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ORIGINAL RESEARCH

Machine Learning-Based Prognostic Prediction Models in Calcium Channel Blockers Poisoning

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Abstract: **Introduction:** Calcium channel blocker (CCB) poisoning is a critical toxicological emergency that can result in severe complications, particularly cardiovascular effects. This study aimed to evaluate the accuracy of Machine learning (ML) models in predicting the outcomes of CCB poisoning. **Methods:** This retrospective cross-sectional study analyzed the medical records of patients diagnosed with CCB poisoning at Loghman Hakim Hospital between 2019 and 2024. The accuracy of machine learning (ML) models in predicting the outcomes of CCB poisoning and identifying its predictive factors was evaluated. Various ML models, including XGBoost, CatBoost, Random Forest, and AdaBoost, were trained on clinical and laboratory data. Then, feature selection was performed to identify the most relevant variables. The hold-out set was randomly selected to avoid selection bias. Model performance was assessed using accuracy, precision, recall, F1-score, and macro-averaged area under the receiver operating characteristic (ROC) curve (AUC).

Results: 274 CCB poisoning cases with the mean age of 31.99± 17.47 (range: 1.5 to 89) years were evaluated (70.4% female). Feature selection identified 18 key prognostic factors, including body temperature, whole bowel irrigation, need for cardiology consultation, arterial oxygen saturation, Glasgow coma scale (GCS)-eye response, electrocardiography (ECG) findings, serum level of alkaline phosphatase (ALP), pH-venous blood gas (VBG), HCO3-VBG, serum level of lactate dehydrogenase (LDH), blood sugar, pulse rate, fraction of inspired oxygen (FiO2), time elapsed from ingestion to admission, troponin, serum level of alanine aminotransferase (ALT), serum level of creatinine, and serum level of potassium. Among the ML models, XGBoost and CatBoost demonstrated the highest predictive performance, with macro-averaged AUC values of 0.9899 (95%confidence interval (CI): 0.98-0.99) and 0.9983 (95%CI: 0.997-0.999), respectively. These models outperformed traditional statistical approaches, providing enhanced risk stratification for patients with CCB poisoning. **Conclusion:** This study highlights the potential of ML-based models for predicting outcomes in CCB poisoning, offering a data-driven framework for early risk stratification. The superior performance of XGBoost and CatBoost suggests their clinical applicability. Future research should focus on external validation in multi-center settings and real-time integration into clinical decision-making systems.

Keywords: Calcium channel blockers; Poisoning; Prognosis; Machine learning

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1. Introduction

Since 1970, calcium channel blockers (CCBs) have been broadly utilized for various medical conditions. Up to now, this class of drugs has been used in the treatment of hypertension, coronary artery disease, stable angina, supraventricular tachyarrhythmias, post-intracranial hemorrhage-associated vasospasm, and migraine headaches (1, 2).

Regardless of their widespread use and the associated risk of accidental toxicity within the therapeutic range, this class

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of cardiovascular drugs has significantly contributed to both intentional ingestion for suicide and unintentional ingestion in children. Such incidents frequently lead to fatal outcomes, primarily due to cardiovascular failure (1-3). CCBs are among the top 10 most common pharmaceutical causes of poisoning-related mortality (4). The severity of the symptoms associated with CCB overdose depends on dose and formulation, co-ingestion with other medications, the patient's age, and comorbidities. Symptoms may vary from nausea and vomiting, dizziness, and fatigue to syncope, loss of consciseness, coma, and sudden death (2).

In 2022, the National Poison Data System (NPDS) from America's Poison Centers documented 2,483,183 total encounters, which included 15,718 cases of poisoning caused solely by calcium antagonists. Of these instances, 29 cases resulted in death, and 101 cases revealed severe outcomes (4). In a regional context, a retrospective review of 70 cardiovascular drug poisoning cases from Razi Hospital in Ahvaz (2005–2009) showed that 10% (7 cases) involved CCBs as the second leading cause of cardiovascular drug poisoning (5). However, to our knowledge, no study in Iran has specifically examined prognostic prediction in CCB poisoning.

Nowadays, Artificial intelligence (AI) and its subfields, including machine learning (ML), have emerged as powerful and highly reliable tools for predictive analytics. ML has demonstrated its value in medicine by effectively analyzing datasets to deliver precise predictions regarding patient survival and overall outcomes (6). The rising utility of AI in toxicology is due to its bottom-up approach, which does not rely on predefined models. This flexibility allows AI systems to evaluate a wider range of complex factors and their interrelationships, resulting in more accurate predictions of outcomes and prognoses compared to traditional methods. Indeed, machine learning models achieve higher c-indices than conventional statistical approaches, underlining their superior predictive performance (7).

Recent advancements highlight AI applications in toxicology. The machine learning models performed best, predicting the severity of organophosphate poisoning (8, 9). Deep learning models have been utilized to identify causative agents in acute poisoning (10). A decision tree algorithm has been used to predict the outcome of RSTI (Repeated Self-Induced Toxic Injury (exposure to acetaminophen (11). Random Forest and Light Gradient Boosting Machine (LGBM) models have been employed to predict the prognosis of patients with diphenhydramine exposure (12). Similarly, XGBoost and LGBM algorithms have shown success in forecasting outcomes for patients with methadone poisoning (13).

Considering the growing incidence of CCB poisoning and the lack of an effective predictive framework, the current study aims to identify the most impactful variables in CCB poisoning and improve the accuracy and reliability of outcome predictions in critical cases by achieving an advanced predictive model via AI. To the best of our knowledge, our work represents the first machine learning–based attempt to address this gap.

2. Methods

2.1. Study design and setting

This retrospective cross-sectional study followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and was done at Loghman Hakim Hospital utilizing patient's medical record data from 2019 to 2024. Loghman Hakim Hospital is one of the busiest poison control centers in the world and is the referral center for poisoning in Tehran, Iran.

Several machine learning (ML) algorithms were carried out to provide an accurate and efficient prediction model for the outcome of calcium canal blocker poisoning. The study was structured as follows: 1-Data collection and preparing dataset, 2- data preprocessing, 3- feature selection, 4- cross-validation and hyperparameter tuning, 5- choosing the best model, and 6- evaluation (Figure 1).

The ethics committee of Shahid Beheshti University of Medical Sciences approved the study (IR.SBMU.RETECH.REC.1402.648). All methods were performed in accordance with the relevant guidelines and regulations by ethics committee of Shahid Beheshti University of Medical Sciences. Informed consent was obtained from all patients upon their arrival. For participants who were unable to provide consent personally, informed consent was acquired from their families or legal representatives. The consent process at our institutions also included permission for potential future retrospective studies.

2.2. Participants

Medical records of patients diagnosed with CCB poisoning at Loghman Hakim Hospital between 2019 and 2024 were evaluated, with no restriction on age or sex. Exclusion criteria were as follows: incomplete medical records, multiple drug toxicity, comorbid conditions (such as malignancy, chronic kidney disease, cardiovascular disorders, chronic liver disorders, hypertension, chronic obstructive pulmonary disorders, diabetes, neurological disorders, etc.), and referrals of patients who had already received treatment prior to admission. Patients who were transferred from other centers and those with repeat admissions were excluded in order to minimize sampling bias.

