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Machine Learning–Driven Prediction of Intensive Care Unit Admission in Acute Psychotropic Poisoning: A Two-Center Prospective Study

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Abstract

Psychotropic medications act on the central nervous system to modulate mood and behavior, and their use has increased in recent years, accompanied by a parallel rise in hospitalizations due to acute toxicity. In this cohort study, 232 patients with acute psychotropic poisoning were recruited from two centers, including 112 admitted to the intensive care unit (ICU) and 120 managed in the ward, to evaluate the performance of four machine learning (ML) models, binary logistic regression (BLR), random forest (RF), support vector machine (SVM), and gradient boosting (XGBoost), in predicting ICU admission. Antipsychotics accounted for approximately 70% of exposures, and 48.3% of patients required ICU admission. Among the tested models, RF achieved the highest accuracy (0.80) in correctly classifying patient disposition, while forward stepwise BLR, RF, and linear SVM demonstrated the strongest discriminative performance (AUC = 0.8) in distinguishing between ICU and ward admissions. Across the models, three common predictors of ICU admission were identified: oxygen saturation (SpO_2), QRS duration, QTc interval and serum troponin levels. If integrated into clinical practice, these ML models could enhance the management of acute psychotropic poisoning by enabling early identification of high-risk patients and supporting timely, objective decision-making regarding ICU admission, particularly in resource-limited settings.

Introduction

Psychotropic drugs are a category of medications that modulate brain functions and affect mood, perception, cognition, and behavior [1]. Psychotropics are increasingly prescribed to treat various mental disorders, including depression, psychosis, insomnia, and anxiety, and acute mania. The primary classes of psychotropic drugs include antipsychotics, antidepressants, mood stabilizers, sedative-hypnotics, and anxiolytics[2]. The hospitalization rate for psychotropic medication poisoning increased by 20% in the United Kingdom from 1999 to 2020[3]. Similarly, in Australia, the most common form of self-harm leading to hospital admissions between 2008/2009 and 2020/2021 was intentional self-poisoning involving psychotropic drugs. Psychotropic drugs accounted for 40% of all intentional self-harm hospital admissions[4].

The most prevalent method of suicide attempts involves using an overdose of psychotropic medications. This pattern of exposure was frequently described in patients using illicit drugs[5, 6]. Among psychotropics, antipsychotics and antidepressants are associated with the most frequent and severe toxicities[5]. Various Egyptian poison control units have reported that exposure to psychotropics is the most reported poisoning[7–11]. The most severe and potentially fatal symptoms of acute psychotropic overdose include disturbed consciousness, seizures, hypotension, prolonged QT interval, and dysrhythmias, such as torsade de pointes. Coma, circulatory instability, and target organ damage are ominous events, necessitating intensive care unit (ICU) admission. Mortality is another common serious outcome associated with exposure to high doses of acute psychotropic medications[12, 13]. In the absence of specific antidotes for poisoning with psychotropic drugs, the treatment for severe cases primarily relies on adequate supportive measures[14].

Shi et al. mentioned that psychotropic drug poisoning is the most common type of poisoning that requires accurate predictions of severity and a potential need for ICU admission[15]. The primary aim of ICU admission in different types of poisoning is the need for continuous monitoring of the patient's clinical condition and assessing the life-supporting measures, such as mechanical ventilation (MV) and circulatory support[16, 17]. The timing of the transfer to the ICU is an essential factor in patient outcomes as early supportive action might prevent the development of critical complications[18]. On the other hand, unnecessary ICU admission may consume precious resources[19].

There is a shortage of effective predictive tools for assessing the need for ICU admission in acute psychotropic poisoning, including the use of predictive scores and nomograms[20]. Nevertheless, the developed ICU predictive models depended on vital signs recorded at the time of ICU admission rather than those taken during the initial presentation[16]. The suggested nomograms designed to predict the need for ICU care in such cases have been tailored for specific individual agents, such as clozapine[21] and lithium[22]. Furthermore, the studies introduced these models were mostly conducted at a single poisoning center, focusing on specific age group[20–22].

Machine learning (ML) is a branch of artificial intelligence (AI) that encompasses computerized mathematical algorithms that are adept at completing certain statistical tasks by inference rather than explicit instructions, by studying and learning from input data[23]. The application of ML models can enhance predictive power compared to traditional statistical methods. These models can identify complex non-linear relationships within inputs by managing multiple intricate factors and measuring their interrelationships. This capability leads to more precise predictive outcomes[24]. The use of ML algorithms in clinical toxicology for diagnosing and predicting the severity of poisoning cases is a relatively recent development[25].

There is a pressing need for developing an accurate and highly sensitive tool that facilitates the challenging decision of ICU admission in psychotropic-exposed patients. This tool should encompass various psychotropic drug classes across different contexts. Therefore, the current study aimed to evaluate the effectiveness of several ML-driven models in predicting the severity of acute psychotropic poisoning. The model utilized early admission indicators to forecast late outcomes of poisoning, thereby aiding emergency clinicians in making more effective decisions regarding patient management and the necessity for ICU.

Results

The current study was conducted among 232 patients with a median age of 20 years, where 48.3% of them were admitted to ICU. About 70% of the investigated patients were females, living in urban areas. There were no significant differences between the studied patients regarding their sociodemographic characteristics. There were significant differences between the studied patients admitted to wards and ICU regarding their

occupation, where 79.3 % of children (23 out of 29) were not admitted to ICU, about 60% of those admitted to ICU were students (p = 0.01). The majority (92%) of those admitted to ICU consumed the drug in a suicide attempt. Three categories of psychotropics were identified, including antipsychotics (typical and atypical generations), antidepressants (tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), noradrenergic and specific serotonergic antidepressants (NaSSA) and sedative hypnotics (Benzodiazepine and Non-benzodiazepine containing). The majority (69.8%) of investigated patients presented with acute antipsychotic toxicity, where the risperidone exposure was significantly associated with lower need for ICU admission (p<0.05). Clozapine exposure constituted 48.2% of total ICU admissions. The antidepressants toxicity affected 15.5% of investigated patients, with TCA constituting the majority of this poisoning category. The sedative hypnotics toxicity was reported in 14.7%. The patients admitted to ICU showed significantly higher PSS (p<0.05) as **Table 1.** depicts.

Analyzing the clinical findings on admission revealed that patients presented with lethargy were in significant need of ICU. Furthermore, the patients admitted to the ICU suffered from fainting and palpitation, as well as excessive salivation, dryness of skin and mucous membranes, pallor and cyanosis. The presence of extrapyramidal manifestations and agitation was significantly associated with lower need for ICU admission. **Table 1.** also shows that patients presented with desaturation are at increased the risk of ICU admission (p<0.05). The random blood glucose of patients admitted to the ICU was significantly higher than that of those who were not. Signs of impending cardiotoxicity were characteristic features of ICU admitted patients, namely, an elevated serum troponin, and prolonged duration of QRS complexes and QTc interval (p=0.01). Sinus tachycardia was significantly associated with a higher need for ICU admission. Likewise, patients admitted to the ICU spent significantly longer times in the hospital compared to those not admitted to the ICU.

In this study, we attempted to determine the separation pattern and predictors of admission to ward vs ICUs using several ML models. Generally, the t-SNE plot showed partial separation between the ICU and ward patient groups along the first t-SNE dimension (Dim1), with ICU patients tending to cluster toward higher Dim1 values and ward patients toward lower Dim1 values **(Figure 3A)**. Among the 5-trained BLR models, the forward model has the lowest AIC followed by the stepwise model, whereas null, full and backward models have higher AIC with poor performance **(Table S1** and **Figure 4A)**. Both forward and stepwise models achieved similar, yet higher performance on test data (accuracy:0.7, sensitivity: 0.7 and specificity: 0.8) compared to other models **(Tables 2 and S2).** In terms of predictability, the two models achieved area under curve (AUC) of 0.8 compared to lower AUCs obtained by null (0.5), full (0.6) and backward models (0.6) **(Figure 3B).** As shown in **Figure 4B** and **Table S3,** the forward and stepwise models predicted the same ranked predictor variables, with SpO_2, QRS width (msec) and serum troponin (ng/l) ranked top predictors**.** As shown in **Tables S1** and **3**, both forward and stepwise models resulted in identical parameters for most variables. Lower SpO_2, wider QRS width, and higher serum troponin levels were all significantly associated with ICU compared with ward admission. Specifically, SpO_2 has a negative coefficient ($\beta = -4.1$) with a highly significant p-value ($p < 0.001$) and a very low odds ratio, indicating that lower oxygen saturation strongly increases the likelihood of ICU admission. On the other hand, QRS width ($\beta = 2.0$, $p < 0.001$) and serum troponin ($\beta = 13.3$, $p < 0.001$) have positive coefficients and large odds ratios (7.7 and ~590,000, respectively). This means that a wider QRS and higher troponin levels greatly raise the chances of being admitted to the ICU. The forward and stepwise models revealed 10 mismatches patients **(Table S1)**.

The trained RF models (n = 49) obtained accuracies, sensitivities and specificity ranging from 0.7-0.8 (SD = from 0.02-0.03) **(Table 2)**. However, the best model according to performance on the test data was the one with 100 tree to grow (*ntree*) and 8 variables tried at each split *(mtry*) **(Figure S1 and Table S4 A&B**). The RF model showed similar degree of separation and overlap between patients admitted to ICU vs ward as that of BLR model **(Figure 5A)**. The RF model was able to truly classify 80% of the patients (accuracy = 0.8) with lower misclassification error compared to both BLR models and SVM models. Model predictability was 0.8 **(Figure 5B)**. When using mean decrease in accuracy as indicator for variable importance, serum troponin (ng/l), SpO_2, scientific drug category, drug name and QTc (msec) were the top ranked variables. Whereas using mean decrease in GININ index showed that SpO_2, QTc (msec), serum troponin (ng/l) and drug scientific name were top variables **(Figure 6 and Table S4 C)**. The best RF model revealed 8 mismatches patients **(Table S4)**.

