Original Research

Development and Validation of Machine Learning-Based Models for Prediction of Intensive Care Unit Admission and In-Hospital Mortality in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Background: This present work focused on predicting prognostic outcome of inpatients developing acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and enhancing patient monitoring and treatment by using objective clinical indicators.

Methods: The present retrospective study enrolled 322 AECOPD patients. Registry data downloaded based on COPD Pay-for-Performance Program database from January 2012 to December 2018 were used to check whether the enrolled patients were eligible. Our primary and secondary outcomes were ICU admission and in-hospital mortality, respectively. The best feature subset was chosen by recursive feature elimination. Moreover, seven machine learning (ML) models were trained for forecasting ICU admission among AECOPD patients, and the model with the most excellent performance was used.

Results: According to our findings, random forest (RF) model showed superb discrimination performance, and the values of area under curve (AUC) were 0.973 and 0.828 in training and test cohorts, separately. Additionally, according to decision curve analysis, the net benefit of RF model was higher when differentiating patients with a high risk of ICU admission at a <0.55 threshold probability. Moreover, the ML-based prediction model was also constructed to predict in-hospital mortality, and it showed excellent calibration and discrimination capacities.

Conclusions: The ML model was highly accurate in assessing the ICU admission and in-hospital mortality risk for AECOPD cases. Maintenance of model interpretability helped effectively provide accurate and lucid risk prediction of different individuals.

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Introduction

As the chronic condition, chronic obstructive pulmonary disease (COPD) shows typical features of chronic airway obstruction, chronic bronchitis, and emphysema. COPD patients usually have the progressively and irreversibly declined lung function[1]. As suggested by the WHO statistics, COPD may rank third among factors inducing death by 2030 worldwide [2]. Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) refer to sudden airway functional deterioration or respiratory symptom aggravation among COPD cases [3], and is tightly associated with COPD occurrence and progression. The onset of AECOPD is a major factor inducing hospitalization and mortality of COPD cases. As previously reported, hospitalized AECOPD recurrence usually take place within a short period, and can exacerbate the COPD course even after treatment, eventually increasing the hospitalization and mortality rates[4, 5]. It is the key factor leading to declining lung function and health status. Therefore, it is important to explore the influence on AECOPD prognosis to improve treatment for COPD cases.

It is suggested that AECOPD prognosis is related to some factors, like traditional laboratory and clinical parameters[6]. COPD progression is the key factor resulting in the greater AECOPD severity and occurrence frequency[7]. Factors, like >65 years in age, chronic mucus hypersecretion (CMH), obvious comorbidities, and mild airflow obstruction with forced expiratory volume in 1 second (FEV1) < 50% of predicted, are associated with a higher hospital admission, readmission and disease exacerbation risk [8-10]. Pneumonia and dyspnea severity have been identified to be predicting factors for early readmission and in-hospital mortality of AECOPD[11]. Chronic comorbidities that are not related to lung involvement, such as diabetes mellitus, arterial hypertension, ischemic heart disease, etc., and Charlson index (two or > two comorbidities other than COPD) are related to poor short-term prognosis[12]. Biomarkers can also predict the prognosis of AECOPD patients. Leukocytosis in the stable phase, elevated CRP, increased stable-phase fibrinogen level, and acute-phase D-dimer have been found to be involved in early relapse of AECOPD[6]. Putcha N et al. found that subnormal IgA content in serum was related to a higher acute exacerbation risk, which supported that the mild impairment of IgA

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level was the contributor for COPD incidence. Besides, the decreased serum IgA was dose-dependently related to numerous exacerbations in patients whose serum IgA levels were within the lowest decile, which supported the relation of serum IgA level with exacerbation incidence[35]. In addition, some radiographic features (such as elevated chest CT-derived muscle and bone measures capture markers) on chest imaging examinations are suggested to be the alternative markers for comorbidities among COPD patients[36-37]. Otherwise/Meanwhile, it is worth mentioning that inadequate antibiotic treatment can be regarded as a related factor to long-term outcomes in AECOPD[6]. To reduce the risk of poor prognosis in AECOPD, a comprehensive multivariate analysis of prognosis is needed. Machine learning (ML) has been widely applied to disease prognosis and prediction because it can estimate unknown dependencies through the given dataset and use this to predict new output[13]. The application of health care administrative data or electronic medical records (EMRs) has provided real-world data for ML, promoting the potential for ML in predicting the prognosis of diseases affected by multiple factors. Recently, ML is applied in predicting and analyzing AECOPD with more precision and better performance [14,1 5].

To our knowledge, there has been no study applying ML methods to explore the multivariate impact on the severity and survival outcome of AECOPD patients. This work focused on using ML models for constructing the effective prediction models to identify the severity and risk of in-hospital mortality among AECOPD patients.

Materials and Methods

Study population

This work gained approval from the Institutional Review Board (IRB) from University of Chinese Academy of Sciences Shenzhen Hospital. Protocols were established to ensure ethical compliance. Before collecting data, informed consents were obtained from every included patient for using the data in later health-related studies. Methods in this work were conducted strictly following relevant laws and regulations. In order to preserve and uphold the privacy and

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confidentiality of all patients, we carried out an extensive process to remove any sensitive or personally identifiable information before commencing with our analysis, including name, address, and contact details.

The present study began by selecting the initial study population in COPD Pay-for-Performance Program database, encompassing those with COPD from 2012 to 2018 years. This database was based on Department of Pulmonary and Critical Care Medicine, University of Chinese Academy of Sciences Shenzhen Hospital. All patients admitted for acute COPD were included in this database. The purpose of this program was to rationalize quality improvement spending on the care quality and health insurance costs in COPD cases. The preliminary study population comprised over 4,900 patients, serving as a foundation for our research. Focusing on our goal in the present work, which aims to establish the early risk evaluation tool for AECOPD inpatients, this study narrowed our population by identifying 1,954 AECOPD patients who were discharged as our intermediate study population. In order to further solve the heterogeneity of the study population, we limited the study object to the patient admitted with acute COPD as the primary symptom (the principal admission diagnosis was AECOPD).

Subsequently, the distinction between severe and non-severe patients was introduced by evaluating the occurrence of ICU admission within the intermediate population. Our final sample size included 322 hospital records procured in AECOPD patients aged above 18 years, chosen through the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code for COPD (J44.100, J44.101) in primary diagnosis field [16]. To achieve methodological coherence, patients with ICU admissions were categorized into severe, whereas patients who did not need ICU admission were labeled as non-severe. Based on this classification, we calculated the severe AECOPD patient proportion, and our results indicate that 36.6% (118/322) of the patient sample were classified as severe AECOPD patients. Whereas the rest 63.4% (204/322) were non-severe patients.