2.3. Data collection

Four individual researchers reviewed the patient's medical records. A pre-designed questionnaire was used to gather data from electronic databases of Loghman Hakim Hospital (Sabara and Shafa databases). The questionnaire included data on age, sex, underlying disease, type of CCBs medication used, time elapsed from exposure to admission into the hospital, patient's outcome, duration of hospitalization, admission to the intensive care unit, tracheal intubation, vital signs at admission, electrocardiography (ECG) findings, and

laboratory reports including blood sugar level, liver function tests (LFTs), arterial blood gas (ABG), serum level of sodium, potassium, creatinine, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH).

In this study, the diagnosis of calcium channel blocker poisoning was established based on the reported history of exposure to calcium channel blockers, alongside the manifestation of clinical symptoms including nausea, vomiting, altered mental status, hypotension, sinus bradycardia, atrioventricular block (evidenced by a prolonged PR interval), or cardiogenic shock, as documented in the patient's medical records.

2.4. Technology and tools

In this study, the Python programming language (version 3.11.5) and associated libraries were used. Libraries such as Matplotlib, NumPy, Seaborn, and Pandas were employed for data analysis and visualization purposes. The scikit-learn library was utilized to create algorithms and evaluate machine learning models. The CatBoost Classifier, KNN, Random Forest Classifier, HistGradiant Classifier, AdaBoost Classifier, XGBoost Classifier, and ExtraTree Classifier libraries were utilized for analysis. Additionally, the XGBoostClassifier library was employed within the Jupyter Notebook environment for feature importance evaluation and the feature selection phase. For calculating statistical analyses, the study utilized the Statistical Package for Social Sciences (SPSS) version 26.

2.5. Data preprocessing

Data preprocessing is an important component of any machine learning project, as it enhances the quality and utility of the collected data. In this study, several preprocessing techniques were applied to the dataset, including an oversampling method for data balancing before splitting data into train and test sections, the k-Nearest Neighbors (KNN) interpolation method (with n_neighbors = 5) for imputing missing values, and the removal of rows with more than 50% missing data. Over-sampling was employed to address class imbalances by increasing the number of instances from underrepresented groups, thereby creating a more balanced dataset and improving the accuracy of predictive models before splitting data into train and test sections, and the train and test data overall percentage, before and after oversampling were mentioned (Table 1). Additionally, since the final outcomes of patients who were discharged against medical advice were not definitively known, these cases were interpolated using the KNN method (n_neighbors = 5) and based on their overall characteristics reassigned to one of three outcome categories: death (label = 0), discharge with sequelae (label = 1), or discharge without sequelae (label = 2). Furthermore, the Standard Scaler was utilized to normalize the data distribution, ensuring that all values were scaled within a consistent range, thereby facilitating more effective analysis and comparison. Finally, predictive models were developed to estimate the probability of each of the three outcomes.

2.6. Feature selection

Feature selection process in machine learning models is an essential step. This approach eliminates irrelevant features, which improves model performance by reducing dimensionality. A dataset containing 48 variables related to patients poisoned with CCBs was assembled. Variables and clinical characteristics recorded on the first day of admission were primarily considered for the predictive models. Consequently, we excluded variables that were not consistently available at admission, such as insulin, glucagon, and calcium administration, intensive care unit (ICU) admission, intubation, and duration of hospitalization. An exception was made for bowel irrigation, which was included due to its significant prognostic value. Furthermore, features with over 50% missing data were omitted from the machine learning analysis. Finally, a total of 39 variables were included for feature selection. In this study the most important and efficient features for predicting the prognosis of CCBs poisoning were selected using XGBoost classifier. The XGBoost as a powerful gradient boosting classifier, provides built-in feature importance scores that can be used for feature selection.

2.7. Statistical analysis

A total of 48 variables related to patients poisoned with CCBs were analyzed. Each variable was classified as either continuous data or categorized into binary or multiple levels for descriptive and statistical evaluation. The Shapiro-Wilk test indicated that all continuous variables were non-normally distributed. Consequently, continuous variables were summarized using medians and interquartile ranges (IQRs), and comparisons among study groups were conducted using the Kruskal-Wallis test. Categorical variables were presented as frequencies and percentages, with group distributions analyzed using the chi-square test. All p-values were two-tailed, and statistical significance was defined as $p < 0.05$. Data analysis was performed using SPSS version 26.0.

2.8. Model development and performance evaluation

Several machine learning algorithms were employed to predict the outcome of CCB-poisoned patients including the Adaboost Classifier, RandomForest Classifier, HistGradiantBoost Classifier, ExtraTree Classifier, DecisionTree, XGBoost Classifier, and k-nearest neighbors (KNN). A ten-fold cross-validation was incorporated, and collected data was divided into a training set (70% of the data) and a test set (30% of the data). Following model development using the training data and hyperparameter tuning, the optimized algorithm was evaluated on the test dataset. Model performance was assessed using key evaluation metrics, including F1-score, macro-averaged area under the curve (AUC), accuracy, precision, and recall. The evaluation metrics for classifiers were

as follows:
1- classification accuracy: true positive (TP)+true negative (TN)/TP+TN+false positive (FP)+false negative (FN)
2- classification sensitivity: TP/TP+FN
3- classification specificity: TN/TN+FP
4- classification error: FP+FN/FP+FN+TP+TN
5- f-measure: 2precision sensitivity/precision + sensitivity

3. Results

3.1. Patient characteristics

During the study period from 2019 to 2024, a total of 296 patients diagnosed with calcium channel blocker (CCB) poisoning had their data recorded in Loghman Hakim Hospital's electronic database. Of these, 22 cases were excluded due to the aforementioned exclusion criteria. Eventually, 274 cases were included in the study and categorized into four groups: patients discharged without sequelae (n=244), patients discharged against medical advice (n=21), patients discharged with sequelae (n=3), and patients who died due to CCB poisoning (n=6). The patient selection process is depicted in Figure 2. The investigation included individuals aged 1.5 to 89 years who were referred to the hospital emergency department 0.5 to 48 hours after CCBs poisoning. The average age of study cohort was 31.99 ± 17.47years (70.4% female). The most frequently ingested CCB was amlodipine (58.8%), followed by diltiazem (19.0%) and verapamil (19.0%).
14.6% of the patients required admission to the ICU, and 9.5% necessitated mechanical ventilation. The demographic and clinical characteristics of the patients in each study group were reported in Table 2.

3.2. Feature selection

Features' importance was computed using the XGBoost Classifier. In the feature selection process, 18 of 39 features with higher impact and efficiency were selected. Feature selection process led to more accurate prediction in most models. The feature importance score is computed based on the model's gradient boosting process, helping identify the most significant variables. The top eighteen features selected by the feature selection methodology in order of their importance are as follows: body temperature, whole bowel irrigation, need for cardiology consultation, arterial oxygen saturation, Glasgow coma scale (GCS)-eye, ECG findings, serum level of ALP, pH-venous blood gas (VBG), HCO3-VBG, serum level of LDH, blood sugar, pulse rate, fraction of inspired oxygen (FiO2), time elapsed from ingestion to admission, troponin, serum level of alanine aminotransferase (ALT), serum level of Creatinine, serum level of potassium (Figure 3).

