A machine learning-based prediction of hospital mortality in patients with postoperative sepsis

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Abstract

Background: The incidence of postoperative sepsis is continually increased, while few studies have specifically focused on the risk factors and clinical outcomes associated with the development of sepsis after surgical procedures. The present study aimed to develop a mathematical model for predicting the in-hospital mortality among patients with postoperative sepsis.

Methods: Surgical patients in Medical Information Mart for Intensive Care (MIMIC-III) database who simultaneously fulfilled Sepsis 3.0 as well as Agency for Healthcare Research and Quality (AHRQ) criteria during ICU admission were incorporated. We employed both extreme gradient boosting (XGBoost) and stepwise logistic regression model to predict in-hospital mortality among included patients with postoperative sepsis. Consequently, model performance was assessed from the angles of discrimination and calibration.

Results: We included 3713 patients who fulfilled our inclusion criteria, in which 397 (10.7%) patients died during hospitalization, while 3316 (89.3%) of them survived through discharge. Fluid-electrolyte disturbance, coagulopathy, renal replacement therapy (RRT), urine output, and cardiovascular surgery were important features related to the in-hospital mortality. The XGBoost model had a better performance in both discriminatory ability (c-statistics, 0.835 [95% CI, 0.786 to 0.877] *vs.* c-statistics, 0.737 [95% CI, 0.688 to 0.786]) and goodness of fit (visualized by calibration curve) compared to the stepwise logistic regression model.

Conclusion: XGBoost model appears to be a better performance in predicting hospital mortality among postoperative septic patients compared to the conventional stepwise logistic regression model. Machine learning-based algorithm might have significant application in the development of early warning system for septic patients following major operations.

Background

Sepsis is severely complicated by major surgery, and responsible for poor outcomes by inducing multiple organ dysfunction and increasing in-hospital mortality. Although great progress has been made in the early recognition and therapeutic strategies, the incidence as well as mortality of septic complications remain unacceptably high (1–3). It has been documented that there are approximately 30% of septic patients after surgical procedures, and the proportions of patients who developed postoperative sepsis increase annually (4, 5). Given the high prevalence and poor prognosis, the Agency for Healthcare Research and Quality (AHRQ) defined the ‘postoperative sepsis’ as a critical indicator for patients’ safety, which mainly focused on preventable surgical complications and iatrogenic events after surgical procedures (6, 7).

Various evidences have demonstrated that immunocompromised state is strongly associated with the pathogenesis of postoperative sepsis due to collapsed physical barrier and immune function by surgical insults (8). For example, impaired antigen presenting capacity of monocytes and dominant differentiation

of type 2 helper T cells were all characterized in the animal models of postoperative sepsis (9–11). Meanwhile, researchers identified disparate gene expression profiles of whole blood cells from surgical patients with or without postoperative sepsis, in which they found that the expression patterns of interleukin (IL) 1 beta (IL-1β), tumor necrosis factor (TNF) superfamily, member 2 and CD3D were significantly different (12). However, the 'Surviving Sepsis Campaign' (SSC) guidelines didn't provide distinctive treatments for postoperative sepsis from other types of sepsis (13). Moreover, there were insufficient clinical trials that specifically testified the guidelines in the postoperative sepsis cohort. Most of the studies examined the short-term mortality in septic patients admitted to emergency department or intensive care unit (ICU) that contained all types of sepsis (7, 14, 15). On the contrary, few studies specifically targeted ICU surgical patients complicated with postoperative sepsis and their clinical outcomes.

In the present study, we aimed to establish a prediction model on in-hospital mortality among patients with postoperative sepsis. Given the limitation of conventional statistical method in processing retrospective data contained covariates of high correlation and inevitable missing values, we enrolled advanced machine learning algorithm, called extreme gradient boosting (XGBoost) to identify the important clinical features for predicting hospital mortality.

Methods

Database

Medical Information Mart for Intensive Care (MIMIC-III), a large online critical care database was applied for the current study (16). Of note, MIMIC-III was a comprehensive dataset which contained clinical data of all the patients admitted to ICU of Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, from 2001 to 2012. In brief, it was comprised of more than fifty thousand distinct adult (aged > 16 years) ICU admissions as well as approximately eight thousand neonate admissions. We had obtained the permission for accessing the database after the completion of "Protecting Human Research Participants", an online training course launched by National Institutes of Health (NIH) (certification number: 32450965). We conducted this study in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) recommendation (17).

Study Population

The selection of patients was based on "postoperative sepsis" criteria proposed by AHRQ combining with Sepsis 3.0 criteria, in which sepsis was diagnosed by sequential organ failure assessment (SOFA) score ≥ 2 plus documented or suspected infection (6, 18). Additionally, infection was confirmed in accordance with ICD-9 code found in the MIMIC-III database. Given that, we included all surgical ICU patients (aged > 18 years) in MIMIC-III, who underwent surgical procedures prior to ICU admission and fulfilled Sepsis 3.0 criteria during ICU admission. Patients were excluded even if they were in line with AHRQ selection

criteria: (1) who had a principal or secondary diagnosis of sepsis or infection on admission; (2) who were diagnosed with cancer and having other immunocompromised states, including hematologic malignancies, HIV, prolonged usage of corticosteroids, and organ transplantation; (3) who were admitted to ICU with pregnancy, childbirth, or puerperium; (4) who stayed in hospital less than 4 days; (5) who had incomplete or unobtainable medical data records on admission.