The methodology involving the analysis of how basic indicators, inflammation and

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comorbidities affected frequent severe acute exacerbations (AEs) of COPD patients was used. For ensuring the impartial and robust AE risk evaluation in COPD cases, all cases were classified into training or test cohort according to the respective admission dates before or after December 31st, 2018, separately. Clinical data of patients in the training cohort were employed for developing the prediction models, while those in the test cohort were applied in evaluating model performance. There were 225 cases in the training cohort, which included 83 severe and 142 non-severe ones; meanwhile, there were 97 cases in the test cohort, including 35 severe and 62 non-severe ones. To eliminate bias in the analysis, we excluded samples with numerous missing values. Table 1 displays the distribution of the severe and non-severe groups among AECOPD patients. Table 1 indicates that among 322 cases enrolled into this work, a total of 181 patients had a history of smoking, of which 82 patients were categorized as belonging to the severe group. In comparison, 99 patients belonged to the non-severe group. Conversely, 141 patients had no history of smoking, with 36 and 105 of these patients categorized into severe and non-severe groups, separately. Moreover, out of the total population, 191 patients were male, with 77 patients belonging to severe group, whereas 114 to non-severe group. On the other hand, 131 patients were female, with 41 patients being classified as belonging to the severe group while 90 patients were in the non-severe group.

Outcome

Our primary goal was developing the prediction model for identifying ICU admission within AECOPD cases that were admitted into the hospital. Meanwhile, identification of in-hospital death presence was considered a secondary outcome, which was defined as deaths resulting from adverse events that are related to emergency room visits or admission with an International Classification of Diseases, Tenth Revisions (ICD-10) code of AECOPD (J43.x–44.x, except for J430)[14, 17].

Feature Engineering

The study extracted data from the electronic medical records (EMR) database, the data and

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database repository collected based on diverse EMR systems. This dataset comprised 90 features that were obtained from the clinical records of outpatients (The list of 90 features is shown in Supplementary Table 1). The data were collected within six months preceding the patient's most recent visit before their initial admission due to AECOPD. The features included different perspectives, such as demographic data like age, gender, and BMI; clinical characteristics such as CAT (COPD assessment test) scores, postbronchodilator test results, COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) scores, mMRC (Modified Medical Research Council) dyspnea scores, vital signs, respiratory symptoms, laboratory results, comorbidities, and medication usage. For ensuring feature variability and model accuracy, we eliminated features whose prevalence was <5% out of analysis, as a result, altogether 32 features were excluded [18]. The best feature subset was chosen using recursive feature elimination (RFE) for predicting the AECOPD incidence. There were altogether 38 features chosen by RFE through ten-fold cross-validation conducted in five replicates. Collinearity was assessed using the variance inflation factor (>2), which identified and excluded the following features: postbronchodilator FEV1/FVC ratio, hemoglobin, eosinophil-to-lymphocyte ratio, and COPD GOLD score. Additionally, expert COPD physicians were consulted to finalize the list of 34 included features (gender, age, hypertension, diabetes mellitus, chronic renal dysfunction, pulmonary heart disease, hypothyroidism, coronary heart disease, smoking status, BMI, body temperature, respiratory rate, pulse rate, diastolic blood pressure, systolic blood pressure, mechanical ventilation, HCT, LDH, PLT, WBC, neutrophil ratio, PCO2, PO2, SpO2, pH, total bilirubin, D-dimer, fibrinogen, albumin, creatinine, BNP, malignant tumor, sepsis, mMRC (Modified Medical Research Council) dyspnea scores).

Statistical Analysis and ML Algorithms

First, we abandoned severe data missing variables, accounting for more than 20% of the total variables data. For the variables with missed data less than 20% of the total data, multiple imputations approach was utilized for imputing missing data [38]. This present study reports categorical variables as proportions and corresponding counts, while continuous variables are

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indicated by medians and their interquartile ranges. To compare the categorical variables, we utilized the Chi-square test, and compared continuous variables by employing non-parametric test.

Figure 1 displays a framework utilized in creating prediction models for ICU admission and hospital death in patients with AECOPD, encompassing four primary steps: data preprocessing, feature engineering, ML model establishment, as well as model training. Seven distinct ML algorithms were utilized, including logistic regression (LR), support vector machine (SVM), most minor absolute shrinkage and selection operator (LASSO), random forest (RF), K-Nearest Neighbor (KNN), and extreme gradient boosting (XGB), gradient boosting machine (GBM). We employed exhaustive grid search algorithm to be the hyperparameter tuning approach. We executed five-fold cross-validation for training subset, so as to identify optimal hyperparameter combination. Hyperparameters resulting in greatest area under receiver operating characteristic curve (AUC) of validation set in every ML model were selected. We employed four kernel functions, namely polynomial, linear, radial, and sigmoid, to be basic functions in constructing SVM model. The hyperparameters including gamma, cost, epsilon and degree were adopted for tuning SVM model for each of the kernels, as mentioned above. We obtained altogether 182,000 hyperparameter combinations for SVM model. Moreover, we utilized ntree, mtry, and nodesize as hyperparameters for RF model and conducted altogether 65,322 hyperparameter combinations.

In creating the XGB model, 163,180 hyperparameters were considered, out of which those optimum hyperparameters consisted of gamma, eta, nrounds, and maximal depth of a tree. For developing GBM model, similar hyperparameters were explored, such as interaction.depth, shrinkage, bag.fraction, and n.minobsinnode, with the objective of identifying the hyperparameters that would provide the greatest AUC of validation set. During the development of these ML models, one-hot encoding was employed to handle categorical data, followed by standardization of every continuous feature prior to analysis. Upon finalizing models with training cohort, this study proceeded to assess their predictive performance by measuring AUC

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as well as 5 assessment metrics: sensitivity, specificity, positive/negative predicted value (PPV/NPV), accuracy and F1 score, with respect to test set. Model discrimination was assessed using the concordance index (c-index). We utilized Youden's index for determining threshold that optimally classifies ICU admissions. Given that our primary goal is to predict ICU admissions for assisting patients, we prioritized the increased F1 scores and prediction accuracy while evaluating the models. The F1 score is a performance metric that takes into account both sensitivity and PPV and is scaled between 0 and 1. F1 score can be calculated as follows, F1 = 2 * (precision x recall) / (precision + recall). To further assess the clinical utility of our models, we performed a decision curve analysis. We also evaluated calibration, the measure of agreement between predicted levels and real measurements of ICU admission in AECOPD patients.

Descriptive analysis was conducted with SPSS, while ML models were developed with R software (version 3.6.2; The Comprehensive R Archive Network: http://cran.r-project.org, accessed on 12 December 2019). Statistically significant results were defined as those with $p<0.05$ (two-tailed).

Results

Demographics

The entire program was described, consisting of feature selection, prediction model establishment, as well as performance assessment (Figure 1). There were altogether 322 cases enrolled into the present work, including 225 and 97 in training and test sets, separately. Baseline features in patients from severe and non-severe group from training and test sets were compared (Table 1). The history of pulmonary heart disease and smoking history were significantly different in severe group compared with non-severe group in the training cohort ($P<0.05$).

