Cardiovascular Diabetology

RESEARCH

Open Access

Relationship between atherogenic index of plasma and length of stay in critically ill patients with atherosclerotic cardiovascular disease: a retrospective cohort study and predictive modeling based on machine learning

Yu Guo[1†], Fuxu Wang[2†], Shiyin Ma[1†], Zhi Mao[3], Shuangmei Zhao[2], Liutao Sui[2], Chucheng Jiao[2], Ruogu Lu[4*], Xiaoyan Zhu[2*] and Xudong Pan[1*]

Abstract

Background The atherogenic index of plasma (AIP) is considered an important marker of atherosclerosis and cardiovascular risk. However, its potential role in predicting length of stay (LOS), especially in patients with atherosclerotic cardiovascular disease (ASCVD), remains to be explored. We investigated the effect of AIP on hospital LOS in critically ill ASCVD patients and explored the risk factors affecting LOS in conjunction with machine learning.

Methods Using data from the Medical Information Mart for Intensive Care (MIMIC)-IV. AIP was calculated as the logarithmic ratio of TG to HDL-C, and patients were stratified into four groups based on AIP values. We investigated the association between AIP and two key clinical outcomes: ICU LOS and total hospital LOS. Multivariate logistic regression models were used to evaluate these associations, while restricted cubic spline (RCS) regressions assessed potential nonlinear relationships. Additionally, machine learning (ML) techniques, including logistic regression (LR), decision tree (DT), random forest (RF), extreme gradient boosting (XGB), and light gradient boosting machine (LGB), were applied, with the Shapley additive explanation (SHAP) method used to determine feature importance.

Results The study enrolled a total of 2423 patients with critically ill ASCVD, predominantly male (54.91%), and revealed that higher AIP values were independently associated with longer ICU and hospital stays. Specifically, for

†Yu Guo, Fuxu Wang and Shiyin Ma contributed equally to this work.

*Correspondence:
Ruogu Lu
ruogulu2023@163.com
Xiaoyan Zhu
zxysdjm@qdu.edu.cn
Xudong Pan
drpan022@qdu.edu.cn

Full list of author information is available at the end of the article

each unit increase in AIP, the odds of prolonged ICU and hospital stays were significantly higher, with adjusted odds ratios (OR) of 1.42 (95% CI, 1.11–1.81; $P=0.006$) and 1.73 (95% CI, 1.34–2.24; $P<0.001$), respectively. The RCS regression demonstrated a linear relationship between increasing AIP and both ICU LOS and hospital LOS. ML models, specifically LGB (ROC:0.740) and LR (ROC:0.832) demonstrated superior predictive accuracy for these endpoints, identifying AIP as a vital component of hospitalization duration.

Conclusion AIP is a significant predictor of ICU and hospital LOS in patients with critically ill ASCVD. AIP could serve as an early prognostic tool for guiding clinical decision-making and managing patient outcomes.

Keywords Atherosclerotic cardiovascular disease, AIP, LOS, Machine learning, MIMIC-IV

Introduction

Cardiovascular diseases (CVDs) are one of the major threats to human survival and quality of life in today's world, claiming approximately 17.7 million lives annually [1, 2]. Atherosclerotic cardiovascular disease (ASCVD), encompassing ischaemic heart disease and ischemic stroke, now accounts for over 60% of global cardiovascular deaths, and its burden continues to escalate at an alarming rate [3, 4, 5, 6]. Controlling the growth of the burden of CVD, especially ASCVD, is, therefore, a serious challenge. Addressing this challenge demands innovative and precise strategies to mitigate its progression. However, research on hospital length of stay (LOS), particularly in intensive care units (ICU), in patients with critically ill ASCVD remains relatively limited. While CVD mortality rates have declined over the years, there remains a critical need for further research on the clinical course and prognosis of hospitalized patients, particularly in terms of ICU stays.

Among various indicators, the Atherogenic Index of Plasma (AIP), introduced by Dobiásová and Frohlich, has emerged as a valuable biomarker. Calculated as the log-transformed TG/HDL-C ratio, AIP reflects circulating lipid imbalances and serves as an independent predictor of rapid plaque progression [7, 8, 9]. Mounting evidence links elevated AIP with an increased risk of myocardial infarction, stroke, diabetes, and other metabolic disorders [7, 10, 11, 12]. AIP may influence clinical outcomes in ASCVD patients through mechanisms such as endothelial dysfunction and increased inflammation, which can affect hospitalization duration [13, 14].

In patients with severe ASCVD, the length of hospitalization is a critical metric, reflecting not only disease severity but also treatment efficacy and recovery outcomes. While existing research has demonstrated that factors such as lipid profiles and metabolic characteristics influence hospital stays [15, 16, 17], the role of AIP in this context remains underexplored. Could AIP, as a marker of lipid dysregulation, provide insights into hospitalization dynamics for severe ASCVD patients?

In our study, we sought to bridge this knowledge gap by investigating the relationship between AIP and the length of hospital stay in patients with severe ASCVD. Utilizing the comprehensive MIMIC-IV database and employing machine learning techniques, we aimed to identify key predictors of prolonged hospitalization, shedding light on the intricate interplay between metabolic risk factors and patient outcomes.