Variables Extraction And Outcome Measurement

Clinical and laboratory variables were collected within the first 24 hours since ICU admission. Demographic data was obtained, including age, gender, body mass index (BMI), and elective surgical type. Laboratory findings and blood gas analysis data, including white blood cell (WBC) count, hematocrit, platelet count, glucose, lactate, creatinine, blood urea nitrogen (BUN), coagulation profile, chloride, potassium, sodium, bicarbonate, albumin, bilirubin, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), total CO_2 and pH were incorporated. In addition, vital signs, including blood pressure, respiratory rates, heart rates, and body temperature were included. Comorbidities, including congestive heart failure, cardiac arrhythmia, neurological disorders, diabetes, anemia, and obesity, were also recorded. Prognostic scoring systems, including SOFA score, Oxford Acute Severity of Illness Score (OASIS), Simplified Acute Physiology Score II (SAPSII), and Glasgow Coma Scale (GCS) were calculated and analyzed by using variables obtained in first 24 hours during admission. Notably, both the maximum and minimum values of some indictors were considered and analyzed for multiple measurements.

As severe data missing might render bias, all eligible predictors were screened, and variables with more than 30% missing values were not taken into subsequent model establishment. Correspondingly, we conducted multivariate imputation for variables with less than 30% missing values.

We chose in-hospital mortality as our primary endpoint, which was defined as survival status at hospital discharge. Patients without outcome information were excluded from the final cohort.

Statistical analysis

Baseline characteristics of enrolled participants were presented and compared between survivors and non-survivors by applying either Student t test, Chi-square test and Mann-Whitney U test as appropriate. Continuous variables were characterized as mean (standardized differences [SD]) or median (interquartile range [IQR]), while categorical or ranked data were reported as count and proportion.

We employed stepwise logistic regression model to select predictors of in-hospital mortality. Both forward and backward directions were used in variable selection process, in which Akaike Information Criterion (AIC) was applied as the selection criteria of the optimal model.

Furthermore, we applied Extreme Gradient Boosting (XGBoost) model to predict in-hospital death among patients with postoperative sepsis. XGBoost was a machine learning algorithm, which mainly functioned as iterative refit of weak classifier to residuals of previous models, meaning that the current weak classifier was generated based on previous one in order to optimize the predictive efficiency (19, 20). In each round of iteration, it focused more on misclassified observations. As eligible variables were entered into the model, it outputted the importance score of each variable. Meanwhile, XGBoost could automatically process missing data through assigning a default direction to the null values. To reach the optimal model performance of XGBoost, we assessed and tuned the hyperparameters, including learning rates, maximum depth of a tree, number of estimators, alpha and lambda. In this study, the original dataset was randomly divided into 5 subsets. One subset was used for testing, while the other 4 folds were processed to tune the hyperparameters, in which 20% were applied for calibration, and 3-fold cross validation with grid search was conducted in remaining 80% of data. The hyperparameters with the highest area under curve (AUC) were selected. The sufficiently tuned XGBoost hyperparameters were subsequently added back for training and calibrating the model with 5-fold cross validation, which was further validated in testing subsets (21).

Model performance of both models was assessed in multiple dimensions. To test discriminatory ability, we used receiver operating characteristic (ROC) curve as well as c-statistic. Meanwhile, calibration plot revealed the correlation between observed and predicted risk, which was applied to evaluate the goodness of fit. Aforementioned statistical analyses were performed by using IBM SPSS Statistics software (version 23.0), Python software (version 3.4.3), and R software (version 3.6.1). Two tailed P value less than 0.05 was deemed as statistical significance.

Results

Participants

Among 46520 patients identified in the MMIC-III database, 15302 of them met with Sepsis 3.0 criteria. There were 4653 potentially eligible adult patients (aged ≥ 18 years) who underwent surgical procedures prior to ICU admission. After excluded 940 patients in accordance with the AHRQ exclusion criteria, 3713 patients were deemed to develop postoperative sepsis and were eventually incorporated into the study cohort, in which 397 (10.7%) patients died during hospitalization and 3316 (89.3%) of them survived through discharge. The detailed information with regard to the enrollment and selection process was presented in Fig. 1.

The comparison of baseline characteristic between survivors and non-survivors was summarized in Table 1. Notably, patients of the non-survivor group were much older than those of the survivor group (86.6 ± 59.2 vs. 74.6 ± 48.0; P = 0.001), while more patients in the survivor group underwent cardiovascular surgery prior to ICU admission compared to those in the non-survivor group (42.9% vs. 35.3%; P = 0.04). As for the comorbidities, patients with postoperative sepsis who died during hospitalization had higher incidence of congestive heart failure (40.6% vs. 31.2%; P < 0.001), cardiac

arrhythmias (48.1% vs. 39.4%; P = 0.001), renal failure (24.7% vs. 15.8%; P < 0.001), coagulopathy (30.5% vs. 13.0%; P < 0.001), and digestive disorders (16.9% vs. 7.8%; P < 0.001). The maximum heart rates (107.6 ± 23.4 vs. 105.4 ± 19.4; P < 0.001) and maximum respiratory rates (29.0 ± 8.1 vs. 27.7 ± 6.7; P < 0.001) were significantly higher in the non-survivor group, while the minimum systolic blood pressure (BP) (84.1 ± 18.3 vs. 89.0 ± 16.2; P = 0.036), minimum diastolic BP (55.6 ± 9.7 vs. 58.3 ± 9.4; P = 0.004) as well as minimum mean BP (52.7 ± 14.1 vs. 56.5 ± 12.5; P = 0.015) were lower than those from the survivor group. Compared to survivors, non-survivors had higher levels in blood lactate (2.9 [IQR: 1.8, 5.8] vs. 2.3 [IQR: 1.5, 3.8]; P < 0.001), BUN (30 [IQR: 20, 46] vs. 21 [IQR: 15, 32]; P < 0.001), and creatinine (1.4 [IQR: 0.9, 2.4] vs. 1.1 [IQR: 0.8, 1.6]; P < 0.001). Additionally, higher international normalized ratio (INR) (1.9 ± 1.8 vs. 1.6 ± 1.1; P < 0.001), longer prothrombin time (PT) (16.1 [IQR: 14.1, 20.0] vs. 15.2 [IQR: 13.7, 17.3]; P < 0.001), and activated partial thromboplastin time (aPTT) (39.5 [IQR: 30.6, 71.0] vs. 35.2 [IQR: 29, 48.2]; P < 0.001) were noted in the non-survivor group when compared to those in the survivor group.

