion Assessment Method (CAM) and modified for the critical care environment. The CAM-ICU assesses four key features: (1) acute onset of mental status changes or a fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. A positive CAM-ICU diagnosis requires the presence of both features 1 and 2 and either feature 3 or 4. This tool is favored for its ease of use and quick administration, making it suitable for frequent assessments.

The ICDSC is another tool used to screen for delirium in ICU patients, consisting of an eight-item

checklist that assesses various cognitive and behavioral symptoms associated with delirium. The items include (1) altered level of consciousness; (2) inattention; (3) disorientation; (4) hallucinations or delusions; (5) psychomotor agitation or retardation; (6) inappropriate speech or mood; (7) sleep/wake cycle disturbances; and (8) symptom fluctuation. Each item is scored based on its presence within the last 24 hours, and a total score of four or higher indicates the presence of delirium. The ICDSC provides a comprehensive overview of the patient's condition over a longer period than the CAM-ICU.

In the current study, delirium was assessed using the internationally recognized ICDSC every 8 h after ICU admission. Delirium was diagnosed when the ICDSC score was ≥4 points. We opted for a binary classification approach because this method simplifies the model's output to either "delirium present" or "delirium absent," facilitating smoother decision-making in clinical settings. Another reason for this choice was the diversity in patient conditions in real-world clinical environments, where a few specific atypical cases can skew the predictions of regression models. Binary classification is less susceptible to the influence of such outliers, enabling the development of a more robust model. This method allowed for accurate determination of the presence and severity of delirium.

Development of Machine Learning Models

Ten different algorithms were employed to develop the machine learning models: logistic regression (LR), Random Forest **(**RF), Support Vector Machine **(**SVM), neural network, k-nearest neighbors (k-NN), decision tree, naive Bayes, Adaptive Boosting (AdaBoost), gradient boosting machine (GBM), and linear discriminant analysis (LDA). These models were selected based on the area under the receiver operating characteristic curve (AUC) to compare the accuracy of delirium prediction.

Model Evaluation and SHAP Analysis

Shapley Additive exPlanations (SHAP) analysis was used to reveal the contribution of the top 15 risk factors (features) in each model, enabling the identification of the factors that had the most significant impact on delirium onset.

Ethical Approval

This study was approved by the Ethics Committee of Mie University (H2020-164). We applied the Opt-out method to obtain consent for this study.

Machine learning models

This study used various machine learning models to perform a binary classification and determine the presence or absence of delirium in patients.
Logistic Regression **(**LR): This model is a classification approach based on linear regression. It is commonly used for binary classification tasks and models the probability of a binary response based on one or more predictor variables.
Random Forest **(**RF): As an ensemble learning method, RF combines multiple decision trees to improve the predictive accuracy of a model. Each tree in the forest provided a classification, and the class with the most votes was the model's prediction.

Support Vector Machine **(**SVM): This model focuses on finding the best boundary (or hyperplane) to separate data. SVM is effective in high-dimensional spaces and is versatile because it can be used for linear and nonlinear classification.

Neural networks: From simple perceptrons to complex deep-learning networks, neural networks can

be applied to binary classification problems. They mimic the workings of the human brain and can learn from large amounts of data.

k-Nearest Neighbors **(**k-NN): This model predicts the class of a new data point based on the majority class among its k-NN in the training data. This is a type of instance-based learning, or laundry learning, in which the function is approximated locally.
Decision trees: Used both as stand-alone models and as the foundational model in RFs, decision trees create a model that predicts the value of a target variable based on several input variables. Each internal node of the tree represents a test of an attribute, and each leaf node represents a class label.

Naive Bayes: A probabilistic classifier based on Bayes' theorem; naive Bayes is known for its application in text classification. Despite its simplicity, it has been proven effective for various applications.

Adaptive Boosting (AdaBoost): This boosting algorithm combines multiple weak classifiers to form a single strong classifier. AdaBoost focuses on correctly classifying instances in which previous models failed by adjusting the weights of these instances.

Gradient Boosting Machine **(**GBM): The GBM builds the model in a stagewise fashion, where it combines multiple decision trees and progressively adjusts the weight of misclassified data points to improve the model's predictive performance.

Linear Discriminant Analysis **(**LDA): LDA combines attributes linearly and seeks the best boundary that separates the two classes. It is widely used for dimensionality reduction before classification.

Each of these models was applied to our dataset, and their performances in predicting ICU delirium were compared. The effectiveness of these models was evaluated using the receiver operating characteristic curve and AUC metrics. Additionally, the contribution of the features in each model was elucidated using SHAP analysis, which helped identify significant predictors of delirium.

Data Preprocessing for Machine Learning

Handling missing values: In this study, any data entries with missing values were excluded to ensure the integrity and reliability of the analysis.

Data splitting: The dataset was carefully divided into two main components: the target variable, which is delirium, and the explanatory variables, comprising other relevant features. To evaluate the model's performance effectively, the dataset was split into training and test subsets. Specifically, 80% of the data was allocated to the training set, which was used to develop the predictive model, while the remaining 20% was reserved as the internal validation set to rigorously test and validate the model's accuracy and generalizability.

Data standardization: The features of both the training and test data were standardized (mean 0, standard deviation, 1) using StandardScaler.
Model selection and initialization: Various machine learning models were imported, and specific hyperparameters were set for each model. The models used in this study included SVM, neural network, k-NN, decision tree, naive Bayes, AdaBoost, GBM, LDA, LR, and RF.

Model training and evaluation: Each model was applied to the training data, and its predictive performance was evaluated using the test data.

Statistical Analysis

Continuous variables are presented as median and interquartile range and were compared using the Mann–Whitney U test or Kruskal–Wallis test, as needed. Categorical variables are presented as counts and percentages and were compared using Fisher's exact test or the chi-squared test, as appropriate. All statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Statistical significance was set at P<0.05.

Results

Comparative Analysis of ICU Delirium in Patients with Burns

In this study, ICU delirium occurred in 32 out of 82 patients, representing 39% of the cohort. We compared patients who developed ICU delirium and those who did not (Table 1). Compared to patients without delirium, those with ICU delirium among patients with burns were older (77.0 years vs. 60.5 years; P<0.001), had a similar proportion of airway burns (0.0% vs. 0.0%; P=0.028), had a longer ICU stay (2.5 days vs. 2.0 days; P=0.009), had similar mortality rate (0.0% vs. 0.0%; P=0.001), a higher intubation rate (1.0 vs. 0.0; P<0.001), a larger burn area (16.0% vs. 8.0%; P=0.007), a higher Burn Index (9.5 vs. 4.0; P=0.002), a higher white blood cell count (13,380 cells/μL vs. 8,910 cells/μL; P=0.003), a higher neutrophil count (9,029.0 cells/μL vs. 6,890.0 cells/μL; P=0.004), a higher monocyte count (767.0 cells/μL vs. 570.0 cells/μL; P=0.039), prolonged activated partial thromboplastin time (30.8 s vs. 27.1 s; P=0.007), prolonged prothrombin time (12.2 s vs. 11.2 s; P<0.001), a higher prothrombin time international normalized ratio (1.0 vs. 1.0; P=0.002), increased D-dimer levels (4.0 μg/mL vs. 0.8 μg/mL; P=0.001), slightly decreased pH (7.4 vs. 7.4; P=0.044), increased SaO_2 (98.9% vs. 97.6%; P=0.018), decreased hemoglobin (Hb) (13.5 g/dL vs. 14.6 g/dL; P=0.018), increased methemoglobin (Met-Hb) (0.9% vs. 0.4%; P=0.004), decreased hematocrit (40.0% vs. 43.0%; P=0.008), decreased total protein (6.4 g/dL vs. 7.0 g/dL; P=0.017), decreased albumin (3.6 g/dL vs. 4.1 g/dL; P=0.003), increased blood urea nitrogen (16.9 mg/dL vs. 13.8 mg/dL; P=0.022), decreased calcium (8.4 mg/dL vs. 9.0 mg/dL; P<0.001), increased total bilirubin (T-bil) (0.9 mg/dL vs. 0.6 mg/dL; P<0.001), increased creatine phosphokinase (249.5 U/L vs. 115.0 U/L; P=0.010), increased C-reactive protein (0.5 mg/dL vs. 0.1 mg/dL; P=0.007), greatly decreased daily urine output (412.5 mL vs. 1493.0 mL; P<0.001), and an increased respiratory rate (19.5 breaths/min vs. 16.0 breaths/min; P=0.015).