We also trained 3 different methods of the SVM model on the data after tuning multiple parameters (**Tables 2 and S5**). When using SVM radial methods, the best hyperparameters were sigma = 0.01 and cost = 5 for the all-features and top-10-features models. When using the SvmPoly method, the best hyperparameters selected were degree = 3, scale = 0.01, and cost = 1 (all feature models). When using SvmLinear, cost = 0.1 was the best hyperparameter selected (all-feature model) (**Figure S2**). Using the top 10 features improved model specificity, but not accuracy, sensitivity, or AUCs (**Tables 4 and S5**). The best obtained accuracy was 0.7 (all models except the SvmRadial on all features was 0.6), and AUC was 0.8 for SvmLinear (**Figure 7A**). The SvmLinear revealed 13 mismatched subjects **(Table S5)**. All SVM models revealed an identical order of variable importance, with serum troponin (ng/l), QTc (msec), and SpO_2 ranked the highest (**Figure 7B**).

Using 10-fold cross validation, we have tried 256 XGBoost models, and the best one was found to have mean AUC = 0.9 and accuracy of 0.8 **(Table S6A).** testing this model on the test data revealed predictability of 0.7 **(Figure 8A)** and accuracy of 0.6 **(Table 2** and **S6)**. This model revealed 16 mismatched subjects **(Table S6)**. The most significant predictor variables as revealed by this model are shown in **figure 8B** and **Table S6.**

By intersecting the top 10 significant predictors across the 4-tested models **(Figure 9A)**, we reveal 3 shared variables, namely SPO2, QRS width and serum troponin. These were found to be significantly different among the two-admission group **(Figure 9B)**.

Because all the models revealed misclassification error with variable degrees, we looked at what subjects are misclassified (mismatched) across all models. Three patients were found to be misclassified across all models. However, each of the GBL, SVM and XGboost models misclassified 3-

unique participants and RF models did not misclassify any unique participant.

Methods

2.1. Study Design and Setting

The overall study design is shown in **Figure 1.** This study is a two-center prospective cohort study that was conducted among patients diagnosed with acute psychotropic poisoning (antipsychotics, antidepressants Nand sedative hypnotics) and admitted to Benha Poison Treatment and Toxicological Research Unit (BPTTRU), Benha University Hospitals, and Zagazig Poisoning Unit (ZPU), Zagazig University Hospitals, Egypt, during the period from December 2023 to the end of November 2024. The current study was conducted after consulting the EQUATOR network following the strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.

2.2. Sampling and Sample Size Calculation

Convenience sampling was adopted, where all patients who met the inclusion criteria were considered eligible. Randomization was conducted using a lottery method to select the predetermined number of patients. Sample size calculated using Open Epi software (version 3)[26], considering an anticipated prevalence of ICU admission of 13.6%, following Sharif et al.[27]. The minimal sample size should be no less than 181 patients. This number was increased to approximately 230 to account for dropout of about 20%.

2.3. Eligibility criteria

All patients diagnosed with acute psychotropic poisoning who were admitted during the study period were included. The diagnosis of psychotropic poisoning was based on the history given by the patient or relatives, confirming the type of drug the patient overdosed on. Initial diagnosis was confirmed by clinical signs and symptoms corresponding with the type of exposure and are not explained by pathological conditions or other types of exposure. Additionally, patients had been asked to bring the drug container of the medication they were exposed to, if available. Patients diagnosed with multiple exposures, and those with unclear diagnoses were excluded. We have also excluded patients diagnosed with long-lasting disorders (e.g., cardiovascular, respiratory, renal, or hepatic diseases), patients discharged against medical advice, patients who received prehospital treatments and patients transferred to other hospitals, as well as patients with insufficient data in the hospital records. The recruitment process of the patients investigated is shown in **Figure 1**.

2.4. Compliance with Ethical Standards

Before commencing this study, ethical approval was obtained from the Medicine Ethics Committee at the Faculty of Medicine, Benha University (Approval number RC 12-11-2023). This study was conducted according to the Declaration of Helsinki, 1964, and its later amendments. Informed written consent was obtained from every enrolled patient or their guardians, in incapacitated patients, after describing the study's aim. To ensure confidentiality, all patients' data were deidentified, coded, and anonymously analyzed.

2.5. Assessed outcome and predictor variables

The main outcome investigated in this study was the need for ICU admission. Several predictor variables were obtained upon admission, including demographics and presenting complaints, as well as the findings observed on examination and the results of some investigations. Demographics included the age, sex, residence, marital status, and occupation. The manner of exposure, along with any history of psychological disorders, being on antipsychotic medications, and any previous suicidal attempts, was mentioned. The relatively ingested dose in mg and the delay interval between exposure and approaching the emergency services were reported. Every enrolled patient was scored on admission using the Glasgow Coma Scale (GCS) and the Poison Severity Score (PSS). The type of exposure (category and subcategory of drug, as well as the name of the drug) was reported. Vital signs were reported, and the main presenting complaints were stated. Thorough examination of the nervous system, as well as the cardiovascular and respiratory systems. The skin and mucous membranes were inspected for any abnormalities, and the eyes were examined for any change in pupillary size or nystagmus. Any characteristic toxidromes or syndromes were reported. Arterial blood gas analysis was conducted and the results were evaluated, in addition to any acid-based disturbances. The level of troponin at 6 hours was assessed. An electrocardiography (ECG) was performed and the duration of ORS complexes, and QTc interval were mentioned. Observed cardiac dysrhythmia was reported and the overall duration of hospital stay was documented.

2.6. Baseline data analysis

The Statistical Package for the Social Sciences (SPSS) 28.0 for Windows was used to code, enter, analyze, and display the gathered data in appropriate tables and graphs (SPSS Inc., Chicago, IL, USA)[28]. The Kolmogorov-Smirnov test was used to determine whether the quantitative data's distribution was normal. Data were summed up using the median (IQR) for quantitative nonparametric data, mean ad standard deviation (SD) for quantitative parametric data and numbers and percentages for qualitative data. Comparison between qualitative variables was done using chi square (c2) and Fisher's Exact tests. Mann-Whitney was used for comparison of non-parametric quantitative variables between two groups. Student t test was used for comparison of parametric quantitative variables between two groups. A significant criterion of $p<0.05$ was accepted for all two-sided tests.

2.7. Study roadmap

Figure 2 demonstrates the conceptual framework of developing and validating the ML-driven models for predicting the need for ICU among patients diagnosed with acute psychotropic poisoning. The whole data are split into train and test data followed by data preprocessing, model training and testing including hyperparameters tunning and cross-validation.

2.7.1. Data preprocessing

Patient data were arranged in a spreadsheet, cleaned and curated to be ready for the analyses. The categorical and numerical variables were pre-processed before running the ML models. After data splitting, numeric variables were checked and pre-processed for NAs (using the function "*is.na*", zero and near zero variance variables (using the function "*nearZeroVar*"), pairwise correlation (using the functions "*cor*" and "*findcorrelation*") and Multicollinearity (using *VIF* function from *Caret* package). Two variables were excluded; diastolic and mean arterial blood pressure), scaled using mean and standard deviation and checked for linearity of logit (using the function "*geom_smooth*, method = *loess*). A two-dimensional t-distributed stochastic neighbour embedding (t-SNE) was performed on the scaled predictor variables to explore patterns in patient characteristics associated with admission type.

2.7.2. Models' development and validation

2.7.2.1. Binary logistic regression (BLR) model

We run 5-BLR models using both "*glm*" function (null and full models) and "*step*" function (forward, backward and stepwise selection models). The generated models were compared using Akaike Information Criterion (AIC) and p-values and their performance on test data were evaluated using accuracy, specificity and sensitivity after running 10-fold cross validation. The function "*varImp*" was used to reveal the important predictors for admission based on these models. The misclassified subjects were also obtained.

2.7.2.2. Random forest (RF) model

Random forest model was run using the function "*randomForest*" from "*randomForest*" package. We first used the grid search approach by combining various the *ntree* and *mtry* hyperparameters to build up 49 RF models. These were then evaluated for performance on the test data using "*caret*" package. The best model was tried using various "*node size*". Dimension reduction approach (non-metric multidimension scaling) was done in RF model using "*plotProximity*" function in "*rfPermute*" package. Top predictors from RF model were identified using mean decrease in GINI and accuracy indices. The misclassified subjects were also obtained.

2.7.2.3 Support vector machine (SVM) model

We run several SVM models using the methods SvmRadial, SvmPolynomial and SvmLinear using the package "*e1071*" on the best models revealed by the grid search approach (which generated 16 different models). These methods were run using all features as well as the top 10 important features generated from the model as inputs. The hyperparameters tunned inside each SVM model were Cost and Sigma for SvmRadial, degree of polynomial kernel, scale and cost for SvmPolynomial and cost for SvmLinear. Top features were retrieved using "*varImp*" function. All models were evaluated during the training using repeated 5-fold cross validation approach. Maximum ROC AUC was used as a performance parameter when tunning the hyperparameters. The misclassified subjects were also obtained.

2.7.2.4 Gradient Boosting model (XGBoost)

To run Gradient boosting, we relied on XGBoost method. The data were initially pre-processed by forming a model matrix for both training and test data and then converted to Dmatrix object. Model tuning and evaluation were performed using a systematic grid search and 10-fold cross-validation (CV) approach. First, a grid of hyperparameter combination (n = 256) was constructed, each was cos considered as a unique model, to explore model performance. The hyperparameters were number of boosting round, learning rate, max tree depth and minimum child weight). For each model, 10-fold cross validation was run using xgb.cv function in xgboost package and an early stopping rule of 10 rounds was applied to prevent overfitting. The AUC and accuracy as evaluation metrics. For each model, the mean AUC, accuracy and optimal number of round (based on early stooping) were recorded. The selection of best model was determined based on highest mean AUC across the CV-folds. A final XGBoost model was trained on the full training dataset using the optimal hyperparameters and the best number of boosting rounds identified from CV. To evaluate the model, the predicted probabilities for the test set were converted to class labels using a threshold of 0.5, and performance was assessed using confusion matrix and AUC. Feature importance was quantified using the xgb.importance function, which reports *Gain* (contribution to model performance), *Cover* (proportion of observations influenced by a feature), and *Frequency* (number of times a feature is used for splitting). The top ten most influential features were visualized using a ggplot2-based importance plot. The misclassified subjects were also obtained.