Table 1

Baseline characteristics between survivors and non-survivors.

Characteristics	Survivors (n = 3316)	Non-survivors (n = 397)	P value
Demographic characteristics			
Age, mean (SD)	74.6 (48.0)	86.6 (59.2)	0.001
Gender female, n (%)	1511 (45.6)	170 (42.8)	0.299
BMI, mean (SD)	29 (7.6)	28.1 (7.4)	0.878
Elective surgical type, n (%)			
Cardiovascular surgery	1421 (42.9)	140 (35.3)	0.004
Neurosurgery	462 (13.9)	67 (16.9)	0.113
Orthopedic surgery	178 (5.4)	16 (4.0)	0.258
Thoracic surgery	155 (4.7)	19 (4.8)	0.921
Plastic surgery	23 (0.7)	2 (0.5)	0.662
Comorbidities, n (%)			
Congestive heart failure	1034 (31.2)	161 (40.6)	< 0.001
Cardiac arrhythmias	1306 (39.4)	191 (48.1)	0.001
Diabetes	1018 (30.7)	112 (28.2)	0.309
Renal failure	525 (15.8)	98 (24.7)	< 0.001
Coagulopathy	430 (13.0)	121 (30.5)	< 0.001
Digestive disorders	258 (7.8)	67 (16.9)	< 0.001
Mechanical ventilation, n (%)	2259 (68.1)	284 (71.5)	0.167
Renal replacement therapy, n (%)	153 (4.6)	49 (12.3)	< 0.001
Prognostic scoring system, median (IQR)			

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Acute Severity of Illness Score; BP, blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; PT, prothrombin time.

Characteristics	Survivors (n = 3316)	Non-survivors (n = 397)	P value
SOFA	5 (3, 7)	6 (4, 10)	< 0.001
SAPS II	37 (30, 45)	47 (40, 57)	< 0.001
OASIS	33 (27, 39)	39 (33, 44)	< 0.001
Vital signs, mean (SD)			
Maximum heart rates (/min)	105.4 (19.4)	107.6 (23.4)	< 0.001
Minimum systolic BP (mmHg)	89.0 (16.2)	84.1 (18.3)	0.036
Minimum diastolic BP (mmHg)	58.3 (9.4)	55.6 (9.7)	0.004
Minimum mean BP (mmHg)	56.5 (12.5)	52.7 (14.1)	0.015
Maximum respiratory rates (/min)	27.7 (6.7)	29.0 (8.1)	< 0.001
Maximum temperature (°C)	37.7 (0.8)	37.6 (0.8)	0.065
Laboratory findings			
Minimum WBC (× 10^9/L, median [IQR])	10.2 (7.2, 13.9)	11.1 (7.8, 15.6)	0.005
Minimum platelet (× 10^9/L, median [IQR])	177 (119, 253)	149 (89, 234)	< 0.001
Maximum hematocrit (%, mean [SD])	35.1 (5.2)	34.8 (5.5)	0.233
Minimum hematocrit (%, mean [SD])	27.2 (5.7)	27.4 (5.6)	0.522
Maximum lactate (mmol/L, median [IQR])	2.3 (1.5, 3.8)	2.9 (1.8, 5.8)	< 0.001
Maximum BUN (median [IQR])	21 (15, 32)	30 (20, 46)	< 0.001
Maximum creatinine (μmol/L, median [IQR])	1.1 (0.8, 1.6)	1.4 (0.9, 2.4)	< 0.001
Maximum INR	1.6 (1.1)	1.9 (1.8)	< 0.001

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Acute Severity of Illness Score; BP, blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; PT, prothrombin time.

Characteristics	Survivors (n = 3316)	Non-survivors (n = 397)	P value
Maximum APTT (median [IQR])	35.2 (29, 48.2)	39.5 (30.6, 71.0)	< 0.001
Maximum PT (median [IQR])	15.2 (13.7, 17.3)	16.1 (14.1, 20.0)	< 0.001
Maximum glucose (mg/dL, median [IQR])	172 (142, 207)	175 (140, 222)	0.194
Minimum glucose (mg/dL, median [IQR])	97 (80, 117)	101 (78, 121)	0.271

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Acute Severity of Illness Score; BP, blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; PT, prothrombin time.

Stepwise Logistic Regression Model

We performed stepwise logistic regression analysis with both forward and backward methods, in which the classifier incorporated 36 variables into the final model. As shown in Table 2, it was found that female (odds ratio (OR), 0.65 [95% confidence interval [CI, 30.6 to 71.0]), patients with lower BMI (OR, 0.97 [95% CI, 0.95 to 0.99]), patients with higher PO_2 (OR for with every 10% increment, 0.98 [95% CI, 0.96 to 0.99]), and oxygen saturation (SpO_2) (OR, 0.78 [95% CI, 0.66 to 0.91]) had higher possibility to survive through discharge. Conversely, neurosurgery (OR, 2.53 [95% CI, 1.57 to 4.04]), the complication of multiple comorbidities, especially for coagulopathy (OR, 2.36 [95% CI, 1.49 to 3.68]), greater values of INR (OR, 1.75 [95% CI, 1.15 to 2.70]), and sodium (OR, 1.08 [95% CI, 1.03 to 1.13]) were responsible for increased risk of in-hospital death among ICU patients with postoperative sepsis. As expected, higher scores of several prognostic scoring systems, including SOFA (OR, 1.08 [95% CI, 1.01 to 1.16]), SAPS II (OR, 1.04 [95% CI, 1.02 to 1.06]), and OASIS (OR, 1.05 [95% CI, 1.03 to 1.08]) were linked to increased in-hospital mortality.