Prediction models for ICU admission

There were altogether 7 prediction models regarding different ML classifiers constructed with AUCs being 0.827-0.973 in training group whereas 0.648-0.828 in testing group (Table 2).

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Calibration plots and ROC curves were used for visualizing the two cohorts (Figure.S1). The prediction model on the RF classifier outperformed others with regard to AUC of test set of 7 ML-based models, and its AUC, C-index, accuracy, sensitivity, specificity, PPV, NPV and F1 score were 0.973, 0.973, 92.00%, 93.98%, 90.85%, 85.71%, 96.27%, and 0.897 for training set; whereas the values for test set were 0.828, 0.828, 77.89%, 80.00%, 64.52%, 68.84%, 94.07%, and 0.738, respectively (Figure.S2, Table.2). As revealed by calibration curve, actual observations were consistent with RF-predicted results which indicated great calibration capacity.

Prediction models for in-hospital death

Baseline features between cases with and without hospital death in the two datasets were compared (Table 3). Altogether 23 patients (10.2%) in training cohort and 10 patients (10.3%) in test cohort reported in-hospital deaths. The history of pulmonary heart disease, history of bronchiectasis, and smoking history were significantly different between the live group and dead group in the training cohort ($P<0.05$).

Altogether 7 prediction models regarding different ML classifiers for in-hospital mortality were constructed, and AUCs were 0.957-0.993 and 0.547-0.705 for training and test sets, separately (Table 4). Calibration plots and ROC curves were adopted for visualization in the two cohorts (Figure.S3). The prediction model on RF classifier outperformed others, with regard to AUC of test set of 7 ML-based models, and its AUC, C-index, accuracy, sensitivity, specificity, PPV, NPV and F1 score were 0.982, 0.982, 94.67%, 91.30%, 95.05%, 67.74%, 98.97%, and 0.778, separately, for training set; while those values for test set were 0.705, 0.705, 64.95%, 60.00%, 65.52%, 16.67%, 93.44%, and 0.261, respectively (Figure.S3, Table.4). As revealed by calibration curve, actual observations were consistent with RF-predicted results which indicated great calibration capacity. For comparison, the performance of ICU admission in predicting in-hospital mortality was evaluated, the AUC, C-index, accuracy, sensitivity, specificity, PPV, NPV and F1 score were 0.969, 0.969, 96.00%, 86.96%, 97.03%, 76.92%, 98.49%, and 0.816

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separately for training set; whereas the values for test set were 0.546, 0.546, 65.98%, 30.00%, 70.11%, 10.34%, 89.71%, and 0.154, respectively (Figure.S4, Table4).

We generated an ML signature based on the RF-based model, which was combined with ICU admission to develop an integrated nomogram model for predicting in-hospital death (Figure 2A). The AUC, C-index, accuracy, sensitivity, specificity, PPV, NPV and F1 score were of this integrated model were 0.992, 0.992, 96.00%, 95.65%, 96.04%, 73.33%, 99.49%, and 0.830 for training set; while the values for test set were 0.754, 0.754, 71.13%, 60.00%, 72.41%, 20.00%, 94.03%, and 0.300, respectively (Table.4). This integrated model exhibited excellent classification performance by ROC curves as well as precision-recall plots (Figure.2B and 2C), and had uniform calibration ability (Figure.2D) and high clinical benefit (Figure.2E).

Discussion

The present investigation aimed to construct and validate an intelligible ML-supported risk evaluation tool to anticipate the likelihood of ICU admission and in-hospital mortality of AECOPD patients. According to our results, ML models exhibited superb discrimination performance in forecasting ICU admission, since the AUC was >0.80. These findings indicate that ML has significant potential to be implemented clinically as an estimator of ICU admission and in-hospital death risks in AECOPD patients. Of those ML models used, RF method demonstrated the greatest prediction ability, as a result, it was used for creating an explicable ML-based exacerbation risk assessment approach.

In this work, Gradient Boosting Machine model was most accurate in predicting severe AECOPD (ICU admissions because of AECOPD and in-hospital mortality), and its AUC value reached 0.83. Like Hussain et al.'s model, the ML-based model constructed in this study could precisely forecast severe AECOPD (ICU admission because of AECOPD and in-hospital mortality) without considering the risk factor of exacerbation history of the patient. Nonetheless, it may be a challenge to compare our findings to Hussain et al.'s, because their study did not provide AECOPD definition or specific study population. Consequently, using ML-based

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models, in particular GBM models, is the precise and potential way to predict severe AECOPD (ICU admission because of AECOPD and in-hospital mortality) with no consideration of the exclusive risk factor of exacerbation history. Such ML-based models may be potentially utilized as the clinical decision-making approaches, which can identify high-risk patients for AECOPD that probably gain benefits from specialist referral and treatment adjustment. Moreover, the GBM model did not use exacerbation history as one of its features, but it attained high accuracy comparable to previous GBM models where exacerbation history is used as a feature. Consequently, our prediction model appears to be suitable for assessing the risk of patients with no prior exacerbations, including those diagnosed with COPD for the first time with COPD or those with incomplete medical records.

In the outpatient context of COPD care, the primary objectives are to prevent acute exacerbations and mitigate unwanted outcomes. Despite being a dependable predictor of future exacerbations, a history of AECOPD is insufficient as a definitive basis for identifying trustworthy clinical features that can inform treatment decisions and prevention strategies for AECOPD[19]. Additionally, the discrimination performance of the prediction model that relies only on AECOPD history is lower than that of the ML-based model [15]. To take an example, Tavakoli et al. leveraged ML for developing the model that could identify high-risk patients for AECOPD-related hospitalization. According to their results, GBM model outperformed other prediction model relying only on AECOPD history as a feature. Specifically, the AUC of the GBM model was 0.82 compared to the AUC of 0.68 for the model exclusively considering AECOPD history[18, 20]. Assessing the risk of an initial event of AECOPD based solely on a patient's history of the condition may be insufficient, as some medical records may not contain prior exacerbation information. To overcome these limitations, Hussain et al. developed a prediction model using the Gradient Boosting Machine approach, which excluded any consideration of a patient's AECOPD history. Remarkably, this model performed well in discrimination, as evidenced by the AUC value of 0.96 [21]. In this study, we formulated a framework that leveraged ML-based modeling to predict AECOPD. We included different

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pertinent clinical features with real-world data for interpreting local population features.

Recently, one systematic review examined the existing AECOPD prediction models, which involved 27 models established using traditional statistical techniques, accounting for various patient data, symptoms, lung function, together with COPD-related risk factors. These models demonstrated variable levels of performance, and AUC values were 0.58-0.78. In contrast to conventional statistical approaches designed for verifying certain hypotheses, ML provides an alternative approach to AECOPD prediction modeling that highlights performance optimization. Moreover, ML is constructed on the basis of a minimal number of assumptions regarding the data-generating system, thus potentially improving model accuracy over traditional statistical methods[22]. When assessing the risk of AECOPD, Wang et al. carried out a comparative analysis of conventional logistic regression with ML algorithms, like RF, SVM, k-nearest neighbors, logistic regression, and naive Bayes algorithms. As a result, ML-based models were more accurate than traditional statistical approaches [23]. Likewise, as suggested by Tavakoli et al., GBM model was more accurate in predicting AECOPD than logistic regression, RF, as well as neural network models[15]. This work verified the above results and supported that RF model showed higher discrimination performance in AECOPD (ICU admission because of AECOPD and in-hospital mortality) prediction. Consequently, ML-based models, in particular RF models, perform well in AECOPD (ICU admission because of AECOPD and in-hospital mortality) prediction.