Discussion

The current multicenter prospective study was conducted among patients diagnosed with acute psychotropic poisoning, encompassing three types of toxic exposure, including the antipsychotics, antidepressants and sedative hypnotics. This study aimed to evaluate four types of ML-driven models

in predicting the need for ICU admission. Among the tested models, the RF classifier showed the strongest and most balanced performance metrics, as well as the most statistically significant prediction. The LR (forward/stepwise) was also a fair predictor. The SVM gives very good accuracy, but its sensitivity depends heavily on kernel choice [Radial Basis Function (RBF) gave better sensitivity; linear/polynomial gave better specificity]. Eventually, the XGBoost performs comparatively worse and is not statistically convincing. The proposed models ended up with mutually significant predictors of ICU need among the proposed models, including the SpO_2, QRS width, QTc interval, and serum troponin. The integration of ML models into electronic health records could revolutionize the management of acute poisoning. By automatically flagging patients with high-risk features, these tools can support clinicians in making rapid, objective decisions regarding ICU admission. This is particularly valuable in resource-limited settings where ICU beds are a scarce commodity, and over-triage can strain hospital capacity[29]

While ML remains an underutilized prognostic tool in clinical toxicology, several recent studies have demonstrated its utility in specific poisoning scenarios. Machine learning was adopted to assess the severity of organophosphorus poisoning[30], the risk of seizures in acute tramadol overdose[31], and the prognosis in methanol intoxication[32]. Sharif et al. established eight ML-based models that could identify patients exposed to atypical antipsychotics who were at risk of developing prolonged QTc interval[1]. Beyond these substance-specific applications, other researchers have successfully utilized ML to forecast adverse outcomes across broader, non-specified poisoning cohorts[33–35].

Our findings also highlight the role of sociodemographic factors, where single females predominate. Additionally, students and those attempting suicide show higher ICU admission rates. Agreeing with the obtained findings, another study reported that most admissions following exposure to antidepressants and antipsychotics were females, living in urban areas[36]. Indeed, the females tend to commit suicide by intentional self-poisoning rather than using other aggressive means of suicide[37]. The distribution of ICU admissions in our study reflects the varying toxicity profiles of psychotropic classes. Clozapine accounted for nearly half of all ICU admissions, a finding that correlates with its complex side-effect profile, including severe CNS depression, orthostatic hypotension, and the risk of myocarditis or agranulocytosis[21,38,39]. The predominance of TCAs within the antidepressant category (15.5% of the total cohort) remains a significant concern for clinical toxicologists, as these agents continue to be associated with high morbidity and mortality despite the increasing use of newer, safer antidepressants like SSRIs[40].

The current findings conveyed that cardiotoxicity was a recognized feature of toxic psychotropic exposure. A cornerstone of our findings is the significant predictive value of cardiotoxicity markers as predictors of ICU need, specifically QRS widening, QTc prolongation, and elevated serum troponin levels. In our cohort, cardiotoxicity was strongly associated with ICU admission, particularly in patients exposed to TCAs and antipsychotics. These findings are consistent with the known sodium channel-blocking effects of TCAs and the potassium channel inhibition associated with many antipsychotics, both of which predispose patients to life-threatening arrhythmias[41,42]. Tricyclic antidepressants-associated inhibition of sodium channel conductance delays phase 0 of cardiac depolarization. This can slow conduction through the His–Purkinje fibers and the ventricular myocardium, resulting in QRS complex prolongation on the ECG[43].

An earlier study has established that a QRS duration exceeding 100 ms is a more reliable predictor of seizures and ventricular arrhythmias than serum drug levels in TCA poisoning [44]. Our models extend this by quantifying seven folds increased risk of ICU admission in patients with QRS widening, reinforcing its role as a critical triage tool. However, in most TCA overdose cases, tachycardia is reported as the most common arrhythmia, and it has been linked to anticholinergic activity and/or inhibition of norepinephrine uptake by TCAs. Likewise, antipsychotics can also lead to tachycardia, either as a vasomotor reflex to hypotension or due to anticholinergic effects[45,46].

The primary mechanism of action of antipsychotics is their dopaminergic D2 receptor blockade. However, the newer generations have an additive serotonin-2A (5-HT2A) receptor antagonism. Their cardiotoxicity in the form of conduction defects is attributed to the inhibition of potassium channels, and their resultant delayed rectifier, which disrupts the ventricular repolarization[47]. Prolonged QTc interval, well described with antipsychotics, is a life-threatening presentation if converted into torsade de pointes arrhythmias [48]. Consistently, El-Gharbawy & Ghonem, found a significant association between abnormal ECG findings, prolonged QTc interval and the need for ICU admission in acute antipsychotic poisoning[49]. The associated autonomic dysfunction is another mechanism of cardiotoxicity, where sinus tachycardia is a reported toxic manifestation[47] that was observed in this study and was associated with a significant association of ICU need.

The dramatic association between serum troponin and ICU admission, which was observed in all assessed models, underscores the prevalence of myocardial strain in severe psychotropic overdoses. While troponin elevation in toxicology is often multifactorial, stemming from direct cardiotoxicity, hypotension, myocardial infarction, or stress-induced cardiomyopathy, its role as a high-fidelity marker for ICU-level care is evident. suggest that troponin is a powerful biomarker for toxic cardiac injury, particularly when there is irreversible myocyte damage and loss of sarcolemmal integrity, regardless of the specific cardiotoxic agent involved[50]. Specific antipsychotics, particularly quetiapine are known for their potential higher cardiotoxicity manifested by significant elevation of serum troponin levels[51]. A previous study reported that among patients exposed to TCAs and antipsychotics, those complicated with cardiotoxicity exhibited higher troponin levels than those who were not. Contrary to the findings obtained, there were no significant variations in troponin levels between patients admitted to the ICU and those admitted to wards[36].

Interestingly, our results contrast with some earlier reports that found no significant association between troponin I and clinical severity in general poisoning, suggesting that in the specific context of psychotropic toxicity, myocardial injury is a more sensitive indicator of systemic decompensation[36]. Indeed, cardiac troponin remains controversial as a marker of cell injury, especially when the injury does not involve cell membrane disruption, such as sublethal or cytotoxic damage; in these situations, serum levels may not rise measurably. Sublethal injury can occur

with rhythm changes, altered electrical activity, contractile dysfunction, or reversible ischemic injury[52]. Likewise, in some forms of cardiotoxicity, apoptotic myocardial injury may depend on the degree of subsequent secondary necrosis does not result in troponin release into the serum during the diagnostic time window[53].

Respiratory compromise, as indicated by lower SpO_2 was another top-tier predictor across all ML models. Hypoxemia in these patients typically reflects central nervous system (CNS) depression, aspiration pneumonia, or impaired chest wall mechanics, all of which are hallmark complications of sedative-hypnotic, antidepressants and antipsychotic toxicity[54]. Sedative hypnotics and antidepressants are medications that affect the central neurotransmitters through diverse mechanisms. Gamma-aminobutyric acid (GABA) potentiation is the primary mechanism of sedative hypnotics[55]. Certainly, some sedative-hypnotics generally depress the CNS by acting on other targets, including glutamate, and additional modulatory pathways such as adenosine, serotonergic circuits, and ω (benzodiazepine) receptors. Physical examination is usually not diagnostic of a specific agent, but certain physical and clinical signs may provide clues about the type of sedative-hypnotic exposure[56]. Though Benzodiazepines offer the greatest level of cardiovascular safety, they may cause significant hypotension in hemodynamically unstable patients[57].

Furthermore, in case of combining specific types of psychotropics, the risk of serotonin syndrome (SS) is increased. All patients diagnosed with SS should be admitted to the ICU, with a primary aim of mechanical ventilation[54]. The high sensitivity of SpO_2 as a predictor highlights the importance of continuous pulse oximetry in the initial assessment of poisoned patients, as rapid desaturation often precedes the need for mechanical ventilation and intensive monitoring. Undeniably, antipsychotic medications induce tachypnea that can predispose patients to oxygen desaturation and CO_2 washout. The present findings further support the idea that initial oxygen saturation is a predictor of ICU admission in psychotropic overdose, aligning with earlier research in which oxygen saturation <95% significantly predicted ICU admission among clozapine-intoxicated patients[39]. Sharif et al. reported that patients exposed to antipsychotics and presenting with lower SpO_2 were at increased risk of MV that necessitated ICU admission, and prolonged QTc interval[1]. Similarly, van den Oever and colleagues included oxygen saturation <90% as one of five criteria used to determine ICU admission in cases of acute drug poisoning [58]. Analyzing several predictors of ICU admission among patients exposed to sedative hypnotics revealed that only the HCO_3 was the most likely significant predictor, reflecting the metabolic acidosis state associated with pronounced suppression of respiratory drive[59].