Table 2

Variable selection of stepwise logistic regression model.

Variables	OR [95% CI]	P value
Demographic characteristics		
Gender female	0.65 [0.48, 0.88]	0.006
BMI	0.97 [0.95, 0.99]	0.012
Elective surgical types		
Neurosurgery	2.53 [1.57, 4.04]	< 0.001
Thoracic surgery	1.91 [0.93, 3.71]	0.065
Comorbidities		
Cardiac arrhythmias	1.31 [0.97, 1.78]	0.079
Peripheral vascular diseases	1.61 [1.14, 2.25]	0.006
Coagulopathy	2.36 [1.49, 3.68]	< 0.001
Digestive disorders	2.36 [1.66, 3.34]	< 0.001
Anemia	0.68 [0.46, 0.98]	0.044
Mechanical ventilation	0.71 [0.46, 1.11]	0.133
Prognostic scoring system		
SOFA	1.08 [1.01, 1.16]	0.027
SAPS II	1.04 [1.02, 1.06]	< 0.001
OASIS	1.05 [1.03, 1.08]	< 0.001
GCS	1.10 [1.04, 1.17]	< 0.001
Vital signs		
Maximum systolic BP	0.99 [0.99, 1.00]	0.12
Mean diastolic BP	0.94 [0.91, 0.98]	0.001
Mean mean BP	1.04 [1.00, 1.08]	0.027

Abbreviations: OR, odds ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Acute Severity of Illness Score; GCS, Glasgow Coma Scale; BP, blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; PT, prothrombin time; PO_2, partial pressure of arterial oxygen; PCO_2, partial pressure of arterial carbon dioxide; SpO_2, Oxygen saturation; pH, potential hydrogen; BE, base excess.

Variables	OR [95% CI]	P value
Mean respiratory rate	1.03 [1.00, 1.07]	0.076
Laboratory findings		
Maximum WBC	0.97 [0.93, 1.00]	0.067
Minimum WBC	1.06 [1.01, 1.11]	0.015
Minimum BUN	1.01 [1.00, 1.02]	0.097
Maximum creatinine	0.63 [0.39, 0.98]	0.052
Minimum creatinine	1.50 [0.90, 2.57]	0.127
Maximum INR	1.16 [0.97, 1.40]	0.085
Minimum INR	1.75 [1.15, 2.70]	0.009
Maximum APTT	1.01 [1.00, 1.01]	0.008
Maximum PT	0.96 [0.92, 1.00]	0.043
Maximum sodium	1.08 [1.03, 1.13]	0.002
Minimum potassium	0.78 [0.58, 1.06]	0.115
Maximum chloride	0.96 [0.92, 0.99]	0.025
Maximum PO_2 (with every 10% increment)	0.98 [0.96, 0.99]	< 0.001
Mean PCO_2	0.93 [0.90, 0.97]	< 0.001
Maximum SpO_2	0.78 [0.66, 0.91]	0.002
Minimum SpO_2	1.02 [1.00, 1.03]	0.001
Minimum pH (with every 0.1 increment)	0.51 [0.35, 0.75]	0.001
Minimum BE	1.10 [1.02, 1.18]	0.015

Abbreviations: OR, odds ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Acute Severity of Illness Score; GCS, Glasgow Coma Scale; BP, blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; PT, prothrombin time; PO_2, partial pressure of arterial oxygen; PCO_2, partial pressure of arterial carbon dioxide; SpO_2, Oxygen saturation; pH, potential hydrogen; BE, base excess.

Xgboost Model

After tuning and grid search, the hyperparameters applied in the current XGBoost model were as follows: learning rates = 0.01, number of estimators = 1000, maximum depth of a tree = 5, alpha = 0 and lambda = 0. The importance of feature was assigned by weight which was calculated by the number of times that a feature was used to split the data across all trees. Feature importance revealed the relative contribution of each predictors on predicting in-hospital mortality. As shown in Fig. 2, the fluid-electrolyte disturbance and coagulopathy were the top ranked variables that were correlated to in-hospital death among patients with postoperative sepsis, followed by renal replacement therapy (RRT), urine output, cardiovascular surgery, and digestive disorders.

Evaluation Of Model Performance

The discriminatory power of both stepwise logistic and XGBoost models was evaluated by using ROC analysis and c-statistics (calculated by AUC). The XGBoost had a significantly higher c-statistics compared to that of the stepwise logistic regression model (c-statistics, 0.835 [95% CI, 0.786 to 0.877] vs. c-statistics, 0.737 [95% CI, 0.688 to 0.786]), suggesting a better discrimination of XGBoost (Fig. 3). Meanwhile, as shown in Fig. 4, it presented the calibration curve of both models, in which we could clearly observe that XGBoost showed a greater goodness of fit than logistic regression model.

Discussion

Major findings

In the current study, we identified various clinical indictors that were associated with increased in-hospital mortality among patients with postoperative sepsis admitted to ICU. By applying sophisticated machine learning algorithm, we found that fluid-electrolyte disturbance, coagulopathy, RRT, urine output, and cardiovascular surgery were significant features for predicting in-hospital death. In addition, XGBoost model revealed a better performance in discrimination and calibration than that of the conventional stepwise logistic regression model.