It is an important step to select the best features to enhance the ML model performance. Therefore, Hussain et al. and Tavakoli et al. constructed the GBM models through incorporating related patient features, such as demographic data, vital signs, symptoms, laboratory data, questionnaire responses, hospitalizations, medication dispensation records, and outpatient services. These models performed well, and AUCs were >0.80, indicating their excellent prediction performance. In this study, we added different clinical parameters in developing the RF model, such as demographic data, symptoms, vital signs, comorbidities, prescribed medications, CAT scores and laboratory data. Such features were comprehensive relative to those

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utilized in previous models and had comparable performance. Likewise, a previous model used the RF model according to hundreds of single nucleotide polymorphisms for predicting asthma exacerbation[24]. The integration of genomic data in ML models can more accurately predict AECOPD.

AECOPD is heterogeneous and complicated, suggesting that it involves different non-linearly and dynamically interacting components. Such interactions can not be observed in every case or in one specific case at all time[25]. Such dynamic heterogeneity and complexity suggest that it is important to adopt the precision medicine method for optimizing AECOPD evaluation, management and outcomes[26-28]. ML models have been more and more incorporated in the precision medicine, they shed more lights on the relevant mechanisms and trajectories of chronic disorders, including AECOPD[29]. In many studies, using ML models in predicting AECOPD can achieve favorable results. However, AI has a black-box nature, which hinders its clinical application. When there is no interpretable AI model, clinicians have few data to convey to their patients, which may lead to reduced patient contentment and trust[30]. SHAP accounts for the game-theoretic technology put forward by Lundberg and Lee, which focused on elucidating the contributions of features to output changes in ML models. In addition, SHAP values can offer the locally precise and uniform attribute values for every feature incorporated into this prediction model, which reflects the importance. By visualizing data using SHAP, users can more readily comprehend intricate black-box integration models. SHAP methods are recently used in diverse clinical contexts, such as coronary artery calcification or venous thrombosis among osteoarthritis patients[31,32]. Additionally, local explanation results may be presented as feature changes during prediction, from basic values to model outputs, thereby facilitating to visually present the estimated results for clinicians.

Our predictive model is based on 34 characteristic variables that include clinical history, vital signs, and auxiliary test information during hospitalization. Long-term COPD is often accompanied by pulmonary heart disease, and in general, the occurrence of pulmonary heart disease generally indicates the insufficient compensatory capacity for cardiac function.

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Therefore, once patients with pulmonary heart disease develop AECOPD, the risk of admission to ICU is often significantly increased. One study reported that the N-terminal prohormone in Brain Natriuretic Peptide (NT-proBNP) can serve as the biomarker to diagnose left ventricular systolic dysfunction among AECOPD patients[39]. Our study found that BNP was also a significant predictor for ICU admission due to AECOPD and in-hospital mortality during hospitalization, which was supported by the results of previous studies. In addition, oxygen saturation and the use of mechanical ventilation are essential markers in patients with AECOPD. Intervention with mechanical ventilation often reflected severe respiratory failure in patients with AECOPD. For such patients, it frequently predicted a poor prognosis during hospitalization. Therefore, our study emphasizes the critical effect of heart function and lung function on prognosis prediction of AECOPD patients. Our results have significant clinical value for front-line clinicians in the assessment of AECOPD patients.

Certain limitations in the present work warrant consideration. First, our data used were derived from a single healthcare system, and thus, the generalizability of our findings to those who receive care in additional healthcare institutions may be limited. Therefore, for optimizing the prediction accuracy, multicenter external validation should be conducted. Additionally, documentation habits and accuracy are notable sources of residual confounding, and this may introduce some bias to our results. Secondly, our model was developed using exclusively structured data, and further exploration should be performed for including multidimensional data, such as environmental factors, unstructured data (like images), patient activities, habits, or other relevant factors for improving prediction model accuracy. Third, it is essential to note that our study utilized standard machine learning techniques exclusively to construct a prediction model. Recently, employing deep learning techniques is found to be beneficial in medical modeling. Therefore, future research endeavors should establish the deep learning model to predict first-time AECOPD. Fourth, seasonal alteration of AECOPD prevalence has been the widely recognized phenomenon, with fast temperature change being a contributing factor, as evidenced by two Taiwanese studies[33, 34]. AECOPD patients may exhibit heightened sensitivity

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to temperature changes in comparison to the general healthy population, with short-time exposures to these temperature changes being responsible for exacerbations. Nonetheless, this present work can not obtain real-time data regarding seasonal temperature changes, and this is the notable limitation in the research. Finally, as many variables were incorporated for analysis and our sample size was insufficient, there may be an overfitting of the machine learning model. Therefore, while explaining the accuracy of our prediction model, it should also be noted that our model might be associated with certain bias.

Conclusion

The findings of our investigation indicate that the RF-based model effectively assessed the probability of ICU admission and in-hospital mortality in patients suffering from AECOPD. Furthermore, the utilization of ML-based models allowed for clear and precise explanations of personalized risk predictions that could help clinicians comprehend the significance of critical model features as well as decision-making process. Such approaches may prove to be instrumental in optimizing individualized therapeutic strategies for AECOPD patients by incorporating prognostic risks into clinical decision-making. Ultimately, further implementation of ML methods in clinical practice has the potential to improve patient outcomes through tailored and informed treatments significantly.

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Declarations

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval and consent to participate

This study obtained ethics approval and consent from the University of Chinese Academy of Sciences Shenzhen Hospital, and the need for approval was waived for this study.

Data, Materials and/or Code availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contribution

QJ, YC, QZ, SC, SL, TW, and XY made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. TW revised the manuscript and gave final approval for the version to be published. All authors read and approved the final manuscript.

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Table.1. Clinical characteristics of patients between mild and severe groups for ICU admission in the training and testing cohorts.