3.3. Hyperparameter tuning

Hyperparameter tuning is an essential step in optimizing machine learning algorithms as it significantly enhances model performance. This process improves the evaluation results by identifying the most effective parameters. Grid search with 10-fold cross-validation and iterative decision-making are fundamental to achieving a precise and robust model. The optimal hyperparameters for the XGBoost, Hist-Gradient Boosting, AdaBoost, Extra Trees, Random Forest, and CatBoost classifiers were reported.

3.4. Performance of prediction models

At first, all models were developed using 39 features, with the XGBoost Classifier showing the best performance, achieving a macro-averaged AUC of 0.98 (95%confidence interval (CI): 0.98-0.99), an F1 score of 0.98 (95%CI: 0.96-0.98), an accuracy of 0.98 (95%CI: 0.96-0.98), a precision of 0.98 (95%CI: 0.96-0.98), and a recall of 0.98 (95%CI: 0.96-0.98). To refine the models, a feature selection process was performed, narrowing the number of features down to 18 based on their importance. The models were then retrained using these selected features with optimized hyperparameters, and their performance was compared. The findings revealed that the XGboost and CATBoost Classifiers were the most effective in predicting patient outcomes for CCB poisoning. The performance metrics for the XGBoost classifier were as follows: an accuracy of 0.96 (95%CI: 0.96-0.97), an F1-Score of 0.96 (95%CI: 0.96-0.97), a macro-averaged AUC of 0.989 (95%CI: 0.98-0.99), a precision of 0.96 (95%CI: 0.96-0.98), and a recall of 0.96 (95%CI: 0.96-0.97). In comparison, the CATBoost classifier exhibited performance metrics of an accuracy of 0.96 (95%CI: 0.96-0.98), an F1 score of 0.96 (95%CI: 0.96-0.97), a macro-averaged AUC of 0.998 (0.997-0.999), a precision of 0.96 (95%CI: 0.96-0.98), and a recall of 0.96 (95%CI: 0.90-0.96). Detailed performance metrics for all classifiers are reported in Tables 3 and 4. Additionally, Figures 4 and 5 illustrate the confusion matrices for the XGBoost and CatBoost Classifiers, using the 18 selected features across both the training and testing datasets. Moreover, Figures 6 and 7 present the receiver operating characteristic (ROC) curves for these two models, comparing their performance before and after feature selection.

4. Discussion

To our knowledge, this is the first study to develop and evaluate several machine learning models to predict the prognosis of patients with calcium channel blocker (CCB) poisoning. Among the models tested, gradient-boosting algorithms, specifically XGBoost and CatBoost, exhibited superior predictive performance, achieving area under the curve (AUC) values of 0.9899 and 0.9983, respectively. Feature selection techniques enhanced model efficiency by reducing dimensionality, while maintaining high predictive accuracy. These findings underscore the potential of artificial intelligence (AI)-driven approaches in toxicology, offering improved prognostic precision compared to conventional statistical models.
Machine learning techniques, particularly gradient-boosting algorithms, demonstrated exceptional performance in predicting patient outcomes (14). Boosting algorithms (e.g., XG-

Boost, LightGBM) were chosen because they have demonstrated strong performance on structured clinical datasets with relatively modest sample sizes. These ensemble methods iteratively combine weak learners to capture complex, non-linear relationships, improve predictive accuracy, and provide interpretable feature importance metrics, which are particularly valuable in toxicology research (15). These models outperform traditional statistical approaches due to their ability to capture intricate, non-linear relationships among multiple clinical variables (9, 14, 16-18). Notably, XGBoost's robust feature importance mechanism facilitates the identification of key prognostic factors, enhancing model interpretability. Furthermore, ensemble learning techniques, such as Random Forest and Extra Trees, improved prediction accuracy by reducing variance and mitigating overfitting effects (14). Our findings align with previous research suggesting that boosting-based models often outperform simpler classifiers (e.g., k-nearest neighbors and decision trees) in toxicology-related predictive tasks (8, 12, 13). While similar methodologies have been used to predict outcomes in cases of organophosphate poisoning, methadone toxicity, and diphenhydramine exposure, differences in clinical and pathophysiological profiles may limit direct comparisons to CCB poisoning, and the extent of this advantage depends on dataset features and model optimization techniques (8, 12, 13). These findings provide preliminary evidence supporting the potential generalizability of machine learning frameworks for prognosis prediction across diverse types of poisonings, though further external validation is required.

In this study, we identified 18 key predictive variables from an initial set of 39, which were crucial in determining patient prognosis. Notably, we found that fluctuations in body temperature emerged as a significant prognostic factor. Previous researches have documented the effects of various substances on thermoregulation, with ethanol, phenothiazines, and barbiturates linked to hypothermia, while amphetamines, cocaine, and monoamine oxidase inhibitors induce hyperthermia. Although previous studies have explored the effects of various substances on thermoregulation, there is a lack of direct evidence regarding the prognostic implications of CCB-induced thermoregulatory alterations. Our findings suggest a potential association, but further studies—preferably large-scale prospective investigations—are needed to establish a causal relationship and determine its clinical significance (19-22).

Whole-bowel irrigation (WBI) has been proposed as a decontamination strategy for sustained-release calcium channel blocker (CCB SR) overdoses, which are potentially life-threatening due to their unpredictable absorption, delayed toxicity onset, and prolonged duration of effects. The American Academy of Clinical Toxicology recommends WBI for substances that do not bind well to activated charcoal, including sustained-release medications like CCBs. However, WBI should be avoided in hemodynamically unstable patients. When performed early, before the onset of cardiovascular instability, WBI is theoretically beneficial and supported by anecdotal case reports (23-25). In our study, we found that WBI is a significant prognostic factor among patients who require it and have no contraindications for the procedure. While this predictive effect may be directly attributable to the need for WBI and its administration, it could also be influenced by confounding factors such as the patient's hemodynamic status. WBI is typically performed in hemodynamically stable patients, who generally have a better prognosis compared to those with hemodynamic instability. Therefore, further studies are essential to explore these relationships and clarify the true impact of WBI on patient outcomes.

The significance of cardiology consultation, electrocardiographic (ECG) abnormalities, and troponin elevation as predictive factors align with previous studies linking myocardial injury to increased mortality in CCB poisoning (26). Considering that cardiology consultations are typically requested in cases of necessity, such as cardiovascular collapse (27)It is reasonable to propose that requiring a consultation within 24 hours indicates severe poisoning and could be a significant predictive factor. Additionally, research has demonstrated an association between pre-extracorporeal membrane oxygenation (ECMO) cardiac arrest and increased mortality, supporting our findings (28).

Hemodynamic parameters, including the shock index (SI)—defined as heart rate divided by systolic blood pressure—have been previously identified as strong predictors of mortality, intensive care unit (ICU) admission, and hospital length of stay in CCB poisoning (29). Also, prior studies have indicated that interventions targeting hemodynamic stabilization, such as vasopressor administration, influence poisoned patients' prognosis (26). These results are consistent with our study, highlighting pulse rate as a crucial predictive factor.

Acid-base balance and renal function markers, including venous blood gas parameters (pH-VBG, HCO3-VBG) and serum creatinine levels, were associated with prognosis in our analysis. Prior research has established that severe acidosis (pH < 7.1) and the need for renal replacement therapy (RRT) before ECMO initiation are key mortality predictors, reinforcing the importance of acid-base homeostasis and renal function in CCB toxicity outcomes (28). Additionally, the impact of acute kidney injury (AKI) and multi-organ failure on prognosis has been well-documented, further supporting these findings (3).