Relation To Other Works

Plenty of evidences have indicated that sepsis is a robust predictor of increases in short-term and long-term mortality for postsurgical patients (7, 15, 22, 23). A large nationwide epidemiology of patients with elective surgery revealed an increased incidence of postoperative sepsis, ranging from 0.3% in 1997 to 0.9% in 2006, while they found that the in-hospital morality significantly decreased from 1997 to 2006 (44.4–30%) (22). Recently, Ou and his colleague conducted a population-based analysis in patients who underwent coronary artery bypass grafting (CABG) surgery, and they noticed that the incidence of postoperative sepsis was approximately 2%, and the mortality of those patients admitted to public hospital and private were 11.9% and 18.3%, respectively (15). In a retrospective analysis performed by Mørch et al., researchers specifically focused on the clinical outcomes of patients who developed

postoperative sepsis after hip fracture surgery. They documented a 30-day mortality of 15.8% among those patients, which was significantly higher than patients without postoperative sepsis (23). In our study, we identified an in-hospital mortality of 10.7% among ICU patients who developed postoperative sepsis. We observed an evident decline of mortality rates among surgical patients with sepsis over the past decades, while the morbidity rates remained sustained growth. The reduction of overall mortality rates might be attributed to the progress in perioperative care and use of antibiotics. Meanwhile, the mortality of patients with postoperative sepsis was disparate from that of the other types of septic patients, which could be explained by different clinical settings as well as co-morbidities state.

Clinical Implications

The XGBoost model appears to be capable of accurately predicting in-hospital death among patients developing postoperative sepsis. Although several studies have identified the risk factors for the short-term or long-term mortality of septic patients following major operations, few of them establish feasible models to predict clinical outcomes of those patients. Unlike other types of sepsis, postoperative sepsis shared some unique characteristics in both etiology and pathophysiology, which should be taken into a specific subset (5). Therefore, it is of great importance to early recognize patients with postoperative sepsis who are at high risk of death and identify preventable indictors. Since the recent advancements in machine learning techniques, the magnitude of variables and indictors that we are able to process is largely enriched. Taken together, advanced machine learning algorithm allows us to establish a more optimal model that performed better when compared to the conventional generalized linear models. By applying such model, physician and care givers could be alerted by the time when surgical patients were admitted to ICU complicated with postoperative sepsis, thereby employing efficient yet personalized therapeutic strategies to avoid worsening prognosis. Although the effectiveness of the XGBoost model had been validated in our study, the model was based on a single center retrospective database. Thus, further prospective cohort studies are required to evaluate the unity of this model.

Our results revealed that complication of coagulopathy and coagulation profile during admission, including platelet counts, PT, APTT, and INR, were associated with increased in-hospital death among patients developed postoperative sepsis. The occurrence of coagulopathy was commonly complicated with sepsis, which was strongly related to organ dysfunction and poor outcomes (24, 25). The activation of monocytes and endothelial cells is evident in the early phase of sepsis and results in massive exposure of tissue factor, thereby contributing to the over activation of coagulation and subsequent thrombin generation (26). Concomitantly, anticoagulant pathways, such as protein C system, are impaired by overexpression of proinflammatory cytokines (26). The imbalance between coagulation and anticoagulant pathways can be further augmented by surgical insults, and it leads to the upregulation of plasminogen activator inhibitor and consequent hyperfibrinolysis (27, 28). Coagulation abnormalities have been reported to induce formation of microvascular clots and disseminated intravascular coagulation (DIC), in turn resulting in tissue ischemia and organ dysfunction (29, 30). Of note, majority of patients within our cohort had been exposed with cardiovascular surgery. Some of those patients might

frequently receive anticoagulant agents, which could be an additional cause for coagulation abnormalities. Given that, our study potentially implicated that extensive coagulation monitor as well as immediate postoperative bleeding management were specifically required for patients with postoperative sepsis. Early implementation of rotational thromboelastometry (ROTEM) and thrombelastography (TEG) appears to be beneficial for postoperative sepsis patients who are at high risk of death during hospitalization (31, 32). As documented in large randomized controlled trials (RCTs), the administration of either antithrombin III or human recombinant thrombomodulin could improve short-term mortality among septic patients, but no relevant trails specifically targeted patients with postoperative sepsis (33, 34). The results of our study suggested that secondary analyses of previously published RCTs and future large trails were both needed for septic patients following major operations. In addition, our models identified that fluid-electrolyte disturbance, sodium and chloride levels were associated with the in-hospital mortality, which could be explained by the deteriorative effects of acidosis on fibrin polymerization and clot integrity (27, 35).

From the present observation, we noticed that patients underwent neurosurgery prior to ICU admission showed the highest in-hospital mortality compared to those with other types of surgery. Meanwhile, it revealed that neurosurgery was a robust predictor of in-hospital death among patients with postoperative sepsis in both models. Neurosurgical procedures might cause severe postsurgical complications, including intracerebral hemorrhage, brain edema, and cerebral ischemia, which would have serious impacts on clinical outcomes of neurosurgical patients (36). Furthermore, neurosurgical insults could affect hypothalamic-pituitary-adrenal axis and consequent hormonal generation, contributing to the development of postoperative immunosuppression (37). Therefore, well-performed neurocritical care is warranted for neurosurgical patients complicated with postoperative sepsis (38).

Limitations

Some limitations did exist when interpreting our findings. Firstly, the current study was a single center retrospective analysis using publicly available database, which restricted us to identify the causal relationship between variables and endpoints. Thus, prospective cohorts are needed for further validation. Secondly, there were several potential confounding variables that we were unable to assess due to severe data missing condition and other reasons. However, some of the excluded variables might have predictive value for clinical outcomes. Thirdly, we employed XGBoost model, a machine learning-based algorithm that was not widely applied in clinical research. Although XGBoost possesses a significantly higher accuracy in predicting outcomes compared to generalized linear models, overfitting problem is inevitable. Given that, external validation was required to test its utility. Finally, our study merely focused on the in-hospital mortality of patients with postoperative sepsis, while other outcomes, such as long-term mortality and late prognosis, were also important and deserved further investigation.