Characteristic	Training cohort (N = 225)			Testing cohort (N = 97)		
	Severe Group - high risk (n=83)	Non-Severe Group - low risk (n=142)	P value	Severe Group - high risk (n=35)	Non-Severe Group - low risk (n=62)	P value
Demographic characteristics						
Age (years old)	81.32 ±28.23	81.45±24.62	0.651	82.52 ±31.77	79.73 ±29.25	0.276
Gender, Male, No. (%)	49 (59.0)	81 (57.0)	0.770	28 (80.0)	33 (53.2)	0.100
Clinical features						
Temperature, median (° C)	37.42 ±1.10	37.22 ±0.71	0.101	36.85 ±0.75	36.97 ±1.32	0.925
Systolic BP(mmHg)	146.55±40.12	147.85 ±48.47	0.296	142.25 ±39.36	144.47 ±48.86	0.976
Diastolic BP(mmHg)	86 .13±25.64	86.51±27.68	0.974	82.71 ±27.48	85.88 ±22.91	0.905
Heart rate (beats/minute)	80.35 ±18.67	80.42 ±18.69	0.988	84.29 ±24.17	80.51±20.94	0.860
Respiratory rate (beats/minute)	23.51±4.36	23.74±5.69	0.634	23.28 ±3.37	24.24±3.64	0.847
Medical history						
Pulmonary heart disease, No. (%)	30 (36.1)	27 (19.0)	0.013	12 (34.3)	16 (25.8)	0.167
Bronchiectasis, No. (%)	17 (20.5)	20 (14.1)	0.327	9 (25.7)	8 (12.9)	0.258
Hypertension, No. (%)	43 (51.8)	67 (47.2)	0.503	18 (51.4)	26 (41.9)	0.367
Diabetes mellitus, No. (%)	8 (9.6)	14 (9.9)	0.957	3 (8.6)	6 (9.7)	1.000
Dyslipidemia, No. (%)	3 (3.6)	3 (2.1)	0.672	1 (2.9)	1 (1.6)	1.000
Atrial fibrillation, No. (%)	3 (3.6)	2 (1.4)	0.361	1 (2.9)	0 (0.0)	0.361
Acute coronary syndrome, No. (%)	3 (3.6)	4 (2.8)	0.711	0 (0.0)	4 (6.5)	0.293

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Stroke, No. (%)	0 (0.0)	2 (1.4)	0.532	1 (2.9)	1 (1.6)	1.000
Smoking history, No. (%)	60 (72.3)	67 (47.2)	0.037	22 (62.9)	32 (51.6)	0.118
Drinking history, No. (%)	2 (2.4)	4 (2.8)	1.000	0 (0.0)	0 (0.0)	1.000
Medication history						
Anti-platelet therapy, No. (%)	16 (19.3)	25 (17.6)	0.220	9 (25.7)	12 (19.4)	1.000
Anti-coagulant therapy, No. (%)	17 (20.5)	24 (16.9)	0.104	11 (31.4)	16 (25.8)	0.132

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Table.2. Predictive performance of machine learning model in prediction of ICU admission on AECOPD patients in the training and testing cohort.

Model	Training set							Testing set						
	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 score	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 score
LR	0.933	87.56	83.13	90.14	83.13	90.14	0.831	0.713	72.16	60.00	79.03	61.76	77.78	0.609
SVM	0.889	83.11	74.70	88.03	78.48	85.62	0.765	0.648	61.86	54.29	66.13	47.50	71.93	0.507
LASSO	0.866	78.22	86.75	73.24	65.45	90.43	0.746	0.679	59.79	88.57	43.55	46.97	87.10	0.614
KNN	0.827	74.22	78.31	71.83	61.90	85.00	0.691	0.725	68.04	80.00	61.29	53.85	84.44	0.644
RF	**0.973**	**92.00**	**93.98**	**90.85**	**85.71**	**96.27**	**0.897**	**0.828**	**77.89**	**80.00**	**64.52**	**68.84**	**94.07**	**0.738**
GBM	0.946	87.11	84.34	88.73	81.40	90.65	0.828	0.704	62.89	68.57	59.68	48.98	77.08	0.571
XGB	0.894	77.78	87.95	71.83	64.60	91.07	0.745	0.728	64.95	82.86	54.84	50.88	85.00	0.630

Abbreviations: AUC, Area under the receiver operating characteristic curve; PPV, Positive predictive value; NPV, Negative predictive value; LR, logistic regression; LASSO, least absolute shrinkage and selection operator; SVM, support vector machine; KNN, K-Nearest Neighbor; RF, random forest; GBM, gradient boosting machine; XGB, extreme gradient boosting.

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Table.3. Clinical characteristics of patients between live and dead groups for in-hospital mortality in the training and testing cohorts.

Characteristic	Training cohort (N = 225)			Testing cohort (N = 97)		
	Death (n=23)	Alive (n=202)	P value	Death (n=10)	Alive (n=87)	P value
Demographic characteristics						
Age (years old)	86.48±20.54	82.41 ±26.39	0.205	85.14 ±45.36	81.25 ±25.42	0.799
Gender, Male, No. (%)	15 (65.2)	115 (56.9)	0.446	7 (70.0)	54 (62.1)	0.740
Clinical features						
Temperature, median (° C)	38.15 ±0.33	37.32 ±0.78	0.118	38.01 ±0.53	37.20±0.76	0.246
Systolic BP(mmHg)	135.29 ±46.45	147.85±44.68	0.458	128.24±49	145.31±44.72	0.502
Diastolic BP(mmHg)	90.53 ±25.34	86.27±26.33	0.239	72.73 ±9.64	85.31 ±25.22	0.889
Heart rate (beats/minute)	82.29 ±19.43	80.85 ±17.63	0.675	85.74 ±25.63	80.33 ±23.42	0.705
Respiratory rate (beats/minute)	23.17 ±8.93	21.29±5.46	0.440	24.13 ±2.39	23.92 ±3.86	0.920
Medical history						
Pulmonary heart disease, No. (%)	12 (52.2)	80 (39.6)	0.008	6 (60.0)	36 (41.4)	0.012
Bronchiectasis, No. (%)	5 (21.7)	28 (13.9)	0.027	3 (30.0)	10 (11.5)	0.067
Hypertension, No. (%)	10 (43.5)	100 (49.5)	0.584	5 (50.0)	39 (44.8)	1.000
Diabetes mellitus, Male, No. (%)	3 (13.0)	19 (9.4)	0.478	0 (0.0)	9 (10.3)	0.591
Dyslipidemia, No. (%)	0 (0.0)	6 (3.0)	1.000	0 (0.0)	2 (2.3)	1.000
Atrial fibrillation, No. (%)	0 (0.0)	5 (2.5)	1.000	0 (0.0)	1 (1.1)	1.000

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Acute coronary syndrome, No. (%)	1 (4.3)	6 (3.0)	0.535	0 (0.0)	4 (4.6)	1.000
Stroke, No. (%)	0 (0.0)	2 (1.0)	1.000	0 (0.0)	2 (2.3)	1.000
Smoking history, No. (%)	15 (65.2)	87 (43.1)	0.026	6 (60.0)	43 (49.4)	0.098
Drinking history, No. (%)	1 (4.3)	5 (2.5)	0.480	0 (0.0)	0 (0.0)	1.000
Medication history						
Anti-platelet therapy, No. (%)	6 (26.1)	30 (14.9)	0.256	3 (30.0)	9 (10.3)	0.189
Anti-coagulant therapy, No. (%)	7 (30.4)	32 (15.8)	0.101	3 (30.0)	20 (23.0)	0.256

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Table.4. Predictive performance of machine learning model in prediction of in-hospital mortality on AECOPD patients in the training and testing cohort.