Methods

Data selection

This study is a retrospective observational cohort analysis with longitudinal follow-up of patients. It utilizes the Medical Information Marketplace for Intensive Care-IV (MIMIC-IV-3.1), a publicly available database that includes data from over 70,000 intensive care unit admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, spanning 2008 to 2019 [18]. The MIMIC-IV database provides comprehensive patient information, including demographics, vital signs, examination results, and diagnoses coded using the International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) Editions. Yu Guo was granted access to the database after obtaining certification (Record ID: 66829613) and extracted the necessary variables for this study. As the database anonymizes patient health information, individual consent was not required.

Diagnoses were determined by manual review of ICD-9 and ICD-10 codes (the ICD-9 and ICD-10 codes for all diseases are shown in supplementary material Table S1) [19]. Exclusion criteria were as follows: (1) minors (< 18 years of age), (2) patients with an ICU stay of less than 24 h, and (3) patients with advanced renal impairment, severe liver disease, or malignancy. For repeat admissions, we only collected indicators for the first admission. The flow chart of the study is shown in Fig. 1.

Measurement and calculation of AIP

AIP was chosen as the primary study variable. Serum triglycerides (TG) and serum hyperlipidemia (HLD) cholesterol were measured for the first time after admission to minimize interference with TG and HDL cholesterol values by subsequent treatment [20, 21, 22]. The AIP calculation formula is as follows:

$$\mathrm{AIP} = \log\ (\mathrm{TG\ (mmol/L)}\ /\ \mathrm{HDL\ -\ C\ (mmol/L)}) \quad [23]$$

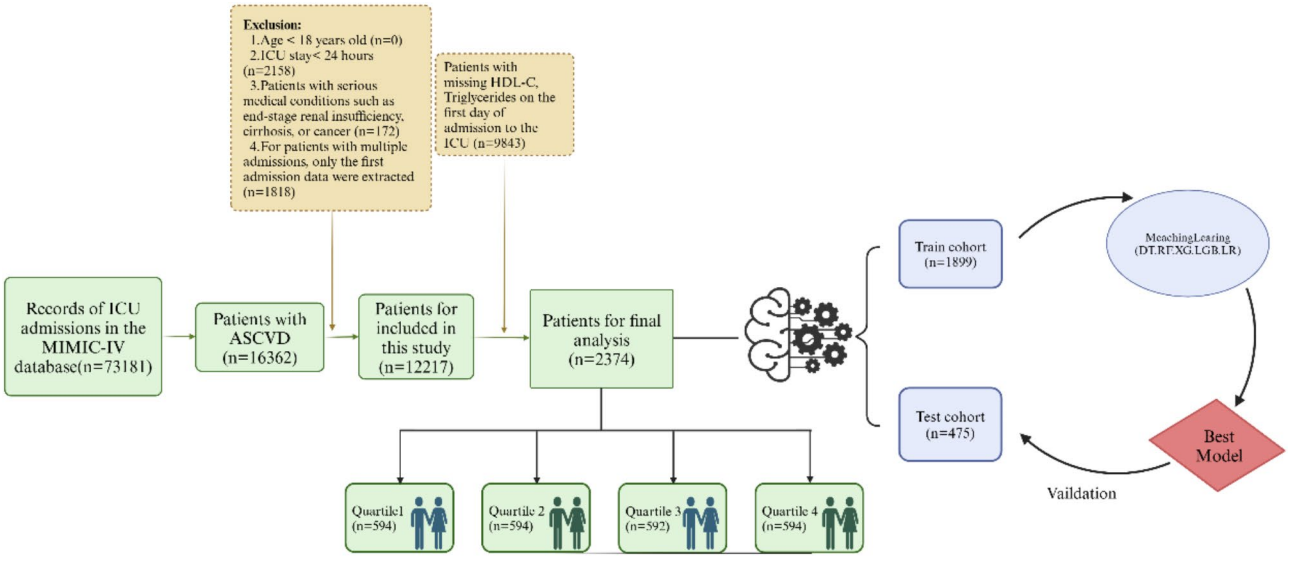

Fig. 1 Flow chart of the study design. LR: logistic regression; DT: decision tree; RF: random forest; XG: extreme gradient boosting; LGB: light gradient boosting machine

Endpoint events

The study endpoints were hospital LOS and ICU LOS.

Data collection

The data extraction tool uses PostgreSQL software (v13.7.1) and Navicate Premium software (version 15) to extract data through the running Structured Query Language (SQL). Potential confounders were extracted including (1) demographics: age, gender, race; (2) Vital signs: heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate; (3) Clinical management: use of aspirin, clopidogrel, warfarin, vasopressin, statins; mechanical ventilation; continuous renal replacement therapy; (4) Comorbidities: acute kidney injury (AKI), chronic kidney disease (CKD), sepsis, chronic obstructive pulmonary disease (COPD), HLD, respiratory failure (RF), heart failure (HF), atrial fibrillation (AF), hypertension, diabetes mellitus; (5) Laboratory indices: red blood cells (RBD), white blood cells (WBC), red blood cell width of distribution (RDW), platelets (PLT), hemoglobin (Hb), hematocrit (HCT), total bilirubin (TB), alanine transferase (ALT), TG, alanine transferase (AST), high-density lipoprotein cholesterol (HDL), serum glucose, prothrombin time (PT), serum creatinine (Cr), blood urea nitrogen (BUN), anion gap (AG), international normalized ratio (INR), serum potassium, serum sodium, serum calcium, and serum magnesium; and (6) severity of disease scores at the time of admission: sequential Organ Failure Estimate (SOFA) score, Acute Physiology Score III (APS III), Systemic Inflammatory Response Syndrome Score (SIRS), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), Glasgow Coma Score (GCS), Charlson Comorbidity Index (CCI).