Conclusions

In summary, these results suggest that some important features are potentially related to the in-hospital mortality among patients who underwent surgical procedures and developed postoperative sepsis at ICU admission. The XGBoost model is capable of processing large amount of variables and further capturing these complicated relationships, which indeed performed better in mortality prediction compared to stepwise logistic model. Further validation of our model in external datasets can prompt us to early recognize patients with postoperative sepsis who are at high risk of death during hospitalization, and to implement efficient yet timely monitors and interventions in the setting of critical illnesses.

Declarations

Ethics approval and consent to participate

The study was an analysis of a third-party publicly available database with pre-existing institutional review board (IRB) approval.

Consent for publication

Not applicable.

Availability of data and materials

The data were available on the MIMIC-III website at https://mimic.physionet.org/.

Competing interests

The authors declared no competing interests.

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Authors' contributions

YMY, CR and ZFX conceived the analysis. RQY and XJ extracted all data. XJ, YY and GSW undertook and refined the inclusion process. RQY, CR and YY co-wrote the paper. RQY, GWW and LL undertook the statistical analyses. All authors contributed to and revised the final manuscript.

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Figures

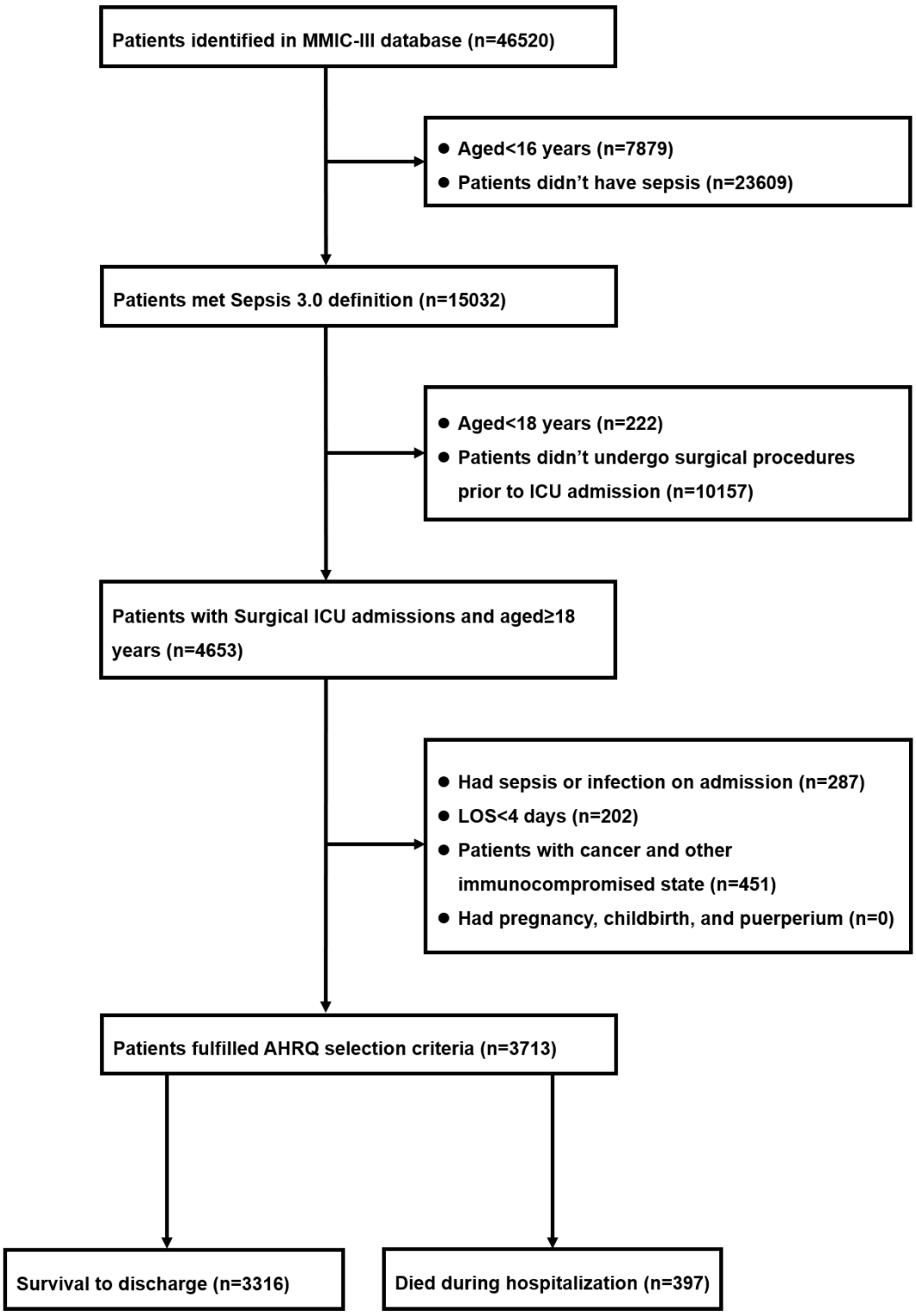

Figure 1

Flow diagram of patient inclusion.