A great piece of literature established several predictive models that stratify the psychotropic-intoxicated patients according to their need for ICU admission. The proposed models exhibited congruent mutual predictors. Most of these studies adopted the BLR approach, which is indeed a simple ML classifier. El-Gharbawy et al. established a nomogram based on multivariate backward BLR analysis to predict the need for ICU admission in acute antipsychotic exposure. The developed nomogram encompassed six predictors, including the seizures, QTc interval, mean arterial pressure, oxygen saturation and GCS[60]. An earlier study conducted among patients admitted with acute clozapine toxicity revealed congruent findings came up with four variable nomogram that could predict the need for ICU admission, where the age, respiratory rate, oxygen saturation and random blood glucose were the main included parameters[61]. Sharif et al. investigated the early predictors of ICU admission in patients admitted with acute exposure to central nervous system-acting xenobiotics, where sedative hypnotics, psychotropics, and antidepressants constituted most ICU admissions. They reported that ICU admission was associated with significantly lower blood pressure, pH, and HCO_3 levels and higher random blood glucose, serum urea, and creatinine levels[59]. The observed hyperglycaemia is not uncommon manifestation of acute psychotropic toxicity that necessitates ICU admission. The action of antipsychotics on pancreatic -cell receptors, which inhibit insulin secretion, as well as an increased insulin resistance, and the distorted regulation of other molecules such as glucagon are suggested mechanism. An associated oxidative stress, which in turn downregulates glucose transporter expression, is another speculated pathogenesis[38,62].

Sharif et al. established eight ML models to predict QTc interval prolongation and the need for MV in acute atypical antipsychotic exposure. Like the current findings, the tree-based models, namely the RF, were the best performing classifiers. Nevertheless, they concluded that random blood glucose level, serum potassium, and delay time were the highest weighing features in several models[1]. In our study, the RF model emerged as the most robust classifier, achieving an accuracy of 0.80 and demonstrating a superior balance between sensitivity and specificity. The strength of RF lies in its ensemble approach, which constructs multiple decision trees and aggregates their outputs to reduce variance and prevent overfitting[63]. This architecture is particularly well-suited for clinical toxicology data, which often features non-linear relationships and complex interactions between variables. Logistic Regression, specifically the forward and stepwise selection models, remained competitive with comparable AUCs. The continued relevance of LR in clinical research is due to its transparency and the ease of interpreting coefficients as odds ratios, which is vital for bedside decision-making[64]. However, the marginal superiority of RF suggests that capturing the "interaction noise" between clinical variables provides an incremental but significant benefit in predicting ICU needs.

The SVM classifier exhibited variable performance that was heavily dependent on kernel selection, where the Svm Linear model provided the highest AUC, while the RBF kernel showed better sensitivity. This suggests that while linear separations exist for some predictors (like troponin), the underlying clinical landscape of poisoning is sufficiently complex to benefit from higher-dimensional mapping[65]. Nevertheless, the XGBoost model performed comparatively poorly in our cohort. While XGBoost is often the "gold standard" for large-scale tabular data; its underperformance here may be attributed to our sample size, as gradient boosting algorithms typically require larger datasets to optimize their numerous hyperparameters and avoid noise-fitting[66]. The identification of the same misclassified subjects across all four machine learning models is clinically noteworthy, as it suggests the presence of patients with overlapping or atypical clinical characteristics lying near the boundary between ICU and ward admission profiles. Rather than representing random model error, these consistently misclassified cases may reflect a subgroup of clinically complex patients

whose disease severity is not fully captured by conventional predictors. From a clinical perspective, recognizing such borderline cases is important because they may represent individuals at increased risk of rapid deterioration or delayed escalation of care. Careful characterization of these patients could therefore improve triage strategies, refine risk stratification tools, and support earlier clinical intervention.

Despite the strengths of the current study, several limitations must be acknowledged. First, the relatively small sample size, while sufficient for initial model development, limits the generalizability of our findings. Larger, multicentre datasets are required to validate these models across diverse populations and healthcare systems. Furthermore, an external validation on an independent cohort is the essential next step before clinical implementation of the proposed models.

In conclusion, this study demonstrates that ML, particularly the RF algorithm, provides a powerful framework for predicting ICU admission in patients with acute psychotropic poisoning. By synthesizing traditional clinical markers, SpO_2, QRS duration, QTc interval, and serum troponin into a cohesive predictive model, we can achieve good accuracy and reliability in risk stratification. These data-driven insights not only reinforce the importance of cardiac and respiratory monitoring in acute psychotropic poisoning but also offer a path toward more efficient and objective clinical decision-making in the field of clinical toxicology.

Declarations

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Author Contribution

Ibrahim A. Mostafa: Writing–original draft, Methodology, Data curation, Formal analysis, Visualization, Conceptualization. **Amina A. Farag:** Writing–original draft, Validation, Methodology, Writing–review& editing, Visualization, Supervision, Conceptualization. **Mohamed Samir**: Data curation, Formal analysis, Methodology, Writing–original draft, Validation, Software, Supervision. **Asmaa F. Sharif:** Formal analysis, Writing – original draft, Writing - review and editing. **Nashwa Nabil**: Methodology, Data curation, Formal analysis, Visualization. **Haidy M. Fakher**: Writing–original draft, Methodology, Data curation, Formal analysis, Visualization.

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Additional Information

Author statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Table 1. Comparison between the studied patients according to their need for intensive care unit admission

admission Variable		All patients n=232	Not admitted to ICU n=120	Admitted to ICU n=112	P value
1. **Demographics and circumstances of exposure**					
Age (years) Median (IQR)		20.0 (16.0-28.0)	21.0(17.5-30.0)	19.0(17.0-27.0)	0.89
Sex n (%)	**Female**	162 (69.8%)	82(68.3%)	80(71.4%)	0.60
	Male	70 (30.2%)	38(31.7%)	32(28.6%)	
Residence n (%)	**Rural**	72 (31.0%)	39(32.5%)	33(29.5%)	0.48
	Urban	160 (69.0%)	81(67.5%)	79(70.5%)	
Marital status n (%)	**Single**	158 (68.1%)	80(66.7%)	78(66.9%)	0.60
	Married	69(29.7%)	38(31.7%)	31(27.7%)	
	Divorced	5(2.2%)	2(1.7%)	3(2.7%)	
Occupation n (%)	**Child**	29(12.5%)	23 (19.2%)	6 (5.4%)	0.007
	Employee	13(5.6%)	7 (5.8%)	6 (5.4%)	
	Farmer	3(1.3%)	1 (0.8%)	2 (1.8%)	
	Student	96(41.4%)	39 (32.5%)	57 (50.9%)	
	Worker	18(7.8%)	6 (5.0%)	12 (10.7%)	
	Vet	1(0.4%)	1 (0.8%)	0(0.0%)	
	Not working	29(12.5%)	17 (14.2%)	12 (10.7%)	
	Housewife	43(18.5%)	26 (21.7%)	17 (15.2%)	
Manner n (%)	**For inebriation**	3 (1.3%)	0(0.0%)	3(2.7%)	0.001
	Accidental	35 (15.1%)	29(24.2%)	6(5.4%)	
	Suicidal	194 (83.6%)	91(75.8%)	103(92.0%)	
Psychological diseases n (%)		36 (15.5%)	16(13.3%)	20(17.9%)	0.43
Previous suicidal attempts n (%)		7(3.0%)	3(2.5%)	4(3.6%)	
Regular antipsychotics drug intake n (%)		38 (16.4%)	18(15.0%)	20(17.9%)	0.79
Relative ingested dose (mg) Median (IQR)		10.0 (5.0-15.0)	250.0(50.0-775.0)	300.0(95.0-600.0)	0.280
Delay interval (hours) Median (IQR)		4.0 (3.0-7.0)	4.0(3.0-6.0)	4.0(2.0-6.5)	0.727
2. **Type of Psychotropic exposure n (%)**					
1. **Antidepressant**		36(15.5%)	16(13.3%)	20(17.9%)	0.369
SSRI	**Paroxetine**	4(1.7%)	2(1.7%)	2(1.8%)	1.000
	Fluoxetine	4(1.7%)	1(0.8%)	3(2.7%)	0.355
	Escitalopram	3(1.3%)	1(0.8%)	2(1.8%)	0.611
NaSSA	**Mirtazapine**	4 (1.7%)	1(0.8%)	3(2.7%)	0.355

TCA	**Amitriptyline**	19(8.2%)	11(9.2%)	8(7.1%)	0.637
	Imipramine	2(0.9%)	0(0.0%)	2(1.8%)	0.232
2. **Sedative Hypnotic**		34(14.7%)	15(12.5%)	19(17.0%)	0.359
Benzodiazepine containing	**Clonazepam**	10(4.3%)	5(4.1%)	5 (4.5%)	1.000
	Bromazepam	1(0.4%)	1(0.8%)	0(0.0%)	1.000
Non-benzodiazepine containing	**Eszopiclone**	23(9.9%)	9(7.5%)	14(12.5%)	0.272
3. **Antipsychotics**		162(69.8%)	89(74.2%)	73(65.2%)	0.154
Atypical antipsychotics	**Clozapine**	106(45.7%)	52(43.3%)	54(48.2%)	0.512
	Risperidone	20(8.6%)	17(14.2%)	3(2.7%)	0.002*
	Quetiapine	12(5.2%)	6(5.0%)	6(5.4%)	1.000
	Olanzapine	7(3.0%)	3(2.5%)	4(3.6%)	0.714
	Aripiprazole	1(0.4%)	0(0.0%)	1(0.9%)	0.483
	Sulprid	1(0.4%)	0(0.0%)	1(0.9%)	0.483
Typical antipsychotics	**Chlorpromazine**	11(4.7%)	8(6.7%)	3(2.7%)	0.218
	Haloperidol	4(1.7%)	3(2.5%)	1(0.9%)	0.623
3. **Scores on admission and presenting clinical picture (Signs and Symptoms)**					
Glasgow Coma Scale Median (IQR)		13.0 (11.0-14.0)	13.0(10.0-14.0)	14.0(11.0-14.0)	0.807
Poison Severity Score (PSS) Median (IQR)		1.0 (1.0-2.0)	1.00 (1.00 - 2.00)	2.00 (1.00 - 3.00)	<0.001*
Consciousness state n (%)	**Alert**	30 (12.9%)	22(18.3%)	8(7.1%)	0.001*
	Confusion	29 (12.5%)	19(15.8%)	10(8.9%)	
	Disturbed consciousness level	102 (44.0%)	55(45.8%)	47(42.0%)	
	Lethargy	71 (30.6%)	24(20.0%)	47(42.0%)	
Neurological signs n (%)	**Agitation**	42 (18.1%)	26(21.7%)	16(14.3%)	0.001*
	Extrapyramidal	20 (8.6%)	10(8.3%)	0(0.0%)	
	Hallucination	23 (9.9%)	15(12.5%)	8(7.1%)	
	Agitation, hallucination and extrapyramidal manifestations	3 (1.3%)	3(2.5%)	0(0.0%)	
Cardiological symptoms n (%)	**Fainting**	46 (19.8%)	23(19.2%)	23(20.5%)	0.35
	Palpitation	47 (20.3%)	22(18.3%)	25(22.3%)	
	Fainting and palpitation	70 (30.2%)	35(29.2%)	35(31.3%)	
Respiratory signs n (%)	**Crepitation**	15 (6.5%)	10(8.3%)	5(4.5%)	0.79
	Wheezes	12 (5.2%)	7(5.8%)	5(4.5%)	
	diminished entry	10 (4.3%)	4(3.3%)	6(5.4%)	
	Wheezes, diminished entry & crepitation	2(0.9%)	1(0.8%)	1(0.9%)	
Gastro-intestinal manifestations n (%)	**Salivation**	60 (25.9%)	28(23.3%)	31(27.7%)	0.66
	Vomiting	3 (1.3%)	2(1.7%)	1(0.9%)	
	Dryness of the mouth	14 (6.0%)	8(6.7%)	6(5.4%)	