Neurological complications have been identified as predictors of mortality among CCB-poisoned patients (28). The present study supports this finding, as the Glasgow Coma Scale (GCS), especially eye response, emerged as an important predictive factor. Prior studies have emphasized the role of high-dose insulin euglycemic therapy (HIET), electrolyte replacement, and ECMO in managing CCB poisoning (1, 3, 26, 28). These interventions target critical metabolic disturbances, such as arterial oxygen saturation,

blood glucose fluctuations, acid-base imbalances, and electrolyte shifts—all of which were among the key predictive factors identified in our study.

Liver function parameters, including serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels, were also recognized as prognostic factors in our study. While calcium channel blocker-induced liver injury is typically mild and reversible, severe cases of hepatotoxicity have been reported (30). Previous studies have further suggested that organ failure, including liver dysfunction, can serve as a prognostic indicator, lending additional support to our findings (1, 3).

The time interval between drug ingestion and hospital arrival emerged as a critical factor in the prognosis prediction of poisoning. In CCB toxicity, the optimal window for initiating life-saving interventions, including gastrointestinal decontamination, high-dose insulin therapy, and vasopressor support, is within the first few hours post-ingestion. While the importance of early intervention is well-recognized, no prior study has precisely evaluated its impact on prognosis in CCB poisoning (1, 3, 31, 32). Our study identifies this factor as one of the most significant prognostic variables, emphasizing the necessity of timely medical intervention.

5. Limitations

This study has several limitations despite its strengths. The reliance on retrospectively collected data introduces potential selection bias and missing information. Additionally, the relatively small number of fatal cases may limit the model's generalizability for mortality prediction. The study was conducted at a single center (Loghman Hakim Hospital), necessitating external validation in multi-center cohorts to ensure robustness and applicability. Furthermore, some critical interventions, such as vasopressor administration and insulin therapy, were not uniformly documented in our dataset. Vasopressor use can reduce severe hypotension and prevent cardiogenic shock in CCB poisoning, so missing this information might have caused the model to rely too heavily on other clinical features, which could affect the importance assigned to those features. Therefore, the results should be interpreted carefully, and future studies including vasopressor data may improve the model's accuracy and generalizability.

6. Conclusions

This study demonstrates the significant potential of machine learning for predicting outcomes in CCB poisoning and supports AI-assisted decision-making in toxicology. Future research should prioritize prospective validation and the integration of real-time monitoring data into electronic health records to enhance clinical applicability. By employing advanced machine learning techniques, medical toxicology can improve prognosis predictions and patient outcomes. Additionally, further studies should focus on validating these models across diverse patient populations and examining the impact of real-time data on accuracy. The advancement of machine learning holds great promise for improving patient care in toxicology and beyond.

7. Declarations

7.1. Acknowledgments

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7.2. Author contributions

B.M. and S.M.H. conceptualized the study design and supervised data collection; Data was collected by P.E., N.B.A., and A.T.; M.M. and E.H. contributed to drafting of proposal and data extracting checklist; Ma.M. and S.A.M. contributed to the analysis and development of machine learning models; M.T. and P.E.T.E. contribute to manuscript drafting; L.A. and H.T. assisted in reviewing and revising the manuscript. All authors read and approved the final version of manuscript.

7.3. Conflict of Interest

The authors declare no conflicts of interest related to this study.

7.4. Funding and Support

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7.5. Data availability

The datasets generated and/or analyzed are not publicly available owing to ethical and legal causes. Nevertheless, they can be made available from the corresponding author Babak Mostafazadeh upon reasonable request.

7.6. Use of Artificial Intelligence Chatbots

No AI-generated content was used to influence study results or conclusions.

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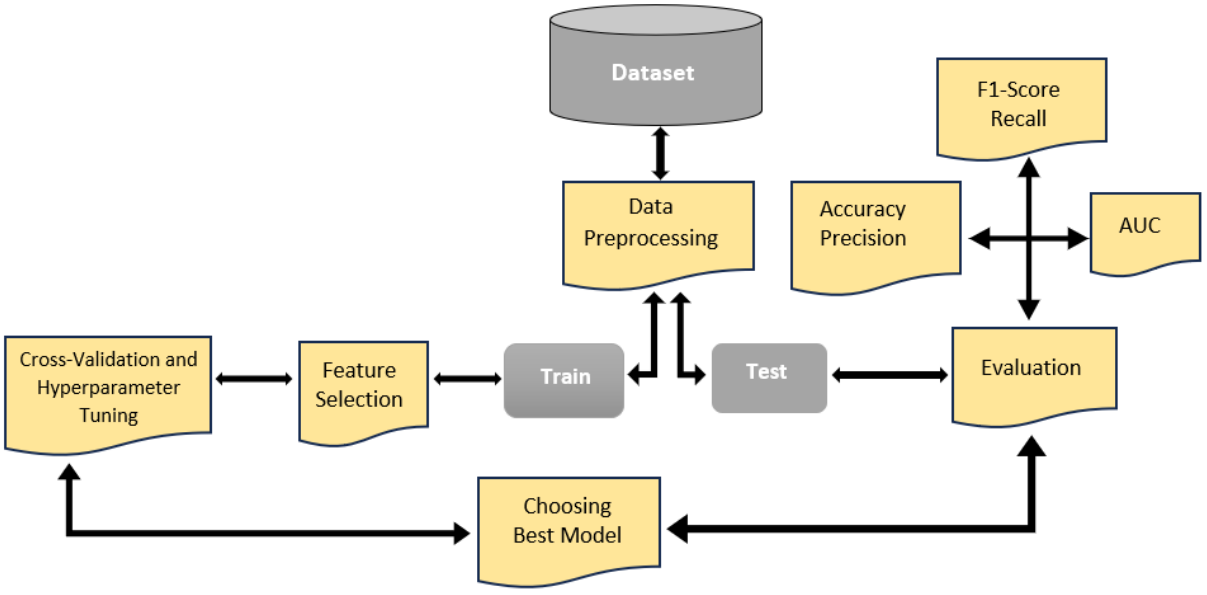

Figure 1: The schematic representation: from dataset making into algorithm evaluation. AUC: area under the curve.

Table 1: Distribution of primary (before oversampling) and secondary (after oversampling) outcome classes to have best prediction

Class type	**Oversampling (30% test, 70% train)**	
	Before	**After**
Death (0)	2.19% of all outcomes	22.13% of all outcomes
Discharge with sequelae (1)	1.09% of all outcomes	21.82% of all outcomes
Discharge without sequelae (2)	96.72% of all outcomes	56.14% of all outcomes

Figure 2: Flowchart of the patient selection process.