Table 1. Characteristics of patients with burns with ICU delirium: Comparison of explanatory factors between patients with and without delirium

	Burn with delirium (n=32) Median (IQR1–IQR3)	**Burn without delirium (n=50) Median (IQR1–IQR3)**	**P-value**
Age	77.0 (69.5–84.5)	60.5 (37.5–73.0)	<0.001*
Sex	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.896
Height	160.5 (150.0–170.0)	162.2 (158.0–168.0)	0.424
Weight	54.4 (44.4–63.3)	60.2 (50.5–67.2)	0.067
BMI	21.2 (19.0–23.4)	23.2 (19.7–25.0)	0.058
Airway burn	12/32 (37.5%)	8/50 (16.0%)	0.028*
ICU length of stay	2.5 (1.8–11.2)	2.0 (1.0–3.0)	0.009*
Dead	7/32 (21.9%)	0/50 (0.0%)	0.001*
Intubation	20/32 (62.5%)	4/50 (8.0%)	<0.001*
Burn Area	16.0 (9.8–34.0)	8.0 (4.6–17.0)	0.007*
Burn Index	9.5 (4.8–25.1)	4.0 (1.0–10.0)	0.002*

WBC	13.4 (9.7–18.8)	8.9 (6.6–11.4)	0.003*
RBC	4.3 (3.7–5.3)	4.6 (4.1–5.0)	0.369
Hemoglobin	13.5 (11.9–15.1)	14.6 (13.9–16.0)	0.018*
Hematocrit	40.0 (35.0–44.0)	43.0 (41.0–47.5)	0.008*
MCV	92.0 (89.9–93.8)	92.9 (87.7–95.8)	0.745
MCH	30.9 (30.1–32.5)	31.4 (29.8–32.9)	0.792
MCHC	33.8 (33.2–34.6)	33.9 (33.0–34.7)	0.855
Platelets	205.5 (165.0–314.8)	248.5 (202.2–289.0)	0.651
Neutrophils (%)	77.0 (73.9–83.7)	74.4 (64.6–79.9)	0.025*
Lymphocytes (%)	15.8 (8.4–17.9)	16.5 (12.7–23.6)	0.029*
Monocytes (%)	6.6 (5.2–7.7)	6.8 (5.9–7.3)	0.566
Eosinophils (%)	0.6 (0.4–1.4)	1.2 (0.6–2.0)	0.038*
Basophils (%)	0.4 (0.2–0.5)	0.4 (0.2–0.5)	0.866
Neutrophils	9029.0 (7047.5–14550.0)	6890.0 (4650.0–9029.0)	0.004*
Lymphocytes	1549.0 (1130.0–1942.5)	1549.0 (1120.0–2130.0)	0.634
Monocytes	767.0 (477.5–992.5)	570.0 (440.0–767.0)	0.039*
Eosinophils	70.0 (37.5–111.0)	90.0 (40.0–160.0)	0.384
Basophils	38.5 (30.0–62.5)	37.0 (20.0–50.0)	0.086
APTT	30.8 (25.9–36.8)	27.1 (25.0–29.7)	0.007*
PT	12.2 (11.5–13.7)	11.2 (10.8–11.8)	<0.001*
PT-%	94.8 (77.0–104.1)	105.0 (97.0–112.2)	0.002*
PT-INR	1.0 (1.0–1.2)	1.0 (0.9–1.0)	0.002*
Fibrinogen	300.0 (248.5–375.5)	272.0 (225.5–305.5)	0.162
D-dimer	4.0 (1.6–8.6)	0.8 (0.2–3.1)	0.001*
pH	7.4 (7.3–7.4)	7.4 (7.4–7.4)	0.044*
pCO_2	38.7 (31.0–44.8)	36.2 (33.1–39.7)	0.441
pO_2	151.8 (92.0–304.0)	103.7 (79.2–151.8)	0.054
sO_2	98.9 (98.2–99.4)	97.6 (94.9–98.9)	0.018*
HCO_3	22.8 (17.5–25.2)	23.0 (20.0–23.9)	0.837
A-gap	10.4 (3.7–17.9)	13.2 (10.4–17.4)	0.34
O_2-Hb	96.1 (93.1–97.3)	95.9 (90.8–96.8)	0.326
CO-Hb	1.6 (1.1–3.3)	1.6 (0.6–3.4)	0.468
Met-Hb	0.9 (0.5–1.1)	0.4 (0.3–0.9)	0.004*
Lactate	2.9 (1.5–5.0)	2.5 (1.8–3.6)	0.841
Total protein	6.4 (6.0–6.7)	7.0 (6.2–7.5)	0.017*
Albumin	3.6 (3.2–3.9)	4.1 (3.3–4.4)	0.003*
BUN	16.9 (12.8–22.8)	13.8 (11.2–19.0)	0.022*
Creatinine	0.8 (0.7–1.0)	0.7 (0.5–0.8)	0.057
eGFR	65.7 (46.6–87.4)	84.5 (63.3–101.4)	0.011*
Na	139.0 (138.0–141.0)	139.5 (138.0–141.0)	0.77
K	4.0 (3.7–4.5)	3.9 (3.7–4.3)	0.387
CL	105.0 (102.0–107.0)	104.0 (103.0–106.0)	0.617
Ca	8.4 (8.2–8.9)	9.0 (8.6–9.3)	0.001*
ion Ca	1.1 (1.1–1.2)	1.1 (1.1–1.1)	0.977
AST	39.5 (22.8–60.5)	29.0 (24.0–36.0)	0.132
ALT	23.0 (14.0–43.5)	20.0 (14.5–29.0)	0.376
LDH	294.5 (216.8–630.8)	255.5 (197.8–303.0)	0.059
ALP	215.5 (154.2–263.5)	179.0 (87.2–221.8)	0.07