	Constipation	9 (3.9%)	5(4.2%)	4(3.6%)	
Dermatological manifestations n (%)	**Dryness of skin and mucous membranes**	37 (15.9%)	19(15.8%)	18(16.1%)	0.68
	Flushing	7 (3.0%)	4(3.3%)	3(2.7%)	
	Cyanosis	8 (3.4%)	2(1.7%)	6(5.4%)	
	Pallor	15 (6.5%)	7(5.8%)	8(7.1%)	
Pupil size n (%)	**Miosis**	138 (59.5%)	69(57.5%)	69(61.6%)	0.62
	Mydriasis	16 (6.9%)	10(8.3%)	6(5.4%)	
Nystagmus n (%)		55 (23.7%)	29(24.2%)	26(23.2%)	0.86
Anticholinergic toxidrome n (%)		137 (59.1%)	76(63.3%)	61(54.5%)	0.17
Serotonin syndrome n (%)		7 (3.0%)	4(3.3%)	3(2.7%)	0.77
4. **Vital signs assessment**					
Heart rate (beats/min) Median (IQR)		100.0 (90.0-120.0)	105.0(90.5-120.0)	100.0(90.0-120.0)	0.112
Systolic blood pressure (mmHg) Median (IQR)		110.0 (100.0-120.0)	110(90-120)	110(100-120)	0.57
Diastolic blood pressure (mmHg) Median (IQR)		70.0 (60.0-80.0)	70(60-80)	70(60-80)	0.21
Respiratory rate (breaths/min) Median (IQR)		19.0 (17.0-22.0)	20.0(18.0-23.5)	19.0(17.0-20.0)	0.041*
Temperature ^{o}C Median (IQR)		37.1 (37.0-37.3)	37.1(37.0-37.3)	37.2(37.0-37.4)	0.014*
SpO_2 (%) Median (IQR)		98.0 (93.0-99.0)	98.0(97.0-99.0)	94.0(91.0-99.0)	0.001*
5. **Investigations**					
Random blood sugar (mg/dl) Median (IQR)		115.5 (98.0-136.0)	107.0(91.5-124.0)	129.0(110.0-158.0)	0.001*
pH Median (IQR)		7.4 (7.3-7.4)	7.40 (7.36–7.44)	7.35 (7.21–7.43)	0.018*
HCO_3 mmol/L Median (IQR)		21.1 (19.0-23.1)	22.5 (21.0–24.5)	21.1 (19.0–23.0)	0.034*
$PaCO_2$ mmHg Median (IQR)		36.0 (31.4-39.4)	40.0 (38.0–42.0)	36.0 (32.0–39.0)	0.067
Six hours troponin (ng/l) n (%)		4.3 (2.5-9.8)	1.40(1.40-1.40)	2.80(1.40-7.77)	0.001*
QRS (m sec) Mean ± SD		91.7 ± 12.0	87.9±9.8	95.7±12.9	0.001*
QTc (m sec) Median (IQR)		427.0 (405.8-456.2)	417.0(398.5-437.5)	446.0(414.5-477.5)	0.001*
Cardiac dysrhythmias n (%)	**Sinus tachycardia**	148(63.8%)	59 (49.2%)	89 (79.5%)	0.001*
	Wide QRS	50 (21.6%)	12 (10.0%)	38 (33.9%)	
	Prolonged QTc	66 (28.4%)	16 (13.3%)	50 (44.6%)	
Duration of admission (hours) Median (IQR)		27.0 (16.0-46.5)	18.0(12.0-24.0)	46.0(36.0-72.0)	0.001*

*Significance at p<0.05

Table 2. Performance of various machine learning-derived models

Model	Model types	Accuracy	Sensitivity	Specificity	P-value	AUC
Binary logistic model	Null	0.4	0	1	For each variable*	0.5
	Full	0.6	0.6	0.6		0.6
	Backward	0.6	0.6	0.6		0.6
	Forward	0.7	0.7	0.8		0.8
	Stepwise	0.7	0.7	0.8		0.8
Random forest**		0.8	0.8	0.8	0.005	0.8
Support vector machine***	Radial basis function (Kernel function)	0.7	0.6	0.8	0.06	0.7
	Polynomial	0.7	0.5	0.9	0.2	0.7
	Linear	0.7	0.5	0.9	0.04	0.8
Gradient Boosting	XGBoost	0.6	0.5	0.7	0.3	0.7

* P-values and other parameters for all variables in all models are indicated in table S2

** Values are for the best RF model (the model with *ntree* = 100 and *mtry* = 8. Values for other RF models are shown in table S4

*** Model runs on top 10 important features. Additional models are shown in table S5

Table 3. Model parameters for the forward and stepwise multiple binary logistic model

Model	Term	Estimate (β)	SE	Z-score	P-Value	AIC*	odds ratio
Forward	SpO_2	-4.1	1.1	-3.7	0.0	139.3	0.0
Stepwise	SpO_2	-4.1	1.1	-3.7	0.0	139.3	0.0
Forward	QRS width (msec)	2.0	0.6	3.5	0.0	139.3	7.7
Stepwise	QRSwidth (msec)	2.0	0.6	3.5	0.0	139.3	7.7
Forward	Serum troponin (ng/l)	13.3	4.0	3.3	0.0	139.3	590018.0
Stepwise	Serum troponin(ng/l)	13.3	4.0	3.3	0.0	139.3	590018.0

*AIC: Akaike Information Criterion

** SE: standard error

Table 4. Performance of various SVM models on the test data

Model	Features	Accuracy	95% CI	NIR*	P-value	Sensitivity	Specificity	PPV**	NPV***	Detection Rate	Kappa	AUC
SVM Radial	All	0.6	0.4599–0.7819	0.6	0.3	0.5	0.8	0.8	0.5	0.3	0.3	0.6
SVM Radial	Top 10	0.7	0.5410–0.8458	0.6	0.1	0.6	0.8	0.8	0.6	0.4	0.4	0.7
SVM Polynomial	All	0.7	0.4865–0.8037	0.6	0.2	0.7	0.6	0.7	0.6	0.4	0.3	0.7
SVM Polynomial	Top 10	0.7	0.4865–0.8037	0.6	0.2	0.5	0.9	0.8	0.6	0.3	0.3	0.7
SVM Linear	All	0.7	0.4865–0.8037	0.6	0.2	0.6	0.7	0.7	0.6	0.4	0.3	0.7
SVM Linear	Top 10	0.7	0.5135–0.8250	0.6	0.1	0.5	0.9	0.9	0.6	0.3	0.4	0.7

*NIR: no Information rate, **PPV: Positive Predictive Value, *** NPV: Negative Predictive Value