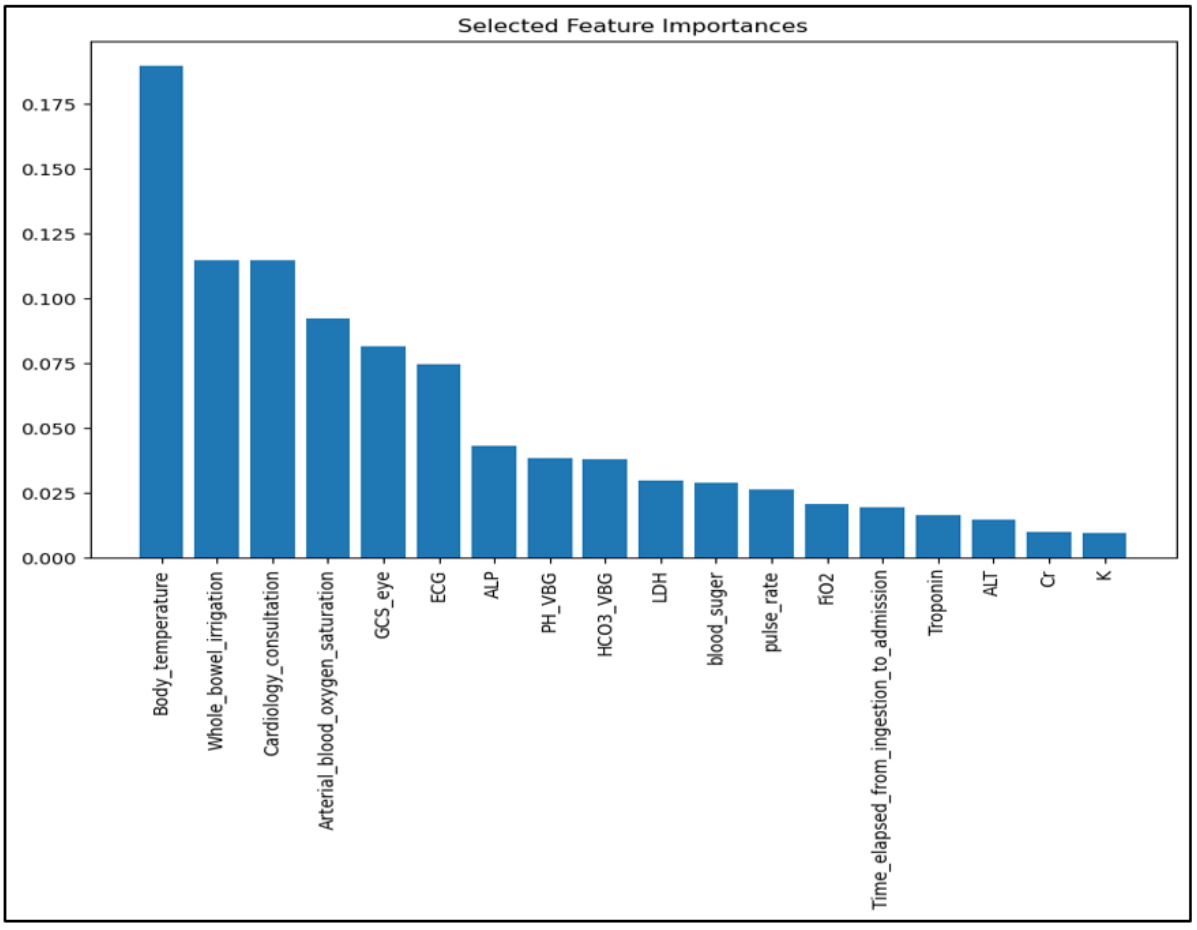

Figure 3: The eighteen top selected features ordered by their importance using XGBoost model. GCS: Glasgow Coma Scale; ECG: Electrocardiography; ALP: Alkaline phosphatase; VBG: Venous Blood Gas; LDH: Lactate Dehydrogenase; FiO2: fraction of inspired oxygen; ALT: Alanine Aminotransferase; Cr: Creatinine; K: Potassium.

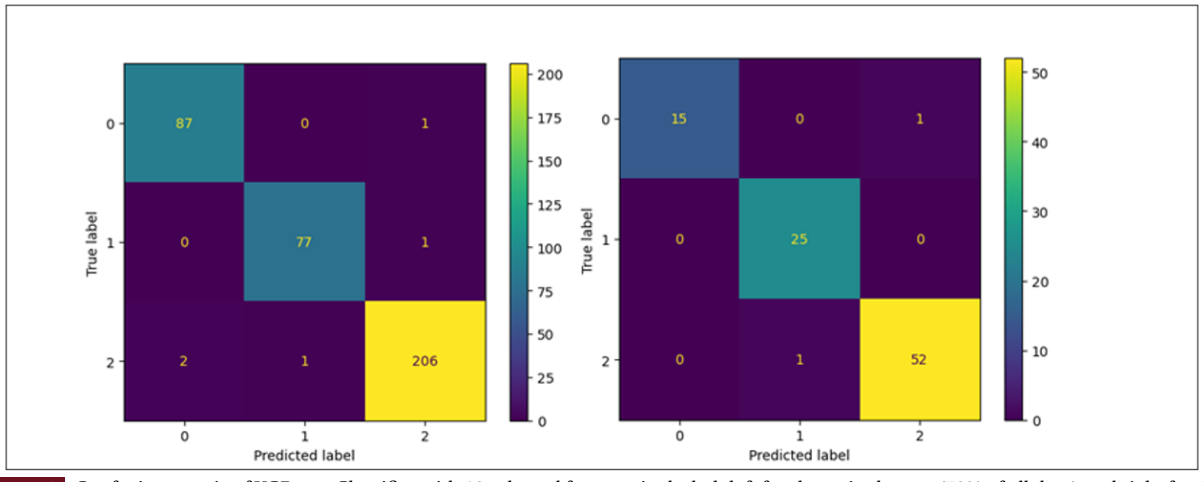

Figure 4: Confusion matrix of XGBoost Classifier with 18 selected features included: left for the train dataset (70% of all data) and right for the test dataset (30% of all data), 0= death, 1= discharge with sequelae, 2=discharge without sequelae.

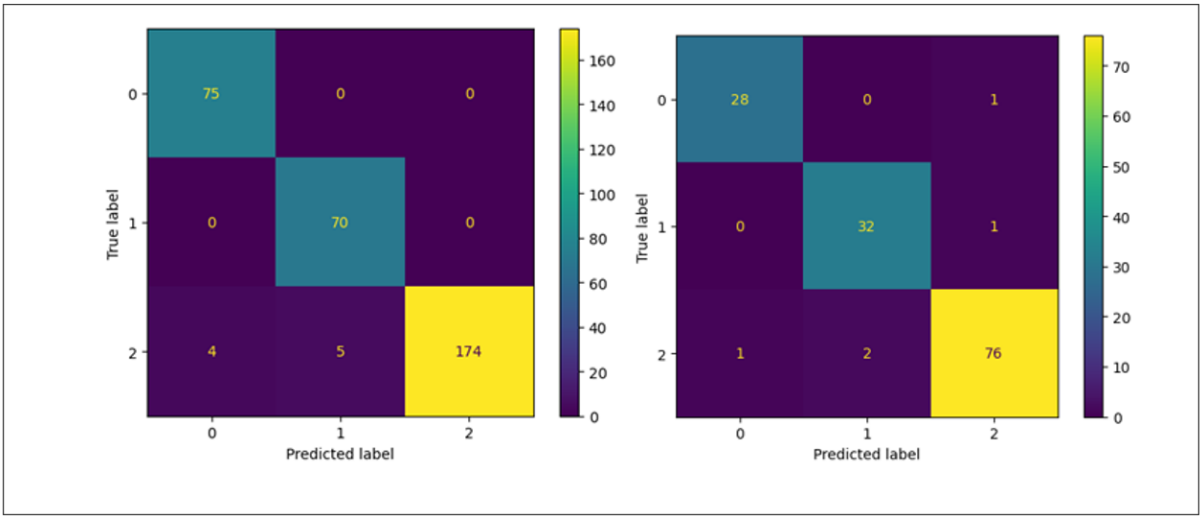

Figure 5: Confusion matrix of CatBoost Classifier with 18 selected features included: left for the train dataset (70% of all data) and right for the test dataset (30% of all data), 0= death, 1= discharge with sequelae, 2= discharge without sequelae.