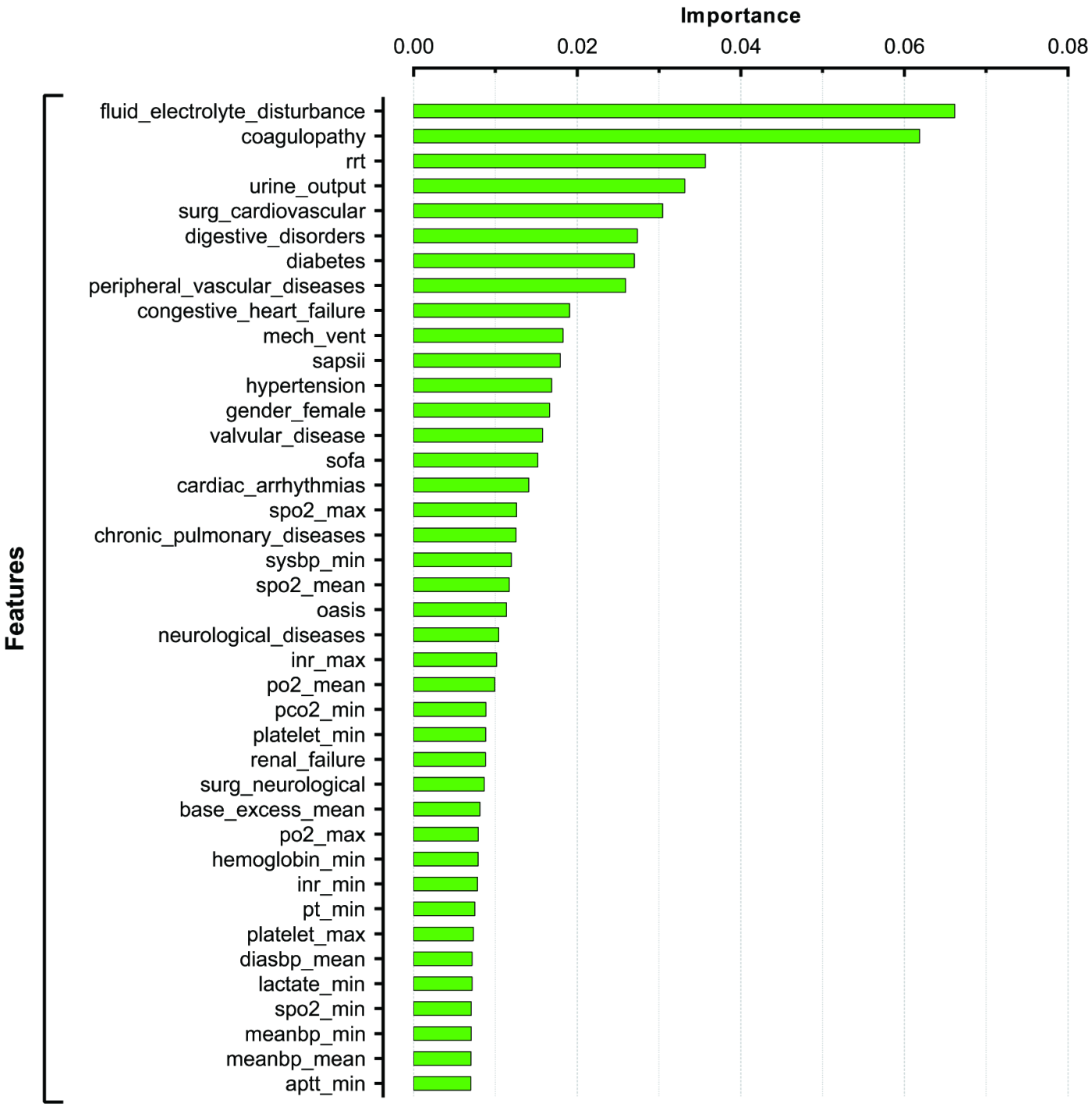

Figure 2

Feature importance derived from XGBoost model.