Model	Training set							Testing set						
	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 score	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 score
ML models														
LR	0.975	95.56	91.30	96.04	72.41	98.98	0.808	0.603	67.01	50.00	68.97	15.63	92.31	0.238
SVM	0.957	93.33	86.96	94.06	62.50	98.45	0.727	0.549	76.29	30.00	81.61	15.79	91.03	0.207
LASSO	0.986	98.22	91.30	99.01	91.30	99.01	0.913	0.607	75.26	30.00	80.46	15.00	90.91	0.200
KNN	0.993	96.00	95.65	96.04	73.33	99.49	0.830	0.654	68.04	20.00	73.56	8.00	88.89	0.114
RF	0.982	94.67	91.30	95.05	67.74	98.97	0.778	0.705	64.95	60.00	65.52	16.67	93.44	0.261
GBM	0.977	95.56	91.30	96.04	72.41	98.98	0.808	0.547	68.04	50.00	70.11	16.13	92.42	0.244
XGB	0.983	96.44	95.65	96.53	75.86	99.49	0.846	0.615	70.10	60.00	71.26	19.35	93.94	0.293
ICU admission	0.969	96.00	86.96	97.03	76.92	98.49	0.816	0.546	65.98	30.00	70.11	10.34	89.71	0.154
Integrated nomogram	0.992	96.00	95.65	96.04	73.33	99.49	0.830	0.754	71.13	60.00	72.41	20.00	94.03	0.300

Abbreviations: AUC, Area under the receiver operating characteristic curve; PPV, Positive predictive value; NPV, Negative predictive value; LR, logistic regression; LASSO, least absolute shrinkage and selection operator; SVM, support vector machine; KNN, K-Nearest Neighbor; RF, random forest; GBM, gradient boosting machine; XGB, extreme gradient boosting.

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Figure legends

Figure 1: The flowchart showing data analysis. (A) Prediction models for identifying the ICU admission risk were constructed via ML methods using clinical indicators. (B) The prediction model in predicting in-hospital death took clinical indicators and the effect of ICU admission into account, and was visualized by nomogram. Abbreviations: ROC, Receiver operating characteristic; ML, machine learning; LR, logistic regression; LASSO, least absolute shrinkage and selection operator; SVM, support vector machine; KNN, K-Nearest Neighbor; RF, random forest; GBM, gradient boosting machine; XGB, extreme gradient boosting.

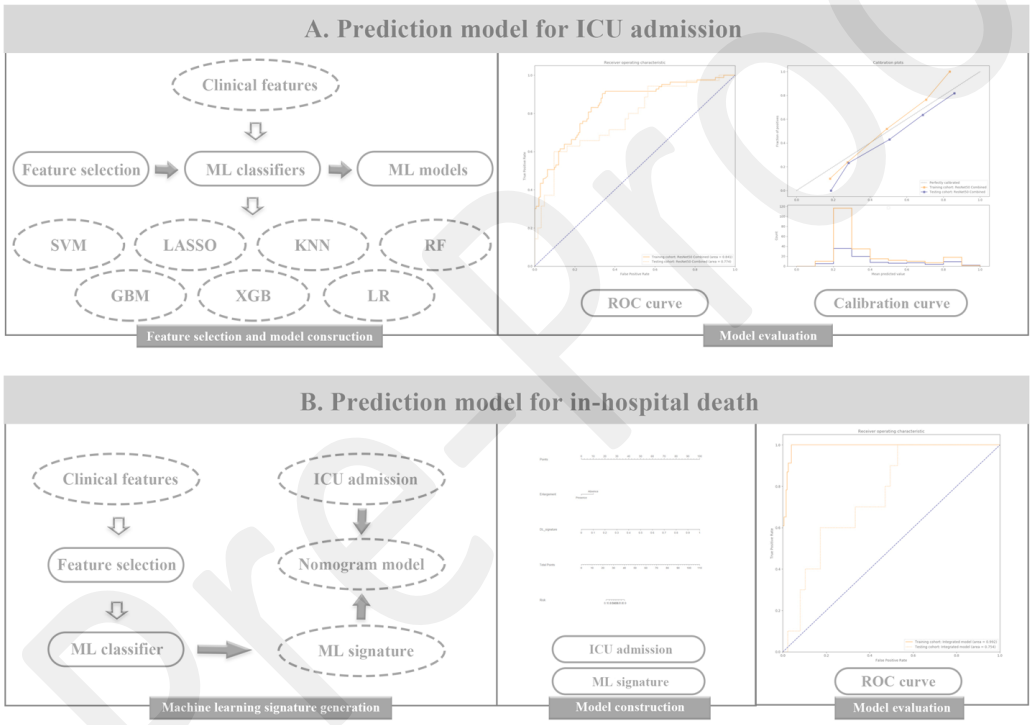

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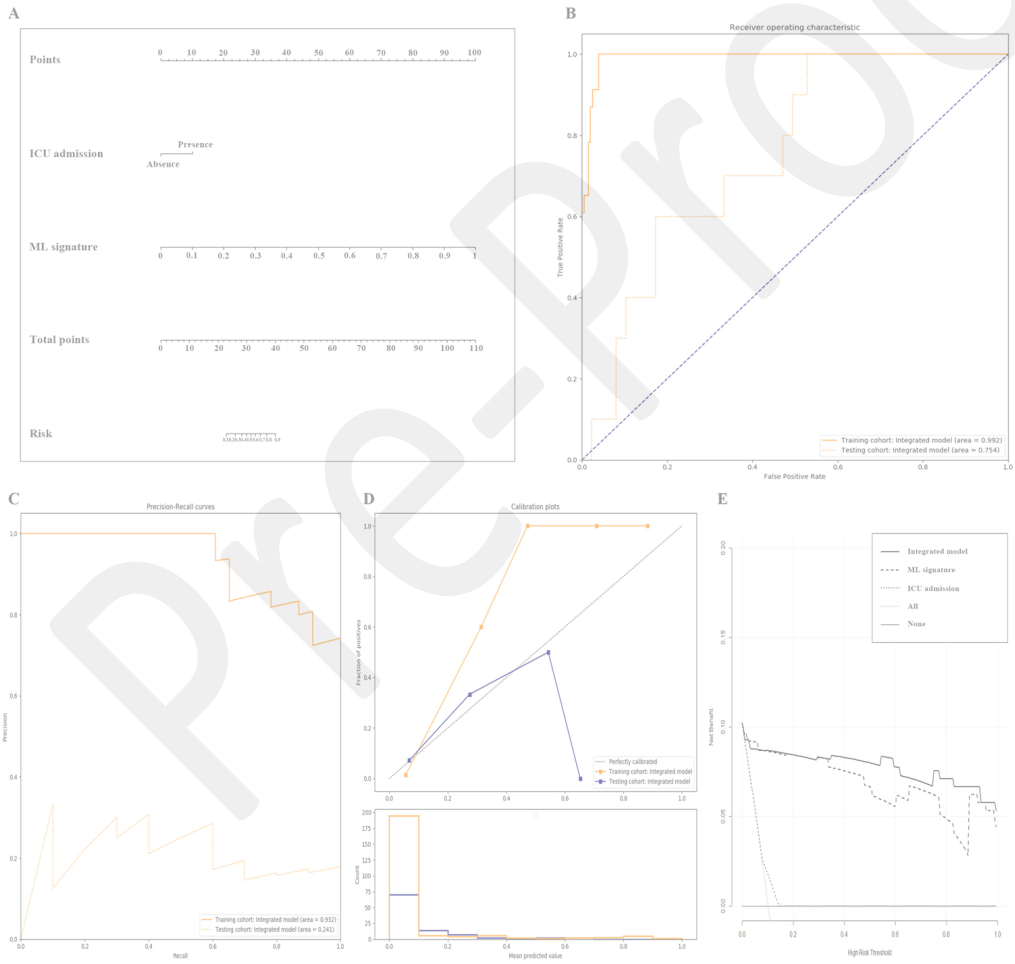
Figure 2: Prediction performance of the combined nomogram model in predicting in-hospital death. (A) The nomogram model incorporating ICU admission and the RF-based ML signature produced by the optimal model that considered the AUC for test cohort. (B) ROC curves showing the prediction performance of the combined nomogram model for training and test sets, separately. (C) Precision-recall plots showing prediction performance of the combined nomogram model for training and test sets, separately. (D) Calibration curve analysis of the combined nomogram model for training and test sets, separately. (E) Decision curve analysis of the combined nomogram model. Abbreviations: AUC, Area under receiver operating characteristic curve; ROC, Receiver operating characteristic; ML, machine learning.