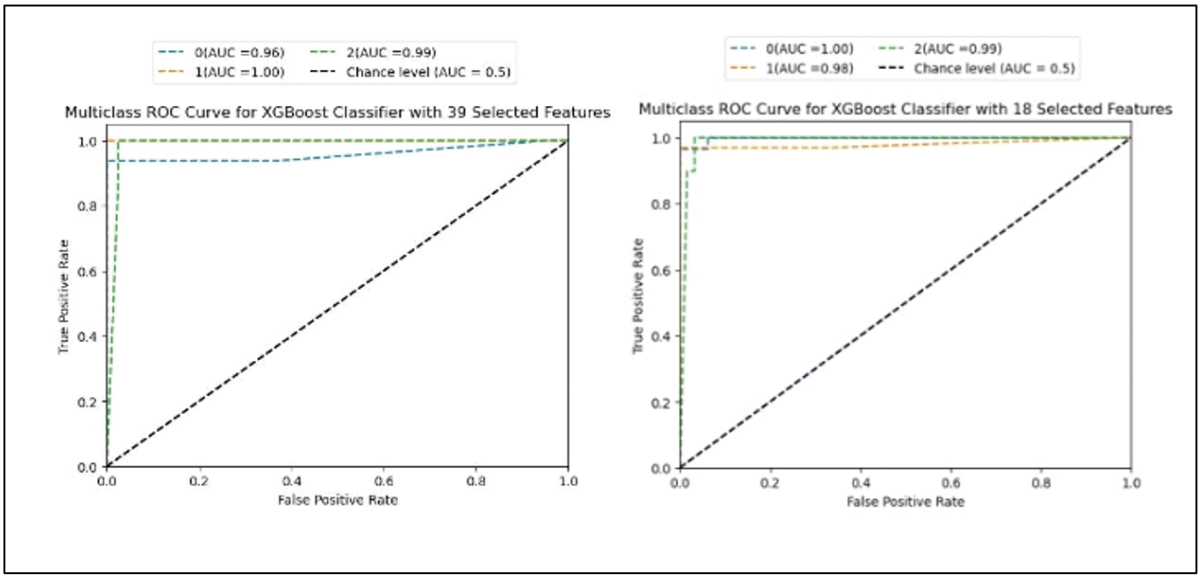

Figure 6: XGBoost Classifier receiver operating characteristic (ROC) Curve: algorithm performance comparison between 18 selected features and primary 39 features. AUC: area under the curve.

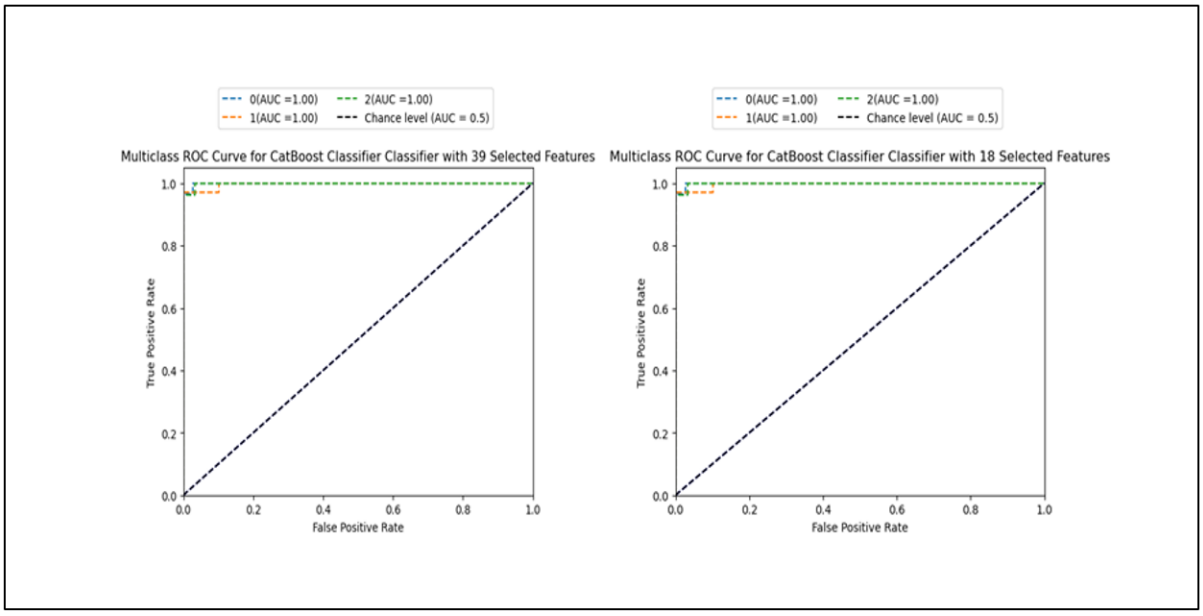

Figure 7: CATBoost Classifier receiver operating characteristic (ROC) Curve: algorithm performance comparison between 18 selected features and primary 39 features. AUC: area under the curve.