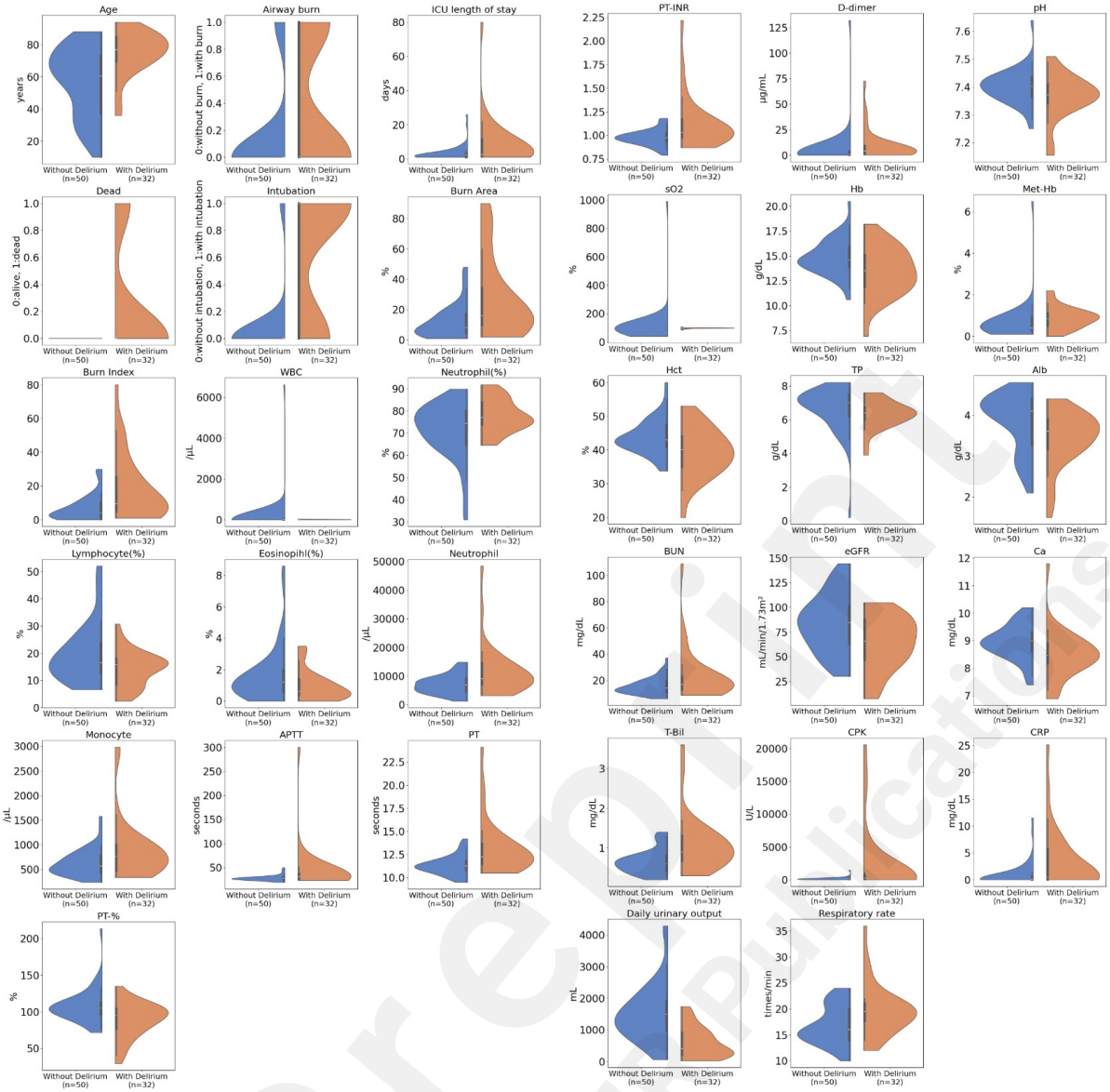
T-bil	0.9 (0.7–1.3)	0.6 (0.4–0.8)	0.001*
Glucose	147.0 (120.5–179.2)	128.5 (113.0–168.0)	0.405
CPK	249.5 (96.5–645.8)	115.0 (73.0–229.0)	0.01*
Amylase	77.0 (57.5–129.5)	78.0 (61.0–94.1)	0.546
CRP	0.5 (0.1–5.6)	0.1 (0.0–0.6)	0.007*
Daily urinary output	412.5 (215.0–908.2)	1493.0 (985.0–1912.5)	<0.001*
Respiratory rate	19.5 (17.8–21.0)	16.0 (14.0–20.0)	0.015*
sBP	146.5 (115.5–160.2)	139.0 (122.2–157.0)	0.915
dBP	81.0 (64.8–88.5)	74.0 (65.5–84.0)	0.784
Heart rate	97.0 (81.0–113.5)	87.5 (81.2–97.0)	0.053
Body temperature	37.0 (36.3–37.5)	37.0 (36.8–37.4)	0.226

*Statistical significance was considered at P<0.05.

Abbreviations: ICU: intensive care unit, IQR1: first quartile, IQR3: third quartile, BMI: body mass index, WBC: white blood cell count, RBC: red blood cell count, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, APTT: activated partial thromboplastin time, PT: prothrombin time, PT-%: prothrombin time percentage, PT-INR: prothrombin time international normalized ratio, pCO_2: partial pressure of carbon dioxide, pO_2: partial pressure of oxygen, sO_2: saturation of oxygen, HCO_3: bicarbonate, A-gap: anion gap, O_2-Hb: oxygenated hemoglobin, CO-Hb: carboxyhemoglobin, Met-Hb: methemoglobin, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, T-bil: total bilirubin, CPK: creatine phosphokinase, CRP: C-reactive protein, sBP: systolic blood pressure, dBP: diastolic blood pressure

Visual Examination of Data Using Violin Plots

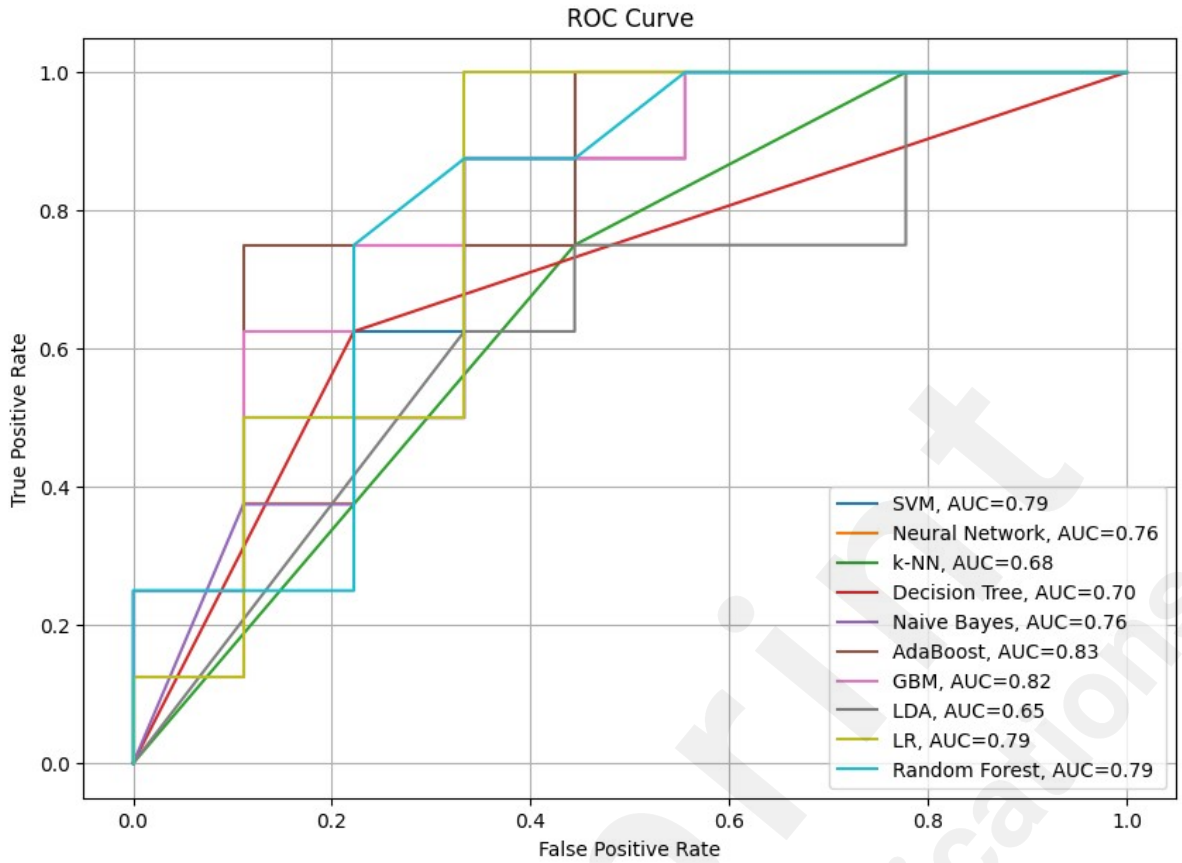
Next, the distribution of data was visually examined between the two groups (those with and without ICU delirium) using violin plots. As shown in Figure 1, violin plots visually represent the density and range of the data, allowing the identification of data dispersion and bimodality, that is, the shape of the distribution. Specifically, it became evident that urine output decreased proportionally, serving as a risk factor for ICU delirium.