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Online Supplement

Supplementary table 1 The list of 90 features for present study.

Gender	Length of stay	PE situation	Age	Smoking
Temperature (℃)	Pulse(times/min)	Breathing (times/ min)	Systolic pressure(mmHg)	Diastolic pressure(mmHg)
Height (cm)	Weight (kg)	Hb (g/L)	HCT	PLT (10^{-9}/L)
LYMPH (*10^{-9}/L)	WBC (*10^{-9}/L)	N%	pH	PCO_2 (mmHg)
PO_2 (mmHg)	SpO_2 (%)	Oxygen saturation	INR fibrinogen	D-dimer (mg/dlt)
TBIL (umol/l)	ALT(IU/L)	AST (IU/L)	Albumin (g/L)	Globulin (g/L)
Antithrombin III(%)	Blood glucose (mmol/l)	Urea (mmol/l)	Creatinine (umol/l)	Uric acid (umol/l)
Triglyceride (mmol/L)	Cholesterol (mmol/L)	Creatinekinase (IU/L)	LDH (IU/L)	Serum Na (mmol/l)
Myoglobin (ng/ml)	Creatine kinase isoenzyme (ng/ml)	Troponin (ng/ml)	＞BNP (ng/ml)	Serum K (mmol/l)
History of inflammatory bowel disease	Anti-platelet therapy	varicose veins	severe lung disease	COPD
malignant tumor (previous history)	malignant tumor(current disease)	cerebral apoplexy (within one month)	Rheumatic disease	Craniocerebral trauma
Atrial fibrillation	Asthma	Interstitial lung disease	Respiratory failure	Bronchiectasis
Pulmonary heart disease	Pulmonary arterial hypertension	Obstructive Sleep Apnea-Hypopnea Syndrome,	Hypertension	Coronary heart disease
Cardiomyopathy	Peripheral vascular disease	Congenital heart disease	Rheumatic heart disease	Chronic hepatitis
Liver cirrhosis	Alimentary tract hemorrhage	Acute coronary syndrome	Chronic gastritis	Chronic nephritis
Nephrotic syndrome	Chronic renal insufficiency	Acute renal insufficiency	Myelodysplastic syndrome	Paroxysmal nocturnal hemoglobinuria
HIV	Anti-coagulant therapy	Drinking history	Dementia	Parkinson’s disease
Dyslipidemia	Hyperthyroidism	Hypothyroidism	Diabetes	BMI

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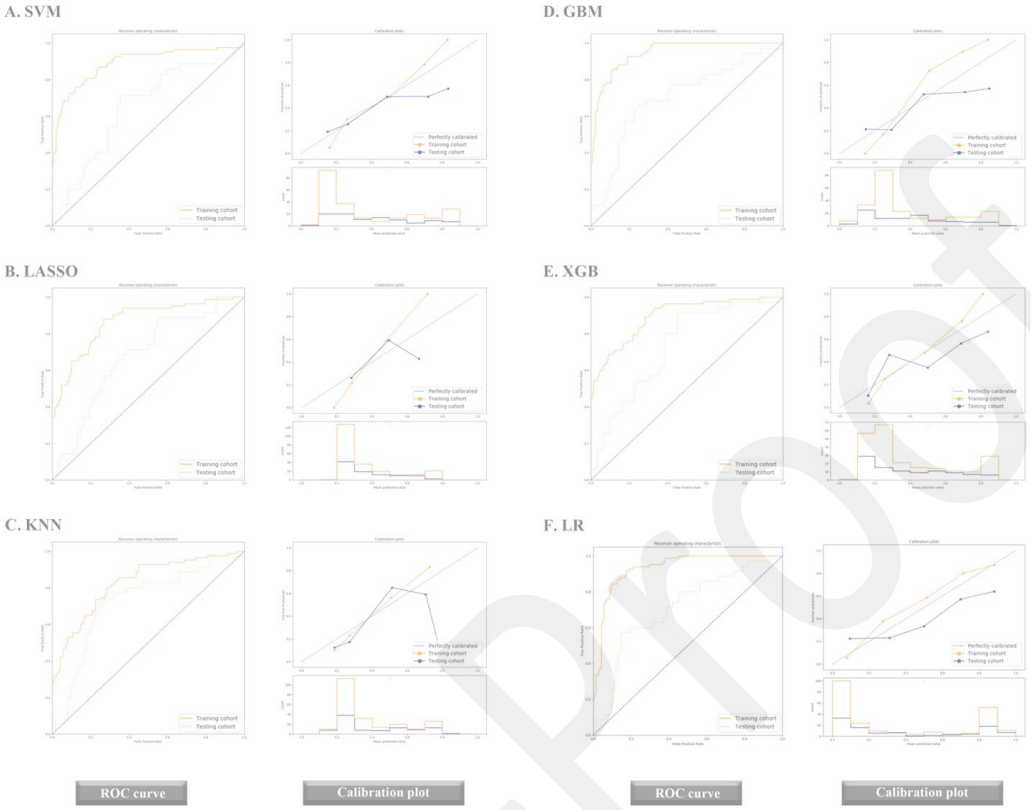
Figure.S1. Evaluation of prediction performance of seven ML models in predicting ICU admission on patients of training and test sets.