Table 2: Patient's demographic and clinical characteristics

Variables	Discharged			
	without sequelae (n= 244)	Against medical advice (n = 21)	with sequelae (n = 3)	Death (n = 6)
Age (Years)				
Median (IQR)	27 (20-42)	30 (19.5-40.5)	24 (12 -24)	32.5 (16.7-68.7)
Sex				
Male	69 (28.3)	7 (33.3)	2 (66.7)	3 (50)
Female	175 (71.7)	14 (66.7)	1 (33.3)	3 (50)
CCB Type				
Amlodipine	144 (59)	13 (61.9)	2 (66.7)	2 (33.3)
Diltiazem	46 (18.9)	6 (28.6)	0 (0)	0 (0)
Verapamil	44 (18)	2 (9.5)	1 (33.3)	3 (50)
Nifedipine	10 (4.1)	0 (0)	0 (0)	1 (16.7)
Co-ingestion				
Yes	162 (66.4)	14 (66.7)	2 (66.7)	5 (83.3)
No	82 (33.6)	7 (33.3)	1 (33.3)	1 (16.7)
History of CCB usage				
Yes	47 (19.3)	5 (23.8)	0 (0)	1 (16.7)
No	197 (80.7)	16 (76.2)	3 (100)	5 (83.3)
Pulmonary heart disease				
Yes	44 (18.0)	9 (42.9)	0 (0)	1 (16.7)
No	200 (82.0)	12 (57.1)	3 (100)	5 (83.3)
Time elapsed from ingestion to admission (hours)				
0.5-1	16 (6.6)	1 (4.8)	0 (0)	0 (0)
1-2	56 (23.0)	7 (33.3)	1 (33.3)	1 (16.7)
2-4	53 (21.7)	6 (28.6)	0 (0)	0 (0)
4-6	40 (16.4)	2 (9.5)	0 (0)	2 (33.3)
6-8	23 (9.4)	2 (9.5)	1 (33.3)	2 (33.3)
8-12	29 (11.9)	2 (9.5)	0 (0)	0 (0)
12-24	14 (5.7)	0 (0)	0 (0)	0 (0)
24-48	6 (2.5)	0 (0)	0 (0)	0 (0)
Unknown	7 (2.9)	1 (4.8)	1 (33.3)	1 (16.7)
Troponin				
Yes	6 (2.5)	0 (0)	0 (0)	2 (33.3)
No	238 (97.5)	21 (100)	3 (100)	4 (66.7)
ECG				
Normal Sinus Rhythm	223 (91.4)	12 (57.1)	1 (33.3)	1 (16.7)
AV conduction abnormalities	16 (6.6)	6 (28.6)	2 (66.7)	3 (50)
Sinusoidal Bradycardia	5 (2.0)	2 (9.5)	0 (0)	0 (0)
Complete Heart Block	0 (0)	1 (4.8)	0 (0)	2 (33.3)
Cardiology consultation				
Yes	17 (7.0)	3 (14.3)	3 (100)	3 (50)
No	227 (93.0)	18 (85.7)	0 (0)	3 (50)
Vital signs				
GCS	15 (15-15)	15 (13-15)	15 (15-15)	6.5 (3-12.75)
GCS-eye	4 (4-4)	4 (3-4)	4 (4-4)	1 (1-3)
GCS-answering	5 (5-5)	5 (4-5)	5 (5-5)	1 (1-4.5)
GCS-movement	6 (6-6)	6 (6-6)	6 (6-6)	1 (1-5)
Puls rate (/min)	80 (70-94)	85 (78-91)	79 (72-79)	82 (45-90)
Respiratory rate (/min)	16 (15-18)	16 (15-18)	20 (17-20)	14 (10-20)
Arterial oxygen saturation (%)	97 (96-98)	96 (93-98)	96 (93-96)	91 (74-96)
FiO2 (%)	21 (21-21)	21 (21-30)	21 (21-21)	100 (80.25-100)
Body temperature (°C)	37 (37-37)	37 (36.65-37)	37 (36.5-37)	37 (37-37)
SBP (mmHg)	110 (100-120)	110 (100-120)	105 (79-105)	70 (60-90)
DBP (mmHg)	70 (60-80)	70 (60-80)	70 (45-70)	50 (30-50)
VBG				
pH	7.39 (7.36-7.42)	7.4 (7.375-7.445)	7.29 (7.25-7.29)	7.225 (7.0975-7.3475)
PCO2	38.2(34.75-42.55)	36.7 (35.25-38.9)	38.1 (25.1-38.1)	45.6 (40.05-57.95)
HCO3	22.7 (20-25)	22.8 (21.25-25.3)	23 (13.5-23)	20.8 (18.15-23.65)
PO2	45 (34.8-59)	40.75 (37.8-50.95)	56 (44-56)	38 (22-38)
Laboratory				
WBC	8.1 (6-11.9)	10.1 (6.9-13.4)	14.4 (10.1-14.4)	10.8 (7.925-18.325)
Hb	12.9 (12-14)	13.45 (12.475-14.325)	15 (12.2-15)	13 (12.25-14.425)

Table 2: Patient's demographic and clinical characteristics

Variables	Discharged			
	without sequelae (n= 244)	**Against medical advice (n = 21)**	**with sequelae (n = 3)**	**Death (n = 6)**
PLT	242 (209-298)	230.5 (203-295)	232 (213-232)	289 (170.5-396.5)
Urea	27.5 (23-35)	31.5 (24.5-41)	34 (20-34)	34 (24.5-36)
Cr	1 (0.8-1.2)	1 (0.875-1.2)	1.5 (0.5-1.5)	1.2 (0.8-1.35)
Na	139 (137-141)	139.5 (138-140.25)	137 (135-137)	138.5 (135-140.25)
K	4 (3.7-4.1)	3.85 (3.5-4.2)	3.7 (3.3-3.7)	4.35 (3.9-5.575)
Ca	9.15 (8.6-9.8)	9.1 (8.78-9.65)	9 (8.8-9)	8.9 (7.45-9.30)
CPK	96 (67-149.5)	86.5 (66.5-152)	378 (112-378)	118 (42-118)
AST	24 (19-32)	27 (22-37.5)	31 (27-31)	33 (31.25-34.75)
ALT	19 (14-31)	20 (14-34)	28 (21-28)	30 (28.25-36.25)
ALP	140 (121-188)	152 (109-198)	169(167-169)	115(159-198.5)
BS	103 (97-117.25)	113.5 (91.75-150.25)	136 (97-136)	110(100.75-169.5)
BS-Max	110 (97-138)	121 (99.5-155.2)	171 (125-171)	122 (95.75-295.5)
LDH	399.5 (338.5-497.75)	369 (350-480)	469 (87-469)	280 (258-280)
Activated Charcoal				
Yes	102 (41.8)	12 (57.1)	1 (33.3)	0 (0)
No	142 (58.2)	9 (42.9)	2 (66.7)	6 (100)
Whole Bowel Irrigation				
Yes	17 (7.0)	2 (9.5)	0 (0)	0 (0)
No	227 (93.0)	19 (90.5)	3 (100)	6 (100)
Insulin administration				
Yes	15 (6.1)	4 (19.0)	1 (33.3)	3 (50)
No	229 (93.9)	17 (81.0)	2 (66.7)	3 (50)
Glucagon administration				
Yes	11 (4.5)	2 (9.5)	0 (0)	2 (33.3)
No	233 (95.5)	19 (90.5)	3 (100)	4 (66.7)
Calcium administration				
Yes	34 (13.9)	4 (19.0)	2 (66.7)	4 (66.7)
No	210 (86.1)	17 (81.0)	1 (33.3)	2 (33.3)
ICU admission				
Yes	29 (11.9)	6 (28.6)	1 (33.3)	4 (66.7)
No	215 (88.1)	15 (71.4)	2 (66.7)	2 (33.3)
Intubation				
Yes	16 (6.6)	4 (19.0)	0 (0)	6 (100)
No	228 (93.4)	17 (81.0)	3 (100)	0 (0)
Duration of Hospitalization				
Median (IQR)	1 (1-2)	1 (1-5)	5 (5-5)	1 (1-3.5)

Data are presented as median (interquartile range) or frequency (%). IQR: Inter Quartile Range; CCB: Calcium Channel Blockers; SBP: Systolic blood pressure; DBP: diastolic blood pressure; GCS: Glasgow Coma Scale; ECG: Electrocardiography; AST: Aspartate Aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine Aminotransferase; VBG: Venous Blood Gas; BS: blood Sugar; LDH: Lactate Dehydrogenase; Cr: Creatinine; Na: Sodium; K: Potassium; Ca: Calcium; CPK: Creatine Phosphokinase; WBC: White blood cells; Hb: Hemoglobin; PLT: Platelet; ICU: intensive care unit; FiO2: fraction of inspired oxygen; AV: Atrioventricular.