(Figure 1)

Machine Learning Model Evaluation for Delirium Prediction

Subsequently, the values of the AUC were derived using multiple machine learning algorithms, as well as the blood test data and clinical data of patients with burns, to predict the occurrence of ICU delirium. Through this analysis, the AdaBoost model exhibited the best performance, showing a significant result with an AUC of 0.83. Furthermore, GBM had an AUC of 0.82, whereas SVM, LR, and RF had AUCs of 0.79, indicating that each was a good model for predicting the occurrence of ICU delirium (Figure 2).



(Figure 2).

Performance Metrics of Machine Learning Models in ICU Delirium Prediction

We present other performance metrics of the model. In this study, four additional metrics, accuracy, precision, recall, and F1 score, were used to evaluate the performance of the multiple machine learning models in predicting ICU delirium (Table 2). AdaBoost and neural networks showed the highest accuracy, achieving a score of 0.765. This was followed by SVM and decision trees, both with a precision of 0.706. In contrast, k-NN and naive Bayes had a lower precision of 0.590 compared with the other models. In terms of recall, neural networks, and LR were the highest, showing recall rates of 1.00. For precision and F1 score, SVM and decision tree both recorded a precision of 0.71 and an F1 score of 0.67, indicating that these two models exhibited a relatively balanced performance. These results indicate that AdaBoost and neural networks demonstrated the best performance in predicting ICU delirium. However, the other models also have competitive strengths in terms of their specific evaluation metrics (Table 2).

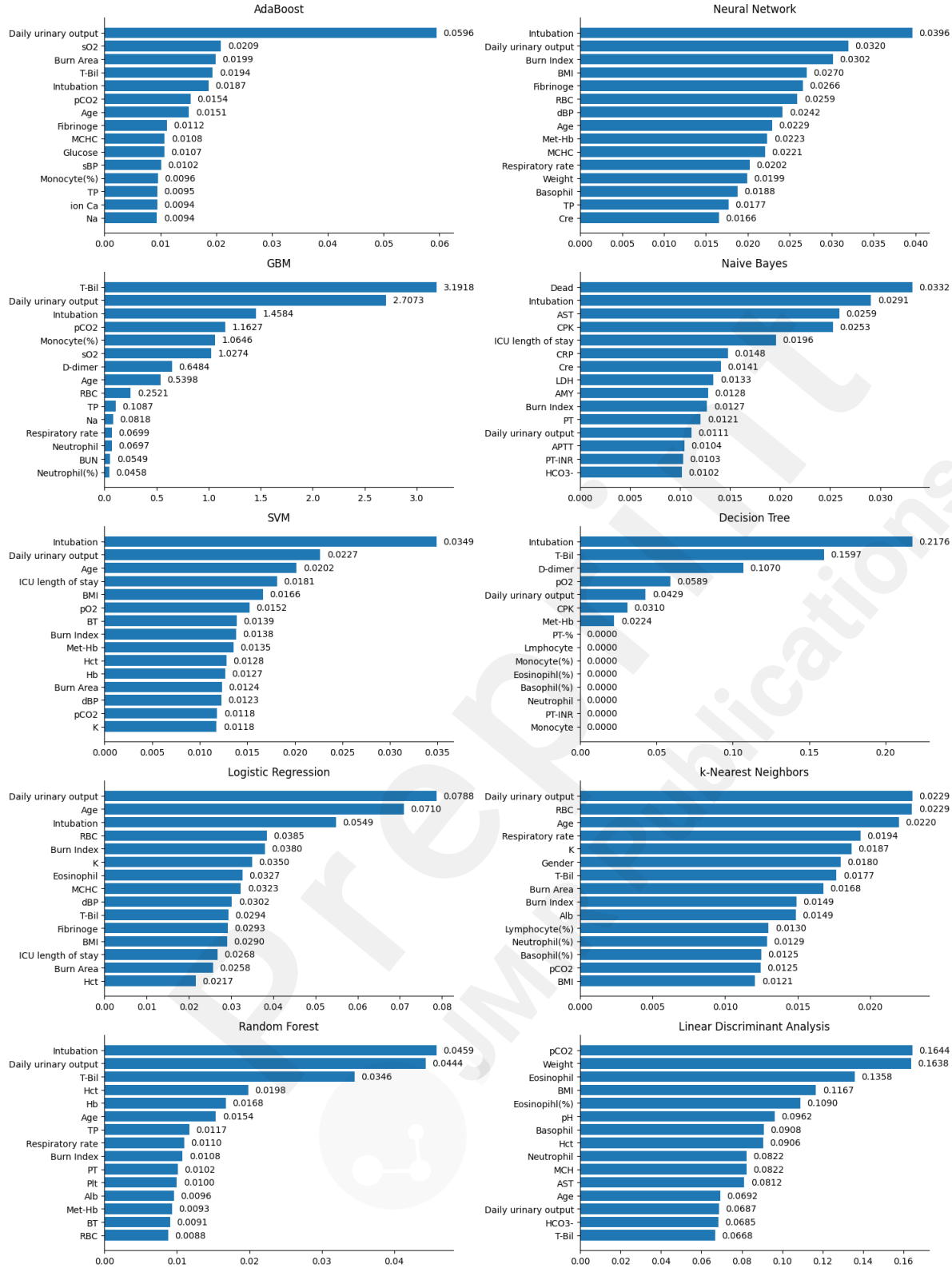
Table 2. Comparison of the accuracy of the machine learning models

Model	Accuracy	Precision	Recall	F1 score
Support vector machine	0.706	0.714	0.625	0.667
Neural network	0.765	0.667	1.000	0.800
k-nearest neighbors	0.588	0.590	0.375	0.462

Decision tree	0.706	0.714	0.625	0.667
Naive Bayes	0.588	0.590	0.375	0.462
AdaBoost	0.765	0.833	0.625	0.714
Gradient boosting machine	0.706	0.667	0.750	0.706
Linear discriminant analysis	0.588	0.556	0.625	0.588
Logistic regression	0.824	0.727	1.000	0.842
Random forest	0.706	0.714	0.625	0.667

Identification of High-Risk Factors for ICU Delirium Using SHAP Analysis

Finally, the top 15 high-risk factors in each model were identified using SHAP analysis of the validated machine learning models (Figure 3). In the AdaBoost model, which has a particularly high AUC and precision, factors, such as urinary output within the first 24 h of ICU admission (daily urine output), SaO_2, burn area, T-bil, and the presence of tracheal intubation at ICU admission, were identified as risk factors. Conversely, in the LR model with high accuracy and a high F1 score, the identified risk factors included daily urine output, age, presence of tracheal intubation, red blood cell count, and burn index. Additionally, in the neural network model with high recall, the identified risk factors were tracheal intubation, daily urine output, burn index, body mass index, and fibrinogen value. Interestingly, among the ten machine learning models, Met-Hb levels and respiratory rate were identified as risk factors in four of the models. Furthermore, in seven of the ten models, leukocyte fractions, such as neutrophil count, monocyte count, eosinophil count, and their ratios, were identified as risk factors, leading to the discovery of new delirium prediction factors.