Figures

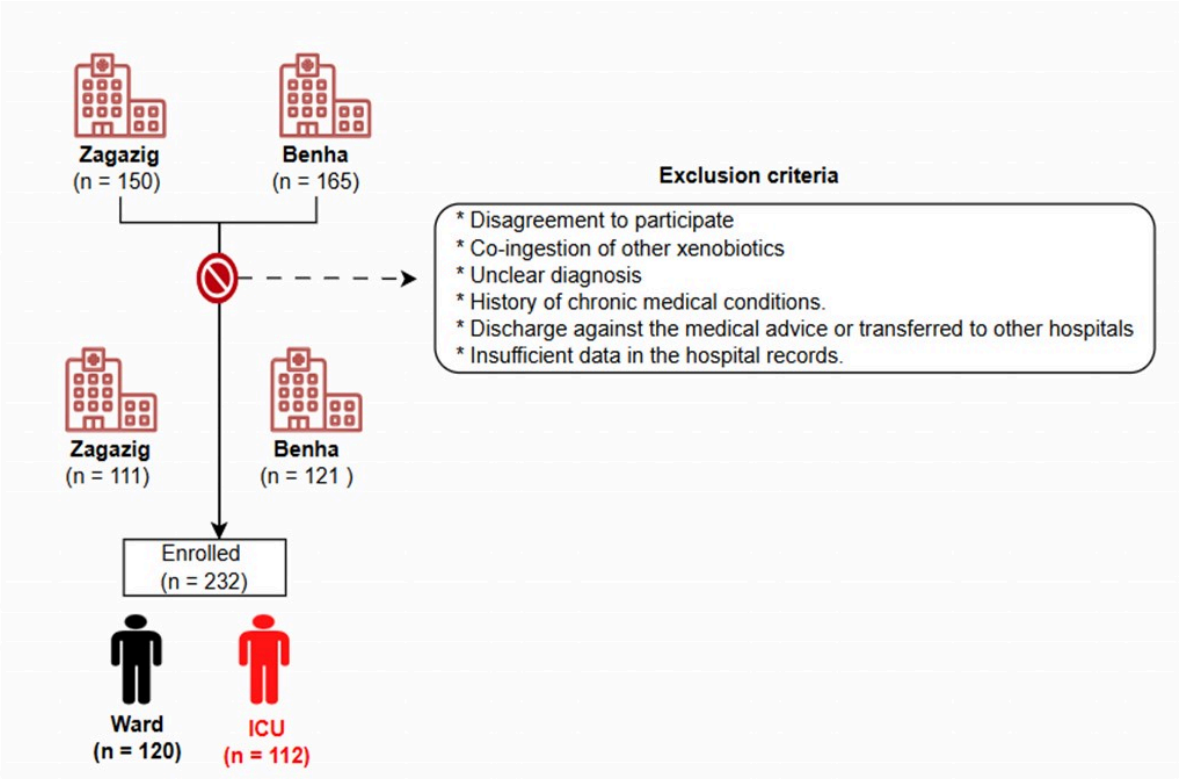


Figure 1

Overview of study design and number of participants from different centres

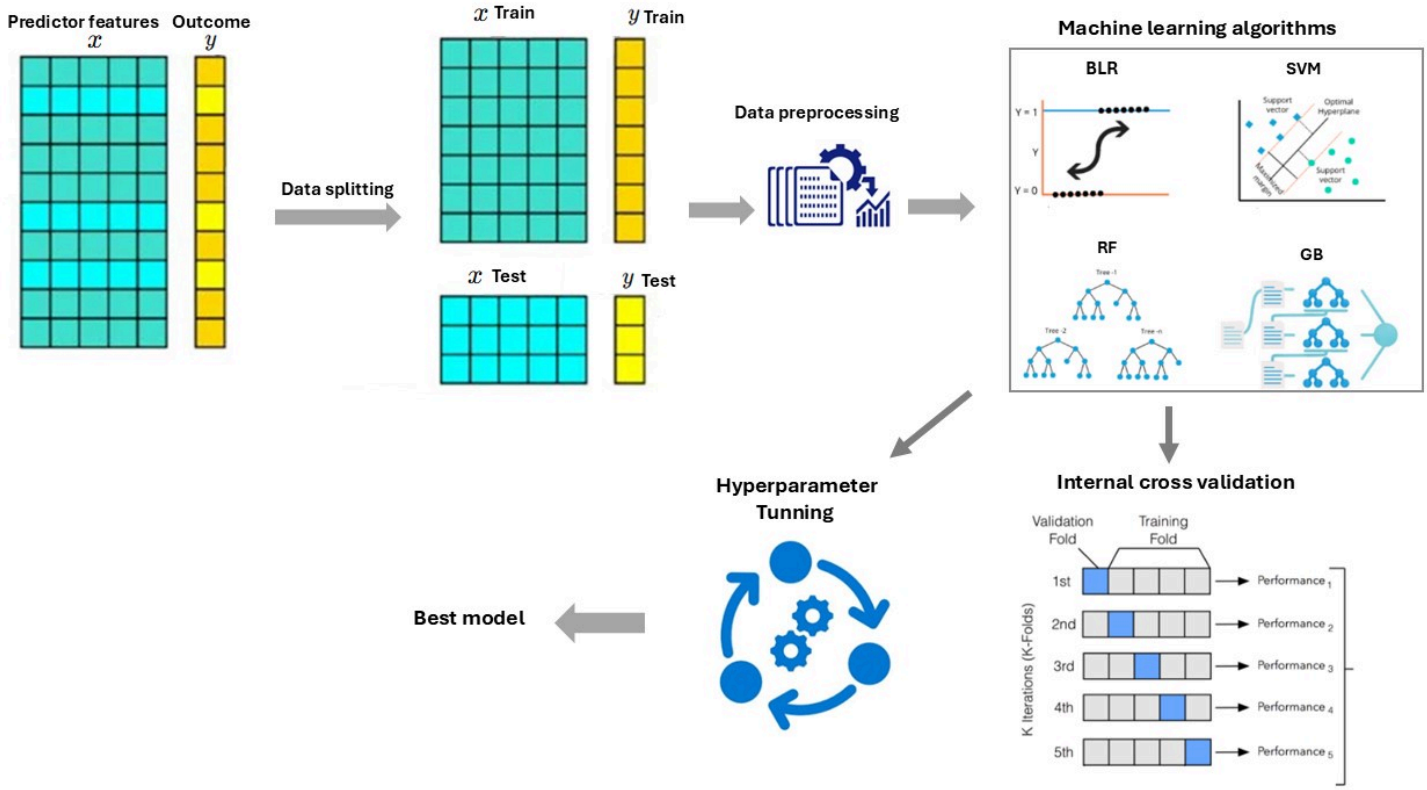


Figure 2

Workflow of machine learning modelling and feature engineering. The whole data are split into train and test data followed by data preprocessing, model training and testing including hyperparameters tunning and cross-validation.

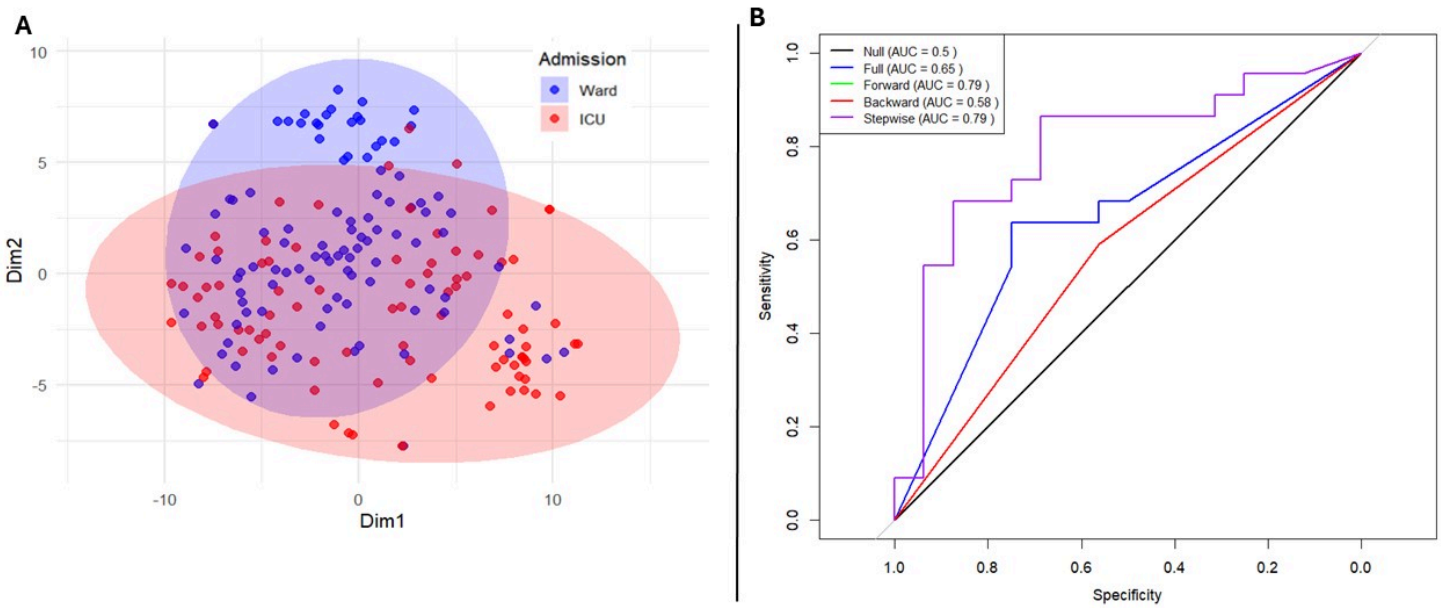


Figure 3

A. non-metric multidimensional scaling showing the degree of overlap between admission to ward or ICU as revealed by binary logistic regression model. Each dot represents one patient, and the ellipse refers to confidence intervals. **B.** Receiver operating characteristic curves for the 5-binary logistic regression models trained and tested on the data. The legend shows the area under the curve.