Table 3: Results of ten-fold cross-validation for machine learning classifiers' performance with 18 selected features

Classifier	Datasets	Accuracy	F1-Score+	AUC*	Precision+	Recall+
XGBoost	Train	0.98 (98.3-98.6)	0.98 (98.3-98.6)	0.99 (0.99-1)	0.98 (0.98-0.98)	0.98 (0.98-0.98)
	Test	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.99 (0.98-0.99)	0.96 (0.96-0.98)	0.96 (0.96-0.97)
CATBoost	Train	0.97 (0.97-0.97)	0.97(0.97-0.97)	0.99 (0.99-0.99)	0.97 (0.97-0.97)	0.97 (0.97-0.97)
	Test	0.96 (0.96-0.98)	0.96 (0.96-0.97)	0.99 (0.99-0.99)	0.96 (0.96-0.98)	0.96 (0.9-0.96)
ExtraTree	Train	0.96 (0.96-0.96)	0.96 (0.96-0.96)	0.99 (0.98-0.99)	0.96 (0.96-0.97)	0.96 (0.96-0.96)
	Test	0.96 (0.95-0.96)	0.96 (0.95-0.96)	0.97 (0.97-0.98)	0.96 (0.95-0.96)	0.95 (0.95-0.96)
GradiantBoosting	Train	0.94 (0.93-0.94)	0.94 (0.93-0.94)	0.98 (0.98-0.98)	0.94 (0.94-0.94)	0.93 (0.93-0.93)
	Test	0.93 (0.92-0.93)	0.93 (0.92-0.93)	0.97 (0.96-0.97)	0.94 (0.93-0.94)	0.92 (0.92-0.93)
RandomForest	Train	0.91 (0.91-0.91)	0.91 (0.9-0.91)	0.98 (0.98-0.98)	0.92 (0.91-0.92)	0.91 (0.91-0.91)
	Test	0.9 (0.89-0.90)	0.89 (0.89-0.90)	0.97(0.97-0.98)	0.90(0.90-0.91)	0.90 (0.89-0.90)
AdaBoost	Train	0.90(0.90-0.91)	0.90 (0.90-0.90)	0.98 (0.98-0.98)	0.90 (0.90-0.91)	0.90 (0.90-0.90)
	Test	0.89 (0.89-0.90)	0.88 (0.88-0.89)	0.97(0.97-0.98)	0.90(0.89-0.91)	0.89 (0.88-0.89)
HistGradiantBoosting	Train	0.89 (0.89-0.89)	0.89 (0.89-0.89)	0.99 (0.99-0.99)	0.90 (0.90-0.91)	0.89 (0.88-0.89)
	Test	0.84 (0.84-0.85)	0.84 (0.83-0.84)	0.98 (0.98-0.98)	0.86 (0.85-0.87)	0.84 (0.83-0.84)
KNN	Train	0.86 (0.86-0.87)	0.85 (0.85-0.86)	0.99 (0.99-0.99)	0.87 (0.87-0.87)	0.86 (0.86-0.86)
	Test	0.81 (0.81-0.82)	0.80 (0.79-0.80)	0.97 (0.97-0.98)	0.83 (0.83-0.84)	0.81 (0.81-0.82)

AUC: Area Under the Curve; KNN: K-nearest neighbor. Here the value of performance metrics was rounded to the nearest ten thousandth except for the XGBoost Classifier that the corresponding value was rounded to the nearest hundred thousandth.
+: weighted average
*: Macro-Averaged area under the receiver operating characteristic (ROC) curve.

Table 4: The performance metrics for all developed classifiers reported separately for each class; 0= death, 1= discharge with sequelae, 2= discharge without sequelae

Classifier	Model Evaluation Details			
	Recall	F1-score	AUC*	Precision+
XGBoost				
0	0.94 (0.94-0.94)	0.97 (0.97-0.97)	0.99 (0.99-0.99)	0.99 (0.99-0.99)
1	1	0.98 (0.97-0.98)	0.98 (0.97-0.99)	0.96 (0.96-0.97)
2	0.98 (0.98-0.98)	0.98 (0.98-0.98)	0.99 (0.99-0.99)	0.98 (0.98-0.99)
CATBoost				
0	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.96-0.96)
1	0.97 (0.96-0.97)	0.95 (0.95-0.96)	0.99 (0.99-0.99)	0.94 (0.94-0.95)
2	0.96 (0.96-0.96)	0.97 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.97-0.98)
ExtraTree				
0	0.96 (0.96-0.96)	0.92 (0.92-0.93)	0.97 (0.96-0.97)	0.87 (0.87-0.88)
1	0.97 (0.97-0.98)	0.97 (0.97-0.97)	0.98 (0.98-0.98)	0.97 (0.97-0.98)
2	0.95 (0.94-0.95)	0.97 (0.97-0.97)	0.98 (0.98-0.99)	0.98 (0.98-0.99)
GradiantBoosting				
0	0.79 (0.78-0.80)	0.88 (0.88-0.89)	0.98 (0.97-0.98)	0.99 (0.99-0.99)
1	0.97 (0.96-0.97)	0.88 (0.87-0.88)	0.95 (0.95-0.96)	0.80 (0.80-0.80)
2	0.96 (0.96-0.96)	0.97 (0.96-0.97)	0.97 (0.97-0.97)	0.97 (0.97-0.98)
Randomforest				
0	0.62 (0.60-0.62)	0.75 (0.74-0.76)	0.99 (0.98-0.99)	0.95 (0.94-0.95)
1	0.97 (0.96-0.97)	0.90 (0.89-0.90)	0.96 (0.96-0.96)	0.84 (0.83-0.84)
2	0.97 (0.97-0.97)	0.94 (0.94-0.95)	0.98 (0.98-0.98)	0.92 (0.92-0.93)
ADABoost				
0	0.58 (0.58-0.59)	0.72 (0.71-0.73)	0.98 (0.98-0.98)	0.94 (0.94-0.95)
1	0.96 (0.95-0.96)	0.97 (0.96-0.97)	0.98 (0.97-0.98)	0.97 (0.97-0.97)
2	0.97 (0.97-0.97)	0.91 (0.90-0.91)	0.96 (0.96-0.97)	0.85 (0.85-0.86)
HistGradiantBoosting				
0	0.79 (0.78-0.79)	0.88 (0.88-0.89)	0.99 (0.99-0.99)	0.99 (0.99-0.99)
1	0.57 (0.57-0.57)	0.70 (0.69-0.70)	0.97 (0.97-0.98)	0.90 (0.89-0.91)
2	0.97 (0.97-0.98)	0.87 (0.87-0.88)	0.97 (0.97-0.97)	0.79 (0.79-0.80)
KNN				
0	0.38 (0.37-0.39)	0.53 (0.53-0.54)	0.97 (0.96-0.98)	0.92 (0.92-0.92)
1	0.97 (0.97-0.97)	0.84 (0.84-0.85)	0.99 (0.99-0.99)	0.74 (0.74-0.75)
2	0.91 (0.91-0.91)	0.87 (0.87-0.88)	0.95 (0.94-0.96)	0.84 (0.83-0.85)

*: Macro-Averaged area under the receiver operating characteristic (ROC) curve; AUC: Area Under the Curve; KNN: K-nearest neighbor.