AdaBoost
Daily urinary output 0.0596
sO2 0.0209
Burn Area 0.0199
T-Bil 0.0194
Intubation 0.0187
pCO2 0.0154
Age 0.0151
Fibrinoge 0.0112
MCHC 0.0108
Glucose 0.0107
sBP 0.0102
Monocyte(%) 0.0096
TP 0.0095
ion Ca 0.0094
Na 0.0094
Neural Network
Intubation 0.0396
Daily urinary output 0.0320
Burn Index 0.0302
BMI 0.0270
Fibrinoge 0.0266
RBC 0.0259
dBP 0.0242
Age 0.0229
Met-Hb 0.0223
MCHC 0.0221
Respiratory rate 0.0202
Weight 0.0199
Basophil 0.0188
TP 0.0177
Cre 0.0166
GBM
T-Bil 3.1918
Daily urinary output 2.7073
Intubation 1.4584
pCO2 1.1627
Monocyte(%) 1.0646
sO2 1.0274
D-dimer 0.6484
Age 0.5398
RBC 0.2521
TP 0.1087
Na 0.0818
Respiratory rate 0.0699
Neutrophil 0.0697
BUN 0.0549
Neutrophil(%) 0.0458
Naive Bayes
Dead 0.0332
Intubation 0.0291
AST 0.0259
CPK 0.0253
ICU length of stay 0.0196
CRP 0.0148
Cre 0.0141
LDH 0.0133
AMY 0.0128
Burn Index 0.0127
PT 0.0121
Daily urinary output 0.0111
APTT 0.0104
PT-INR 0.0103
HCO3- 0.0102
SVM
Intubation 0.0349
Daily urinary output 0.0227
Age 0.0202
ICU length of stay 0.0181
BMI 0.0166
pO2 0.0152
BT 0.0139
Burn Index 0.0138
Met-Hb 0.0135
Hct 0.0128
Hb 0.0127
Burn Area 0.0124
dBP 0.0123
pCO2 0.0118
K 0.0118
Decision Tree
Intubation 0.2176
T-Bil 0.1597
D-dimer 0.1070
pO2 0.0589
Daily urinary output 0.0429
CPK 0.0310
Met-Hb 0.0224
PT-% 0.0000
Lmphocyte 0.0000
Monocyte(%) 0.0000
Eosinopihl(%) 0.0000
Basophil(%) 0.0000
Neutrophil 0.0000
PT-INR 0.0000
Monocyte 0.0000
Logistic Regression
Daily urinary output 0.0788
Age 0.0710
Intubation 0.0549
RBC 0.0385
Burn Index 0.0380
K 0.0350
Eosinophil 0.0327
MCHC 0.0323
dBP 0.0302
T-Bil 0.0294
Fibrinoge 0.0293
BMI 0.0290
ICU length of stay 0.0268
Burn Area 0.0258
Hct 0.0217
k-Nearest Neighbors
Daily urinary output 0.0229
RBC 0.0229
Age 0.0220
Respiratory rate 0.0194
K 0.0187
Gender 0.0180
T-Bil 0.0177
Burn Area 0.0168
Burn Index 0.0149
Alb 0.0149
Lymphocyte(%) 0.0130
Neutrophil(%) 0.0129
Basophil(%) 0.0125
pCO2 0.0125
BMI 0.0121
Random Forest
Intubation 0.0459
Daily urinary output 0.0444
T-Bil 0.0346
Hct 0.0198
Hb 0.0168
Age 0.0154
TP 0.0117
Respiratory rate 0.0110
Burn Index 0.0108
PT 0.0102
Plt 0.0100
Alb 0.0096
Met-Hb 0.0093
BT 0.0091
RBC 0.0088
Linear Discriminant Analysis
pCO2 0.1644
Weight 0.1638
Eosinophil 0.1358
BMI 0.1167
Eosinopihl(%) 0.1090
pH 0.0962
Basophil 0.0908
Hct 0.0906
Neutrophil 0.0822
MCH 0.0822
AST 0.0812
Age 0.0692
Daily urinary output 0.0687
HCO3- 0.0685
T-Bil 0.0668

(Figure 3)

Discussion

Principal Results

Predictive Analysis of Delirium in ICU Patients with Burns Using Machine Learning Models

Among 82 patients with burns aged ≥18 years admitted to the ICU, 32 (39%) developed delirium during their ICU stay. We extracted 70 explanatory variables, including blood data and vital signs, from these 82 patients and tested whether the machine learning models could accurately predict delirium. One of this study's objectives was to identify the machine learning model with the highest accuracy for predicting the onset of ICU delirium in patients with burns. The AdaBoost model achieved the highest AUC, and our hypothesis that delirium in ICU patients could be predicted using machine learning models utilizing clinical data such as vital signs and biological data from blood tests was validated (see Figure 2). Another objective was to identify the risk factors for the onset of ICU delirium. The ten machine learning models utilized in this study not only underscored the significance of established risk factors, such as burn area and the presence of tracheal intubation, but also identified novel potential predictors of ICU delirium. Specifically, daily urine output, total bilirubin (T-bil) levels, respiratory rate, methemoglobin (Met-Hb) levels, and leukocyte fractions emerged as new predictive factors. These findings highlight the importance of incorporating both traditional risk factors and newly identified variables to enhance the predictive accuracy for ICU delirium. In summary, our study suggests that ICU delirium is a complex condition influenced by multiple physiological factors, and machine learning, which can handle multiple factors, is useful for predicting the complex condition of ICU delirium. Moreover, effective management of respiratory, renal, hepatic, and inflammatory functions is essential in preventing and treating delirium in critically ill patients. Future research should aim to further elucidate the mechanisms by which these factors contribute to delirium and explore targeted interventions to improve patient outcomes.

The Role of T-bil levels in Predicting Delirium in ICU Patients with Burns: Connections with Cholestasis and Inflammation

T-bil levels were identified as a risk factor for the development of delirium in ICU patients with burns. However, the direct relationship between burns and cholestasis remains unclear. Cholestasis often occurs after burns, and patients with burns with increased bilirubin levels without a corresponding increase in alkaline phosphatase and gamma-glutamyl transferase levels have a higher risk of mortality. Furthermore, intrahepatic cholestasis is observed in half of patients with severe burns (6). Cholestasis is also associated with hypoxic hepatitis (7). Additionally, hypovolemic shock seen in severe burns may be involved in the elevation of T-bil levels (8). Increases in interleukin (IL)-6 and tumor necrosis factor-α, which are observed in the early stages of severe burns (9), have been reportedly associated with hyperbilirubinemia (10) and organ dysfunction (11). Inflammatory cytokines like IL-6 and tumor necrosis factor-α may reduce the expression of bile transporters on the canalicular membrane of hepatocytes, leading to an increase in T-bil levels (12, 13). These research findings support the validity of our study, which identified an increase in T-bil levels as an important risk factor for predicting ICU delirium in patients with burns.