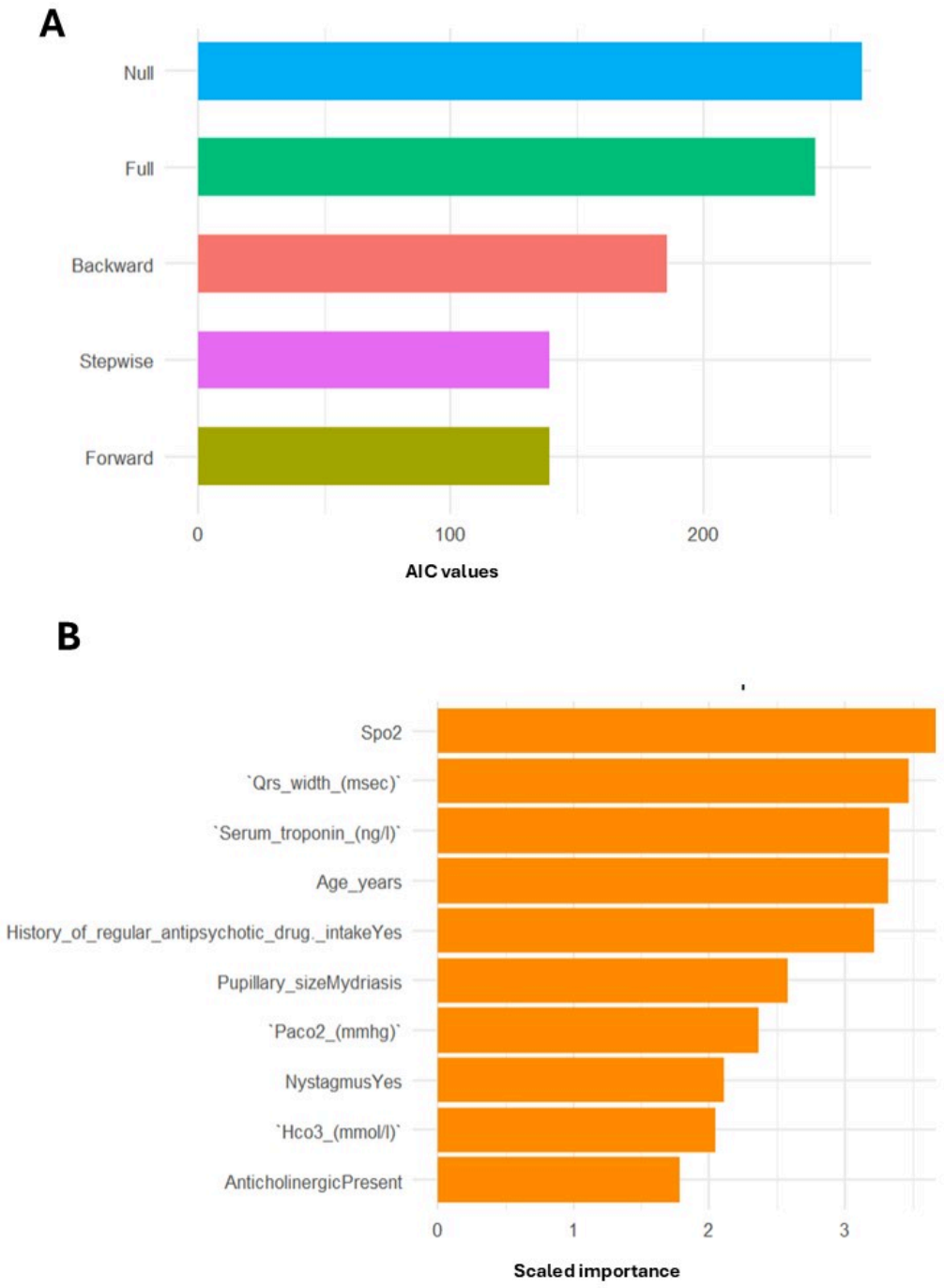


Figure 4

A. The Akaike Information Criterion (AIC) of various binary logistic models. Forward and stepwise models have the lowest AIC, indicating they fit the data well without being very complex. **B.** Top 10 important features as revealed by the forward and stepwise model**.**

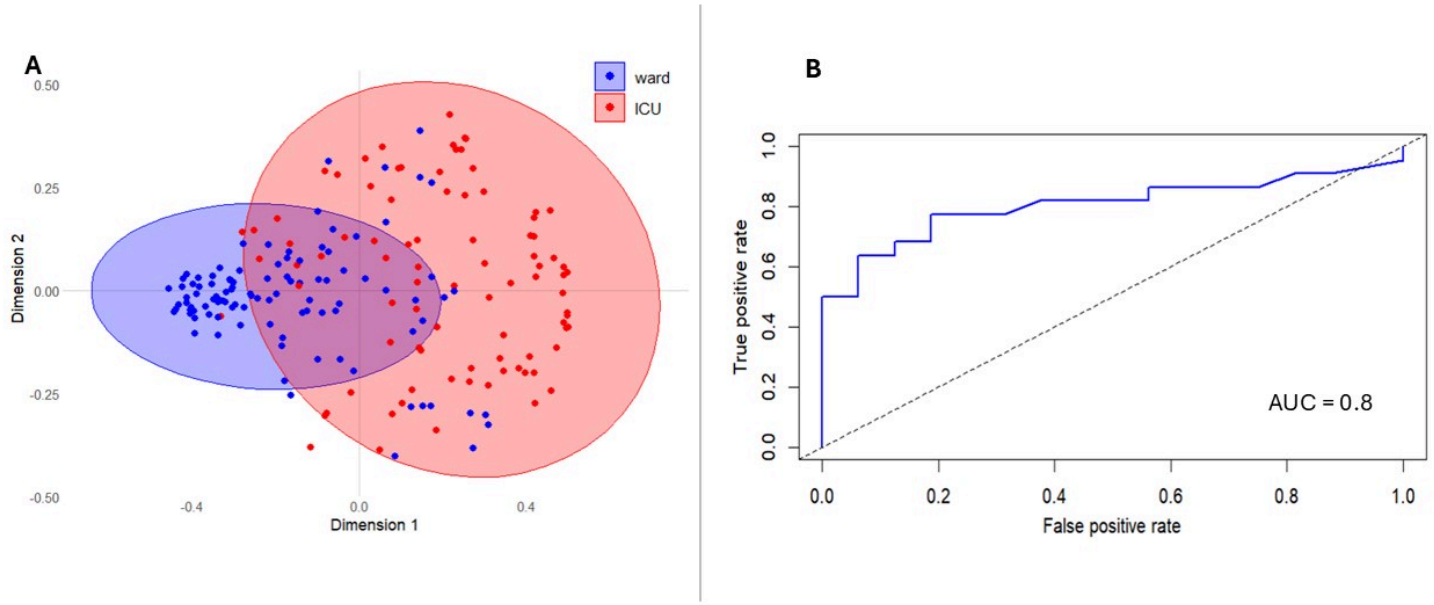


Figure 5

A. non-metric multidimensional scaling showing the degree of overlap between admission to ward or ICU as revealed by prediction from random forest model. Each dot represents one patient, and the ellipse refers to confidence intervals. **B.** Receiver operating characteristic curves for the best random forest model trained and tested on the data. AUC refers to area under the curve.

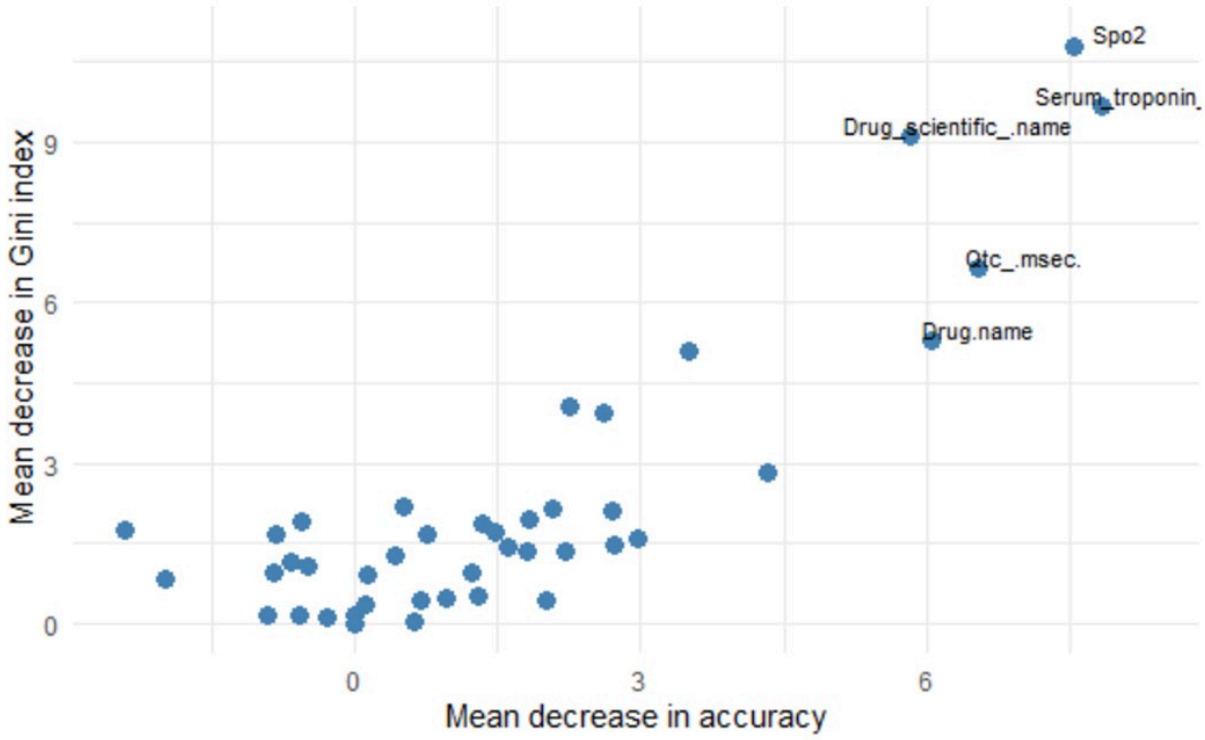


Figure 6

Variable importance as revealed by the best random forest model shown as mean decrease in accuracy (X-axis) and mean decrease in GINI index (Y-axis). Each dot refers to one feature and the ones highlighted are the most significant ones.