Abbreviations: AUC, Area under receiver operating characteristic curve; ROC, Receiver operating characteristic; LR, logistic regression; LASSO, least absolute shrinkage and selection operator; SVM, support vector machine; KNN, K-Nearest Neighbor; RF, random forest; GBM, gradient boosting machine; XGB, extreme gradient boosting.

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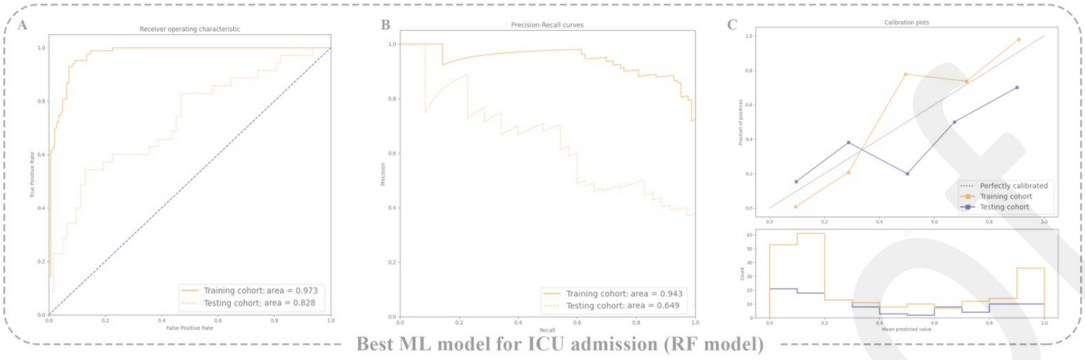
Figure.S2: Assessment of prediction performances for best ML model (random forest) in classifying ICU admission, including ROC curves (Left), Precision-recall plots (Middle), and Curves of calibration analysis (Right) for training and test sets, separately.



Abbreviations: AUC, Area under receiver operating characteristic curve; ROC, Receiver operating characteristic; ML, machine learning.

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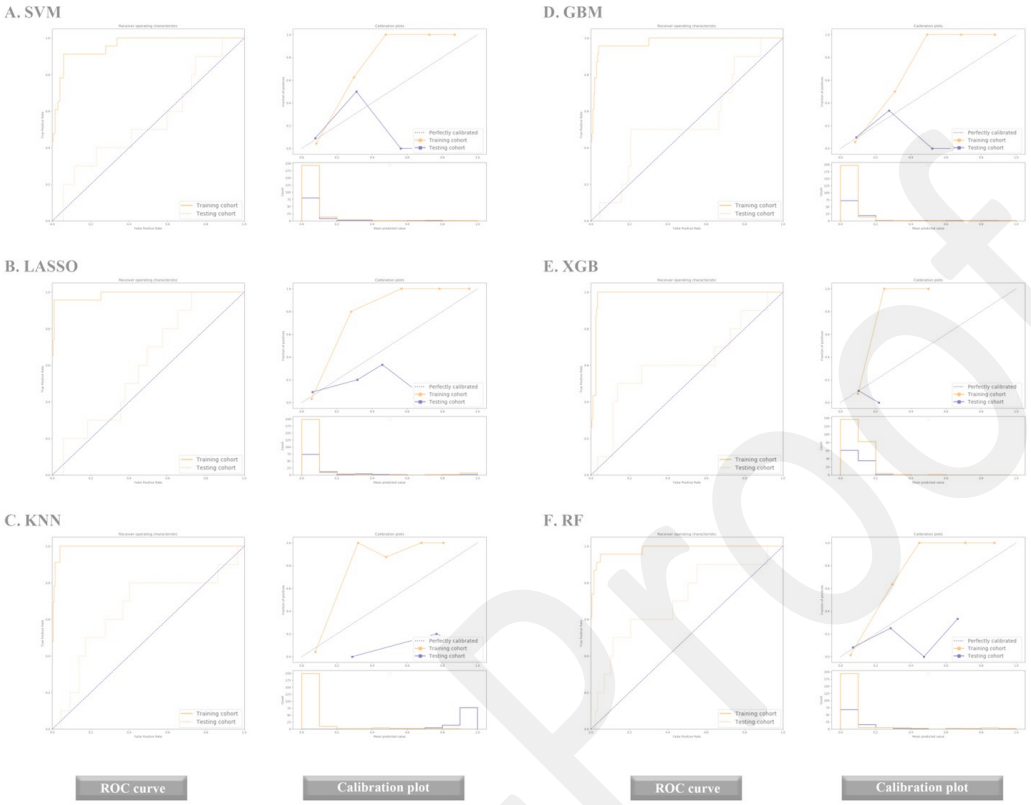
Figure.S3. Evaluation of prediction performances of seven ML models in predicting in-hospital mortality on patients of training and test sets.



Abbreviations: AUC, Area under receiver operating characteristic curve; ROC, Receiver operating characteristic; LR, logistic regression; LASSO, least absolute shrinkage and selection operator; SVM, support vector machine; KNN, K-Nearest Neighbor; RF, random forest; GBM, gradient boosting machine; XGB, extreme gradient boosting.

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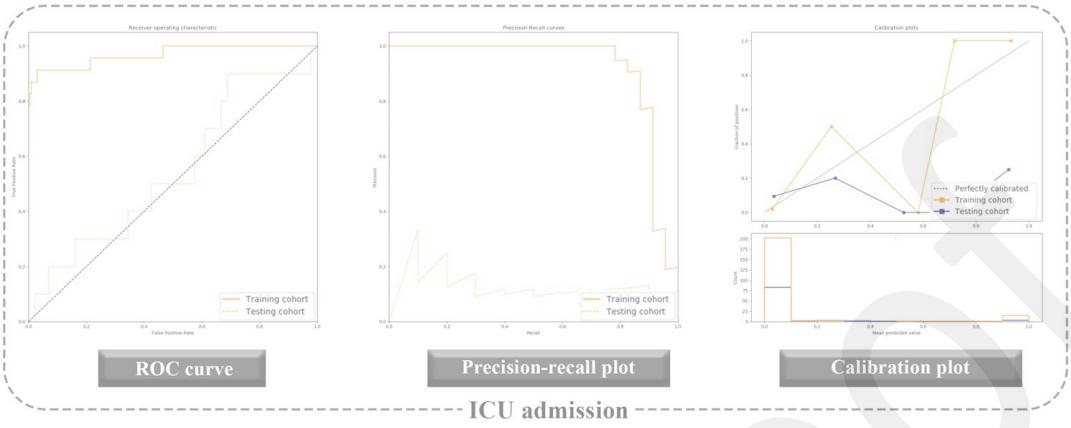
Figure.S4. Evaluation of the predictive performance of the occurrence of ICU admission in the prediction of in-hospital mortality on patients of training and test sets.



Abbreviations: AUC, Area under receiver operating characteristic curve; ROC, Receiver operating characteristic.

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