Met-Hb Level as a Novel Indicator of ICU Delirium in Patients with Burns: Insights from Sepsis and Hemolysis Research

Met-Hb level was identified as an explanatory factor. No previous studies have clearly demonstrated the involvement of Met-Hb level as a risk factor for ICU delirium in patients with burns. However, several studies have shown the involvement of Met-Hb in delirium in patients with sepsis, which, similar to burns, can cause a cytokine storm. Moreover, several mechanisms have been proposed. As

is well known, patients with sepsis have a high incidence of delirium, and in these patients, nitric oxide is released into the bloodstream due to ischemia-reperfusion stimulation. Nitric oxide is converted into Met-Hb and nitrates; as a result, the concentration of Met-Hb in the blood is a useful marker for the onset of sepsis or septic shock (14). However, the molecular mechanisms by which Met-Hb causes delirium in patients with sepsis remain largely unknown (15). In patients with severe conditions, such as trauma or infection, intracellular hemolysis may occur, leading to anemia. Anemia, which develops relatively early in severe conditions, is thought to result from damaged red blood cells processed by the reticuloendothelial system. Acute hemolysis leads to an increase in free Hb in the blood. Subsequently, free Hb and heme are released into the circulatory system, and the wound interstitium is rapidly converted into Met-Hb by oxidants. The increase in Met-Hb levels is more pronounced in the ischemia-reperfusion areas, where activated macrophages and neutrophils accumulate (16). Therefore, Met-Hb produced by ischemia-reperfusion injury and hemolysis, as seen in severe conditions like sepsis, may affect leukocyte cell adhesion, phagocytic ability, and metabolic activation and may be involved in ICU delirium. Previous research has shown a stronger correlation among the total amount of Hb (17, 18), red blood cell count (19), and delirium. Thus, Hb and Met-Hb levels in blood are important factors influencing delirium.

The Impact of Decreased Urine Output on Delirium Risk in ICU Patients with Burns: Insights from SHAP Analysis

Using SHAP analysis, we identified that a decreased daily urine output within 24 h of ICU admission is a risk factor for ICU delirium in patients with burns. Interestingly, daily urine output was identified as an important risk factor in all ten machine learning models. The finding that a decrease in 24 h urine volume is a risk factor for delirium in patients with burns seems reasonable, considering that acute kidney injury can potentially increase the risk of delirium in critically ill patients by tenfold (20). For example, urine output is an important indicator of renal function and hydration status. In patients with burns, a decrease in urine output may indicate insufficient renal perfusion or dehydration. Both factors contribute to the development of delirium (21). Furthermore, patients with burns often require multiple medications, such as sedatives and analgesics. Decreased urine output can affect the metabolism and excretion of these drugs, potentially leading to the accumulation of psychoactive substances that can induce or exacerbate delirium (22). Additionally, a decrease in urine output can lead to electrolyte imbalance, which is known to cause neurological dysfunction and delirium. Electrolyte abnormalities, such as hyponatremia or hypernatremia, can occur in patients with burns because of fluid shifts and inadequate fluid replacement (23).

Leukocyte Biomarkers as Indicators of Delirium in ICU Patients with Burns: The Role of Inflammatory Response

Our study identified the number or proportion of neutrophils and monocytes in the leukocyte fraction as risk factors for delirium development. This suggests that exposure of leukocytes to a cytokine storm due to excessive stress from burns contributes to delirium in patients with burns. Numerous studies have used leukocyte biomarkers to diagnose delirium in the past (24). Inflammatory biomarkers and brain-specific metabolic biomarkers have been extensively studied in delirium, and inflammatory cytokines and activation markers of astrocytes and glial cells (IL-6, IL-8, IL-10, tumor necrosis factor-α, C-reactive protein, and S-100β levels) positively correlate with longer duration of delirium, severity of delirium, and higher in-hospital mortality (25). Additionally, elevated levels of IL-8 and S-100β have been associated with increased mortality in patients with delirium (26). In a mouse model with delirium, the infiltration of bone marrow-derived monocytes into the blood-brain barrier (27) and activation of microglia were observed (28). Although the number and proportion of neutrophils and monocytes were identified as risk factors for ICU delirium, these leukocytes may be involved in the production of inflammatory cytokines and contribute to the onset of ICU delirium.

Respiratory Rate as a Predictor of ICU Delirium in Patients with Burns: New Insights and Implications

In our study, an increase in the respiratory rate was a risk factor for ICU delirium. To our knowledge, no studies have clearly established a link between delirium and respiratory rate. Delirium is generally recognized as a common complication in patients with respiratory failure in the ICU. The incidence of delirium in the ICU ranges from 10% to 78%, with most cases occurring in patients receiving mechanical ventilation. This suggests a significant overlap between respiratory complications and the occurrence of delirium; however, a direct correlation between an increase in respiratory rate and delirium has not been explicitly stated (29). Inhalation injuries occur in approximately one-third of burn hospital admissions and contribute to a high mortality rate (50%) in patients with burns. Therefore, an increase in the respiratory rate may be associated with carbon monoxide poisoning and chemical tracheobronchitis due to the inhalation of toxic combustion products and generally correlates with a higher mortality rate. Unfortunately, many patients with burns receive high-concentration oxygen therapy from emergency teams before being transported to the ICU or emergency room. Therefore, carboxyhemoglobin levels are often adjusted to lower levels, and PaO_2 is frequently high during treatment, which is why carboxyhemoglobin and PaO_2 were not identified as risk factors in our model. Therefore, it might be appropriate to consider respiratory rate as a potential risk factor for ICU delirium in future studies (30, 31).

Advancing ICU Delirium Research: The PRE-DELIRIC Model and the Need for Machine Learning Approaches in Patients with Burns

In the field of delirium research, the PRE-DELIRIC model is considered a seminal study (32). In the ICU, the PRE-DELIRIC model utilizes ten identified risk factors (age, APACHE-II score, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, blood urea nitrogen, and emergency admission) and predicts delirium with an AUC of 0.87 (95% confidence interval 0.85–0.89) within 24 h of ICU admission (32). Furthermore, Lanzhou et al.'s model heavily relies on patients' detailed past medical histories, making data collection challenging in busy clinical settings such as emergency rooms (ERs) and intensive care units (ICUs), where obtaining comprehensive patient histories, diagnoses, and treatments can be difficult (33). Therefore, it is crucial to establish machine learning models that can accurately predict conditions with multifactorial risk factors, such as ICU delirium, using data that are easily obtainable during emergency department visits, like vital signs and blood data. Despite this need, a delirium prediction model for ICU patients with burns utilizing machine learning has not yet been developed. Predictive models for diseases like ICU delirium, which involve numerous risk factors, stand to benefit significantly from machine learning's capability to perform multifactorial analyses, surpassing traditional biostatistical methods. Our proposed machine learning model can more effectively evaluate complex interactions among multivariate data, which is essential for accurately predicting conditions with multifactorial risk factors like ICU delirium. Therefore, although our study had a small number of cases, it is considered valuable for the development of a machine learning-based ICU delirium prediction model and the identification of risk factors.

Comprehensive Model Evaluation for ICU Delirium

When evaluating the performance of different models, it is important to consider not only the AUC but also other metrics, such as accuracy, precision, recall, and F1 score. In a specialized medical environment, such as the ICU, some metrics may become more important than others when dealing with specific diseases. For example, precision is important if avoiding false detections of delirium is crucial. Conversely, if it is vital to avoid missing cases of delirium, recall should be emphasized. In our study, we considered all these metrics comprehensively and selected the model that best suited the objectives of the research and clinical demands.

Comprehensive Model Evaluation for ICU Delirium

WHO Definition and Diagnostic Criteria for Delirium

According to the current International Classification of Diseases (ICD) definition by the World Health Organization (WHO), delirium is classified under F05 and is diagnosed when certain psychiatric symptoms occur due to the influence of some medical or neurological condition [34]. The diagnostic criteria include the following five points:

1. **Disturbance of consciousness:** Reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
2. **Cognitive change:** A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
3. **Psychomotor disturbances:** Hyperactive or hypoactive psychomotor activity, disturbance of the sleep-wake cycle, and emotional disturbances.
4. **Acute onset and fluctuating course:** Symptoms develop over a short period (usually hours to days) and tend to fluctuate during the course of the day.
5. **Evidence of an underlying physical cause:** There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition, substance intoxication or withdrawal, or multiple etiologies.