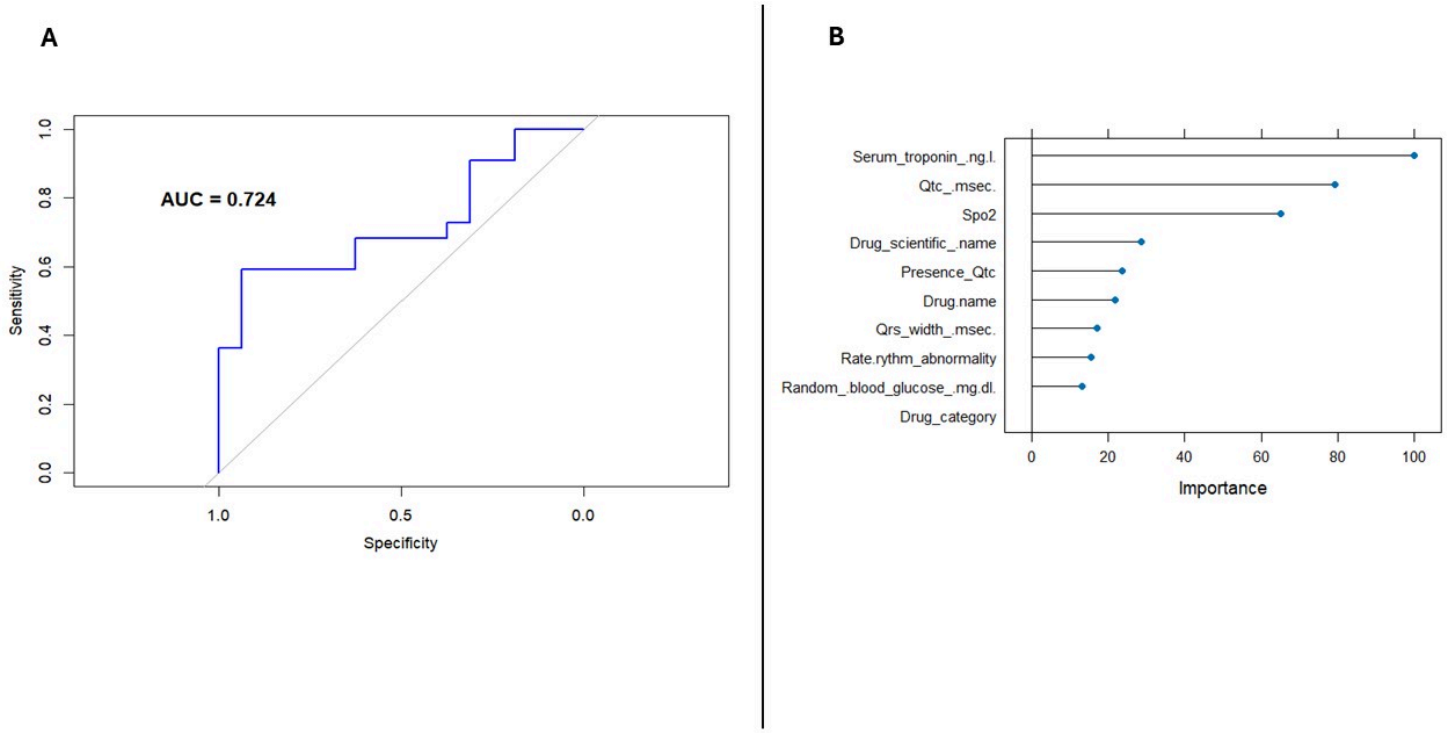


Figure 7

Receiver operating characteristic curve **(A)** and significant features as revealed by the support vector machine models **(B)** of the SVM (SVM Radial based on top 10 features). AUC: area under the curve.

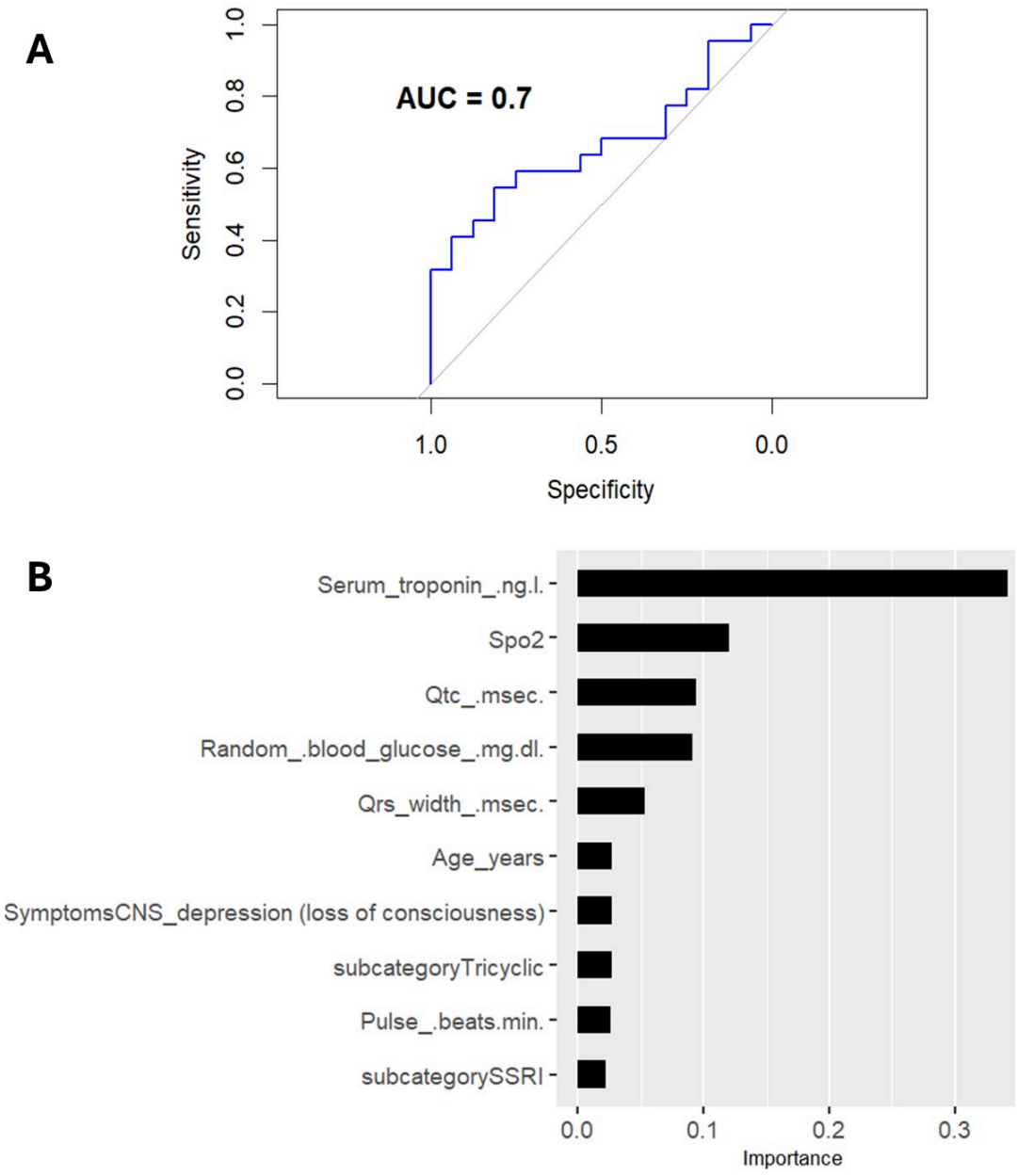


Figure 8

A. Receiver operating characteristic curves of the best XGBoost model showing an area under the curve of 0.7. **B.** Top important features as revealed by the best XGBoost.

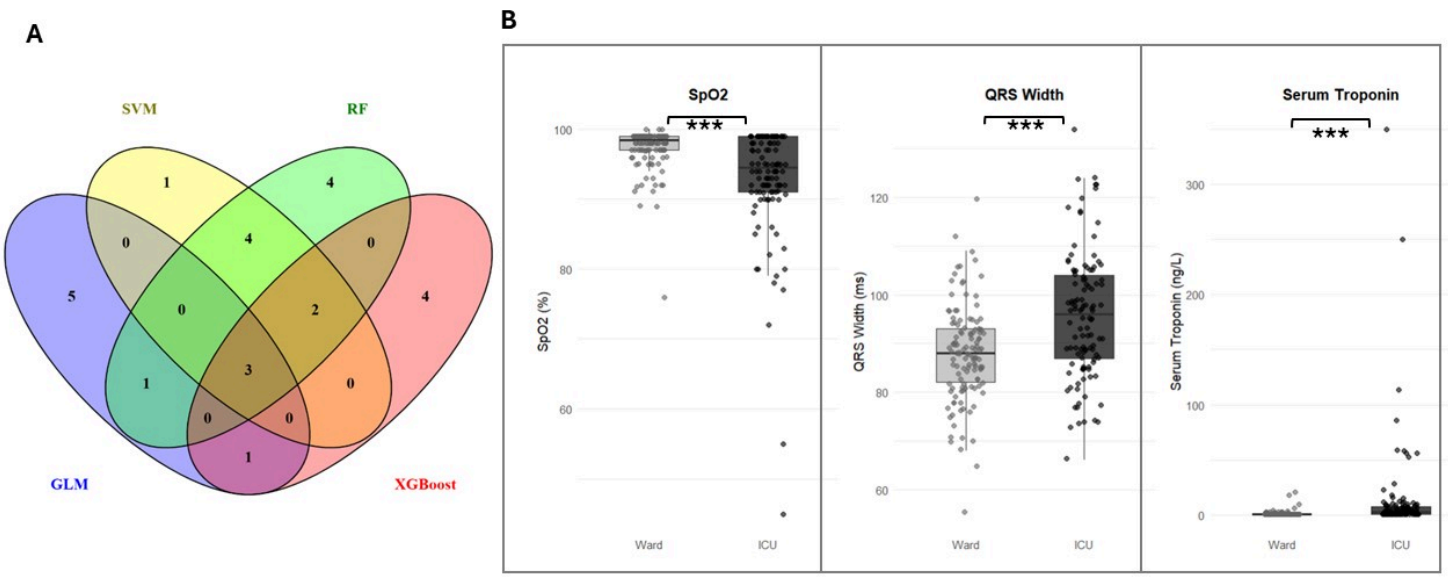


Figure 9

A. Shared and unique important features across the 4-tested models**. B.** Pairwise comparison of the 3-shared top important features between patients admitted to ICU and ward. Asterisks indicate significance levels (at P-value threshold of 0.05).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.jpg
- FigureS2.jpg
- FigureS3.jpg