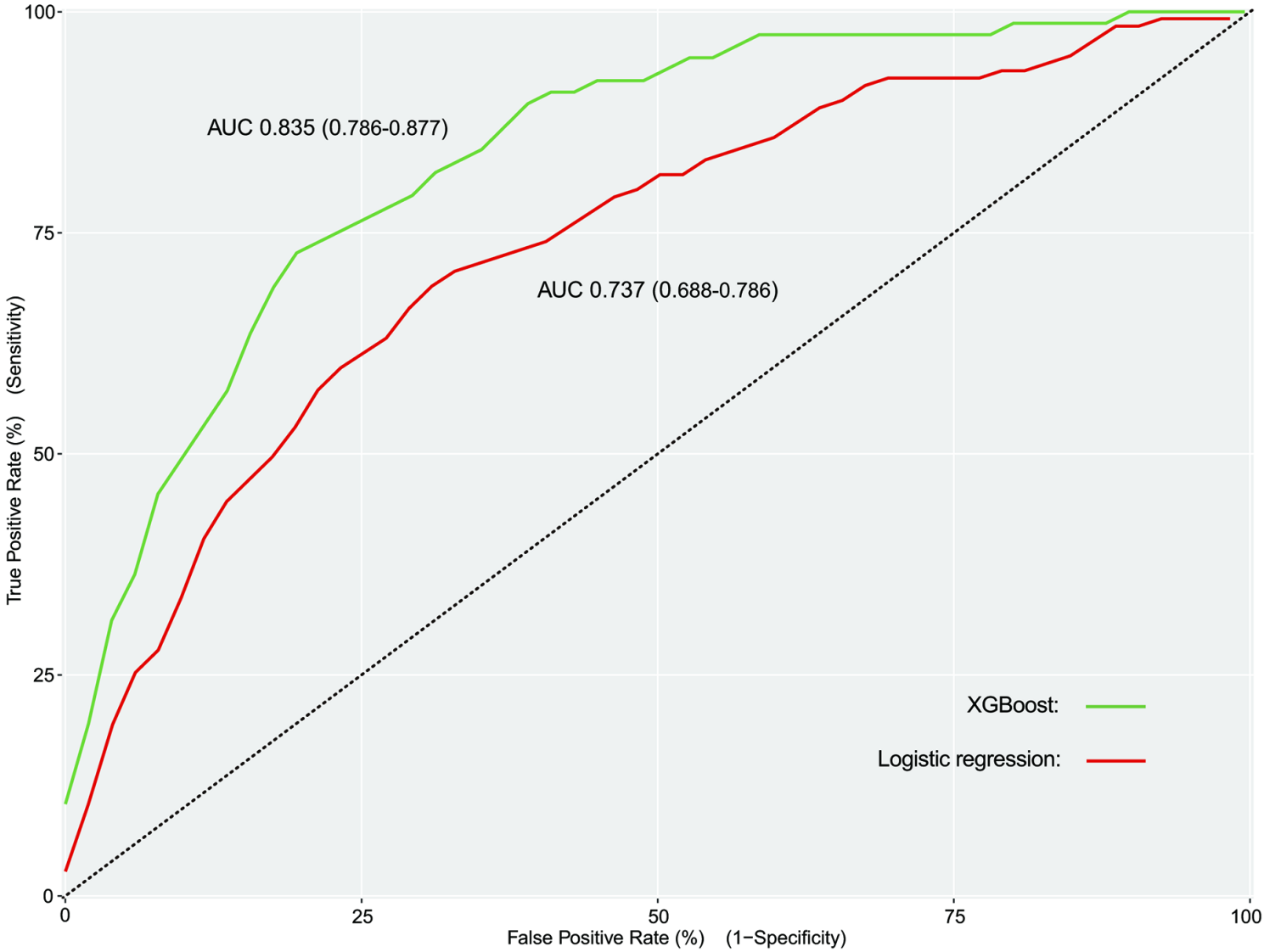

Figure 3

Receiver operating characteristic curve for evaluating the discriminatory ability of both stepwise logistic regression model and XGBoost model.

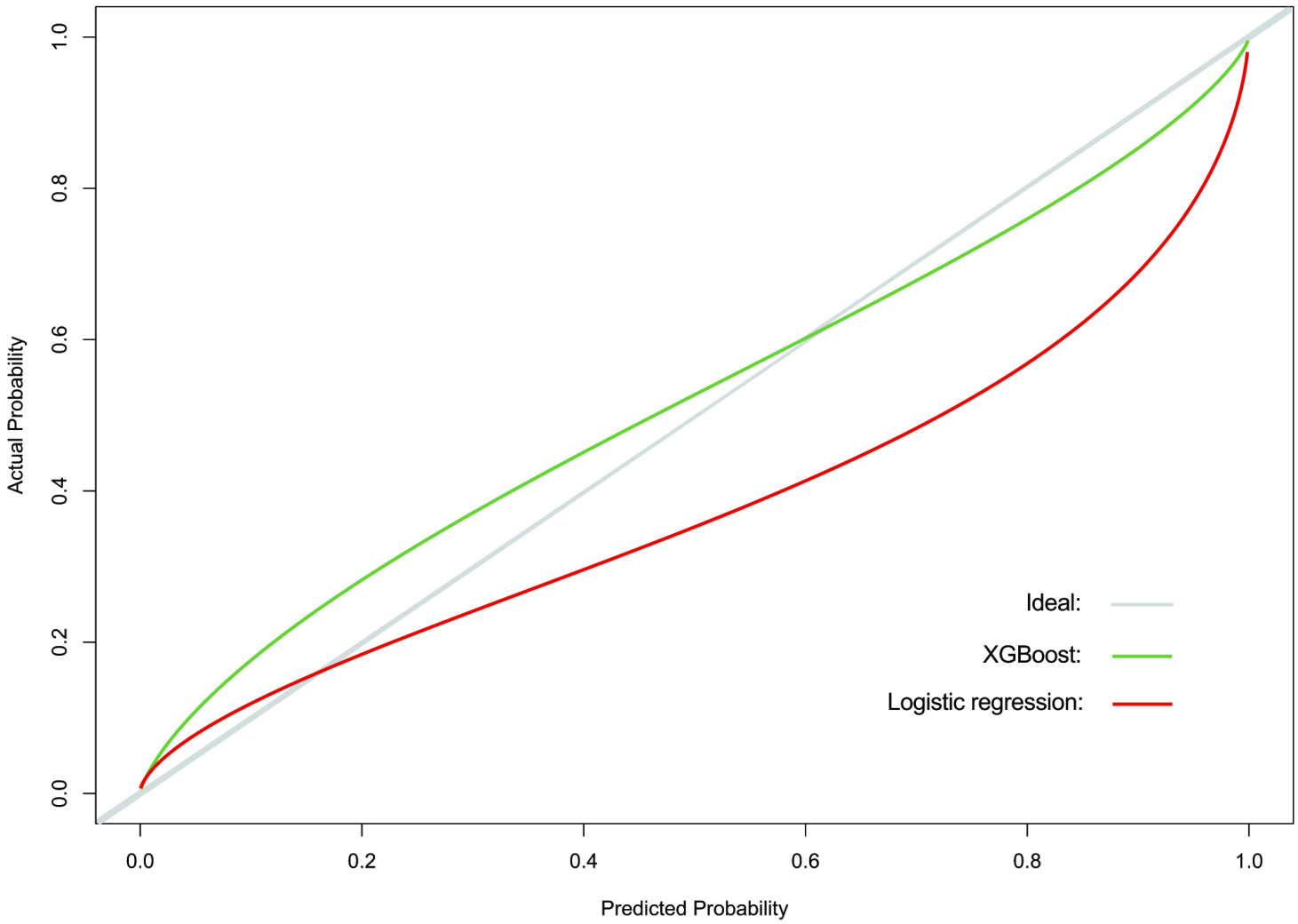

Figure 4

Calibration curve for assessing the goodness of fit for stepwise logistic regression model and XGBoost model.