Current Status and Issues in the Diagnosis of Delirium According to ICD-10

As described in ICD-10, the symptoms of delirium can fluctuate. For instance, a patient who is assessed as not having delirium at the bedside in the morning may be diagnosed with delirium a few hours later when they become agitated. Therefore, there is a question of whether a single short-term assessment is sufficient to diagnose delirium if the patient does not exhibit inattention or cognitive impairment at that moment. It is effective to use screening tools administered several times a day, such as the ICDSC and CAM-ICU, for diagnosing and screening for delirium. Additionally, ICD-10 does not allow for the grading of the severity of delirium. In the ICU, it is important to allocate an appropriate number of staff based on the severity of the condition. The common ICU delirium screening tests used, such as the ICDSC and CAM-ICU, include assessments of severity and are thus useful diagnostic tools for the appropriate management of ICU delirium.

Strengths

Clinical Interpretability and Applicability of the Predictive Model

The explanatory variables in our study were based on blood data collected immediately upon the arrival of patients with burns at the emergency outpatient clinic. Therefore, there was a time lag between the time of collection of these data and those collected at the time of delirium diagnosis using the ICDSC. However, we believe that our model, which accurately predicts the development of delirium during an ICU stay based on blood data and vital signs at the time of patient arrival, can be easily interpreted by clinicians and has high general applicability. This allows clinicians to predict the incidence of ICU delirium, which significantly affects the prognosis of severe burns, from early in the patient's hospitalization, enabling the initiation of early interventions for patients at high risk of ICU delirium.

Limitations

Demerit of Binary Classification for Delirium

A binary classification model was employed for predicting delirium, which simplified the model's output to either "delirium present" or "delirium absent." This approach facilitated decision-making in clinical settings by providing clear, binary outcomes. Conversely, using a regression model would require predicting specific ICDSC scores and interpreting these scores to assess patient status. Thus, binary classification often offers greater practicality in busy clinical environments due to its straightforward interpretation. However, regression analysis may be more appropriate for predicting continuous outcomes, such as the ICDSC score. This method offers detailed information by producing continuous values, allowing for a nuanced understanding of the severity of ICU delirium, ranging from mild to severe. For instance, the difference in delirium between an ICDSC score of 3 and 4 might be minimal, whereas the difference between scores of 1 and 7 indicates substantially different symptoms. Therefore, future research should investigate the benefits of developing regression models that predict ICDSC scores.

Model Selection Criteria for Small Datasets

This study examined delirium in critically ill patients with burns admitted to the ICU and did not include patients with missing data, resulting in a small number of cases. In analyses with small datasets, such as in our 82 cases, it is generally recommended to avoid overfitting and choose a simpler model. In this study, we were cautious about using complex models (such as deep neural networks or RFs with many trees) that are prone to overfitting with limited data. Therefore, simple models are generally recommended for studies with few cases. Typically, models with regularization effects (such as LR) are effective in preventing overfitting. In our study, LR demonstrated a high accuracy (0.824), indicating that overfitting was well controlled during model creation. Linear SVMs have also been proposed to prevent overfitting. Additionally, LDA has linear boundaries, is computationally fast, and can sometimes provide relatively stable results even with a small amount of data. In our study, both SVM and decision tree recorded a precision of 0.71 and an F1 score of 0.67, showing relatively balanced performance, and were considered useful for studies dealing with small datasets.

Limitations and Future Directions for External Validation

The performance of our model was discussed using data from patients in the ICU in a single hospital; however, an external validation was not conducted. Therefore, our study is limited by its single institution setting. Future research could strengthen the reliability of our delirium prediction model for patients with burns in the ICU by conducting external validation using datasets from other hospitals.

Enhancing Predictive Power: Inclusion of Diverse Variables

Seventy variables of patients' vital signs and blood data were included as explanatory variables in the machine learning model. However, other factors were not included in the PRE-DELIRIC model, such as medication history or environmental factors. Including a more diverse set of variables in the future could improve the predictive power of the model.

Generalizability to Other Patient Populations

This study focuses on patients with burns admitted to the ICU. However, it is unclear to what extent these results can be generalized to other patient populations, particularly those with different medical conditions and treatment protocols. Future research should evaluate the applicability of the model to patients with other conditions and in different ICU environments.

Temporal Data Considerations

In this study, the predictive model was constructed using data collected only at the time of ICU admission. Changes in data were not accounted for over time (e.g., variations in vital signs and blood data after admission). Models that consider the temporal dynamics of data may further enhance the accuracy of delirium predictions.

Potential Bias from Retrospective Data

This study is a retrospective observational study, and there may be biases in data collection. For instance, the diagnosis of delirium might depend on the clinical experience and judgment of individual physicians. Future studies should aim to minimize such biases and enhance the reliability of results through prospective study designs.

Impact of Intervention Variability

This study does not account for the extent to which differences in treatment interventions (e.g., different medications or treatment protocols) among patients might affect the model's predictions. Assessing the impact of varying interventions on the occurrence of delirium is crucial for developing a more comprehensive predictive model.

Conclusion

Future Clinical and Research Implications of Machine Learning Models

Our machine learning model, utilizing vital signs and blood test data at ICU admission, was able to predict the onset of delirium in patients with burns after ICU admission. Adopting this model can facilitate the early diagnosis of ICU delirium for emergency room and ICU physicians. Additionally, by identifying patients at high risk for ICU delirium, the model may assist in tailoring preventive and therapeutic measures. Future plans include making the model available online, potentially enabling its use for predicting ICU delirium in other hospitals.

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Author Contributions

Ryo Esumi and Eiji Kawamoto were primarily responsible for the manuscript preparation and drafting of the original text. Motomu Shimaoka oversaw the overall direction and planning of the research. The other co-authors, Ryota Sakamoto, Asami Ito-Masui, Fumito Okuno, Toru Shinkai, Atsuya Hane, Kaoru Ikejiri, Yuichi Akama, Hiroki Funao, Arong Gaowa, Eun Jeong Park, Ryo Momosaki, and Ryuji Kaku, provided supervision and were instrumental in shaping the research, analysis, and manuscript refinement.

Data availability statement

To access the raw data underpinning the conclusions presented in this manuscript, please direct inquiries to the corresponding author.

Conflicts of Interest

None declared.

Abbreviations

AUC	Area under each curve
CAM	Confusion Assessment Method
ER	Emergency rooms
GBM	Gradient boosting machine
ICD	International Classification of Diseases
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
LDA	Linear discriminant analysis
LR	Logistic regression
PRIDE	Prediction of intensive care unit delirium
RF	Random forest
SVM	Support vector machine
WHO	World Health Organization

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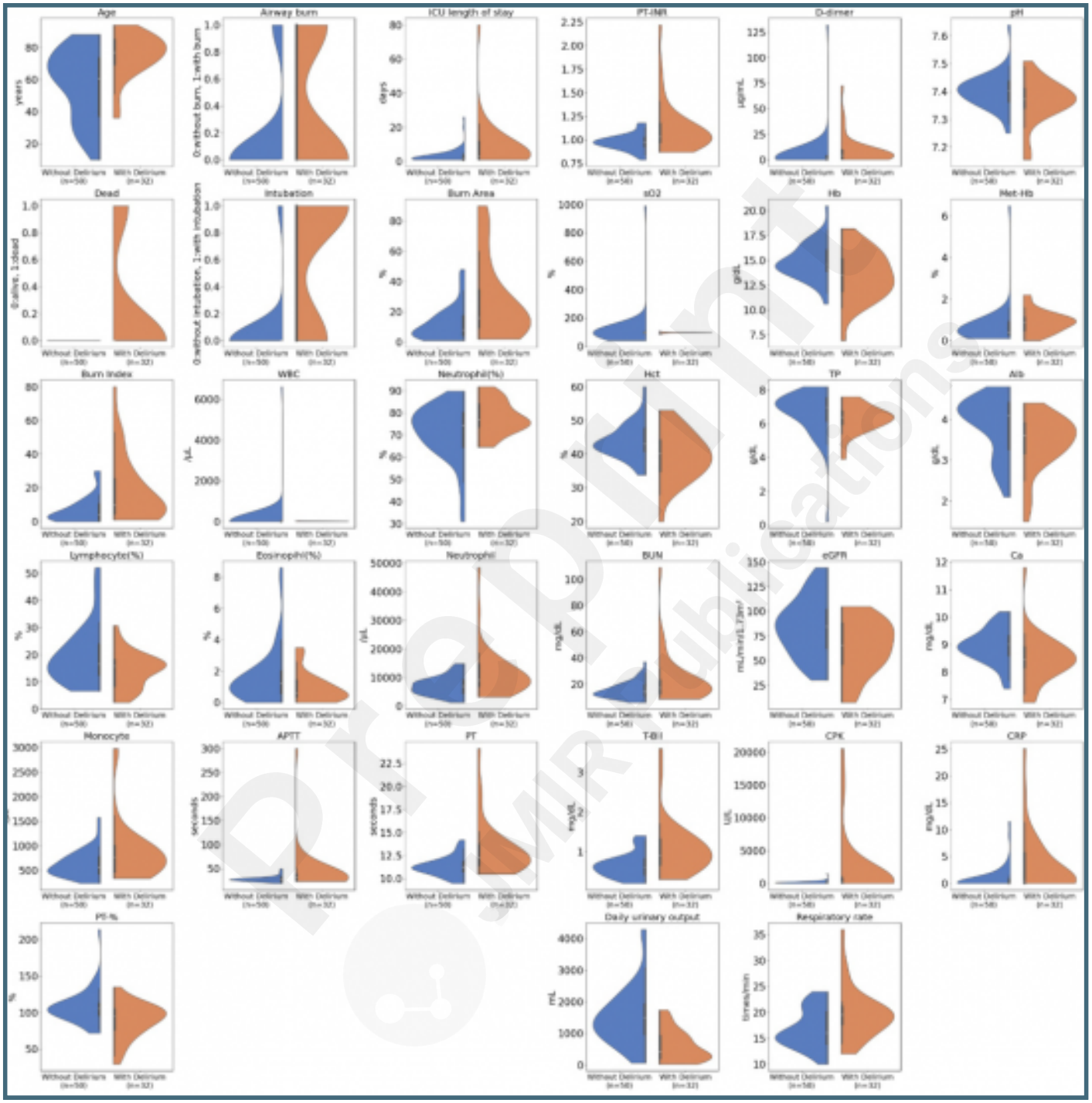
Figure legends

Figure 1. Comparison of explanatory factors. Characteristics of patients with delirium in the ICU in a violin plot show the importance of each feature in two groups: ICU delirium absent (without delirium) and ICU delirium present (with delirium).
Figure 2. Accuracy of ICU delirium prediction in patients with burns using ten different machine learning models.
Figure 3. Importance of the top 15 explanatory factors identified by each model.

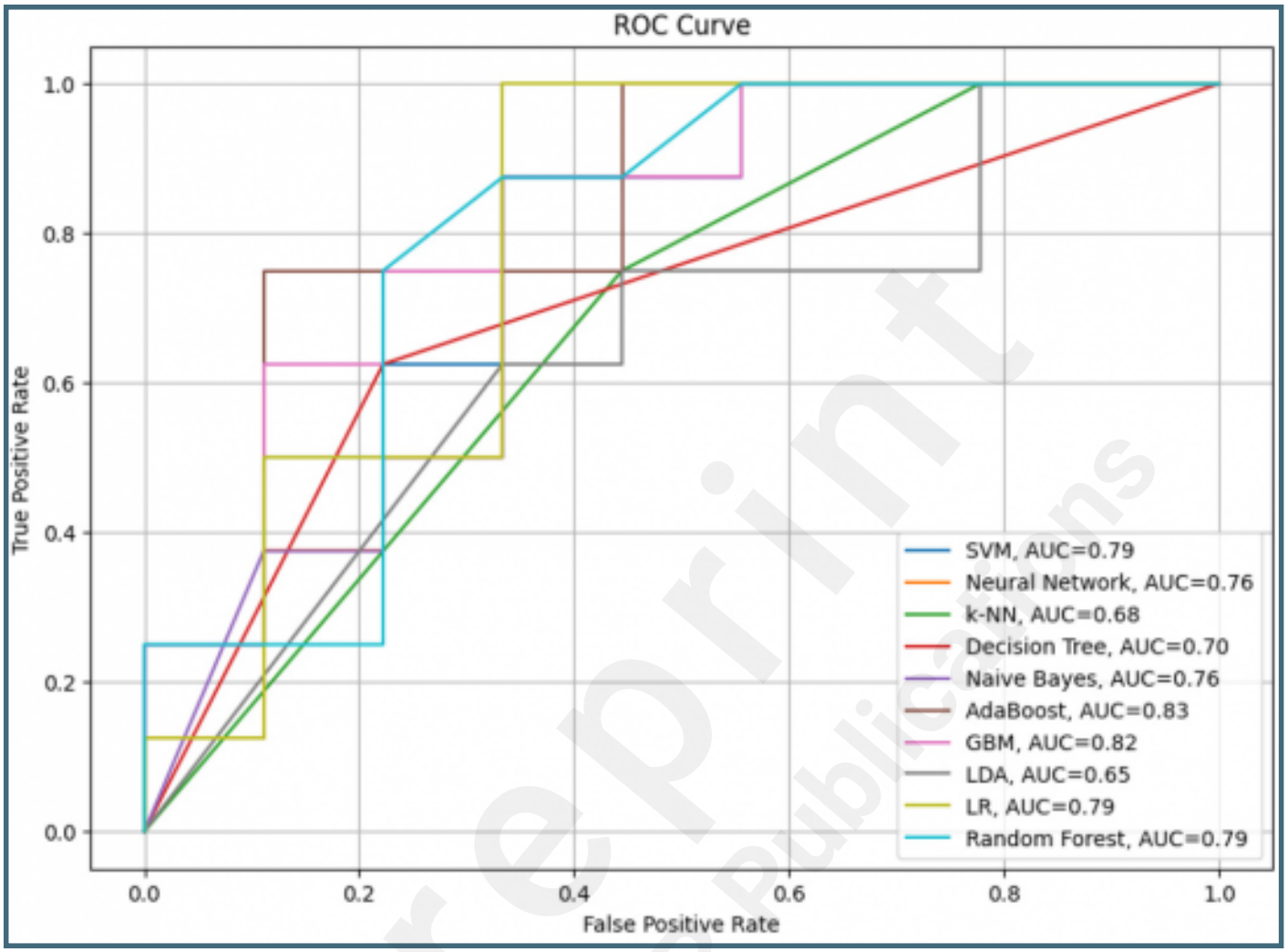
Supplementary Files

Figures

Comparison of explanatory factors. Characteristics of patients with delirium in the ICU in a violin plot show the importance of each feature in two groups: ICU delirium absent (without delirium) and ICU delirium present (with delirium).



Accuracy of ICU delirium prediction in patients with burns using ten different machine learning models.



Importance of the top 15 explanatory factors identified by each model.