In the model, variables with more than 25% missing values are deleted, and missing values are multiple imputations using multiple imputations by chained equations (MICE) [24].

Statistical analysis

Subjects were stratified into quartiles based on their AIP values (Q1-Q4) [12]. Continuous variables were expressed as median (interquartile spacing (IQR)), and comparisons between groups were made using the student's t-test or the Kruskal-Wallis H test, and categorical variables were expressed as frequencies and percentages (%), and comparisons between groups were made using the Pearson's chi-square test or Fisher's exact test. Kaplan-Meyer(K-M) survival analysis and Restricted mean survival time (RMST) were used to estimate ICU length of stay and length of hospitalization grouped according to the AIP index. Multivariate logistic regression analyses examined the relationship between AIP and the two outcomes. Age, weight, gender, RDW, Sodium, PTT, HLD, AKI, Diabetes, and COPD were included as confounders in the Q1 group as the reference group and trend tests were performed. We applied restricted cubic spline (RCS) curves to investigate the potential nonlinear relationship between AIP and outcome events and created a threshold effects model to identify the inflection point of AIP. Furthermore, we performed subgroup analyses to verify the reliability of the findings. To control the risk of false positives due to multiple hypothesis testing, the Bonferroni correction method was used in this study. The statistical analyses for this research were

carried out using Python (version 3.9.12), SPSS (version 26.0), and DecisionLnnc1.0 software. The p-values were set according to the Bonferroni multiple correction criterion. A value of 0.025 (0.05/2) was considered statistically significant in the main analysis and 0.0023 (0.05/22) in the subgroup interaction analysis.

Construction and performance evaluation of machine learning models

The choice of variables is determined by the intersection of lasso regression and Boruta algorithm results together. The patients were randomly assigned to two groups, with 80% allocated to the training set and the remaining 20% assigned to the test set. Using the chosen predictors, five machine learning models were developed, including Logistic Regression (LR), Decision Tree (DT), Random Forest (RF), Extreme Gradient Boosting (XGB), and Light Gradient Boosting Machine (LGB) [25, 26]. LR is highly interpretable and suitable for linear relationships [26]; DT captures nonlinear relationships and interactions; RF is suitable for high-dimensional data and robust to noise [27]; XGB and LGB are optimized versions of the gradient boosting framework that support parallel computation and automatic handling of missing values, and perform well in clinical prediction tasks [28]. The models were evaluated based on the area under the receiver operating characteristic (AUROC) curve, specificity, sensitivity, accuracy, and F1 score, with AUROC serving as the primary metric. The model demonstrating the best predictive performance was selected as the main model for this study. Calibration curves were utilized to evaluate the alignment between observed and predicted outcomes, while decision curve analysis (DCA) helped assess the net clinical benefit. The interpretability of the final prediction model was explored using the Shapley summation interpretation (SHAP) method.

Result

We screened and finally included 2374 patients with a mean age of 71 years, of which 54.91% were male. Missing values have been added using multiple imputations (Supplementary materials Table 2).

Baseline characteristics of study individuals

The patients were grouped into quartiles based on the AIP values calculated at the time of admission as Q1 ($n=594$, -0.813-1.168), Q2 ($n=594$, 1.168–1.521), Q3 ($n=592$, 1.521–1.875), and Q4 ($n=594$, 1.875–2.228). The analysis showed that the patient population with the highest AIP values had the youngest age of 62 (56–75), the highest body weight of 85.5 kg (73-100.57) the highest scores on all scales (SOFA, ASPIII, SIRS, GCS, CCI), higher NBPm, the highest heart rate, respiratory rate, RDW, and BUN, and also demonstrated the highest ICU hospitalization as well as longer length of stay (Supplementary materials Table 3).

Clinical outcomes.

The results of the Kaplan-Meier survival analyses for the two outcomes are shown in Fig. 2, where the horizontal coordinate is the length of hospital stay and the vertical coordinate represents the discharge rate, i.e., as the length of hospital stay increases, the discharge rate decreases progressively. The results for both quartile groupings show significant differences (both $p<0.001$), and both graphs show that the largest quartile group in each group had the longest length of stay for the same discharge rate. In Fig. 3, the difference between the two groups grouped by median AIP was also significant in the different endings.

As shown in Table 1, when AIP was analyzed as a categorical variable, three multivariate logistic regression analyses were used, with model 1 unadjusted, model 2 adjusted for age, weight, gender, and model 3 adjusted for

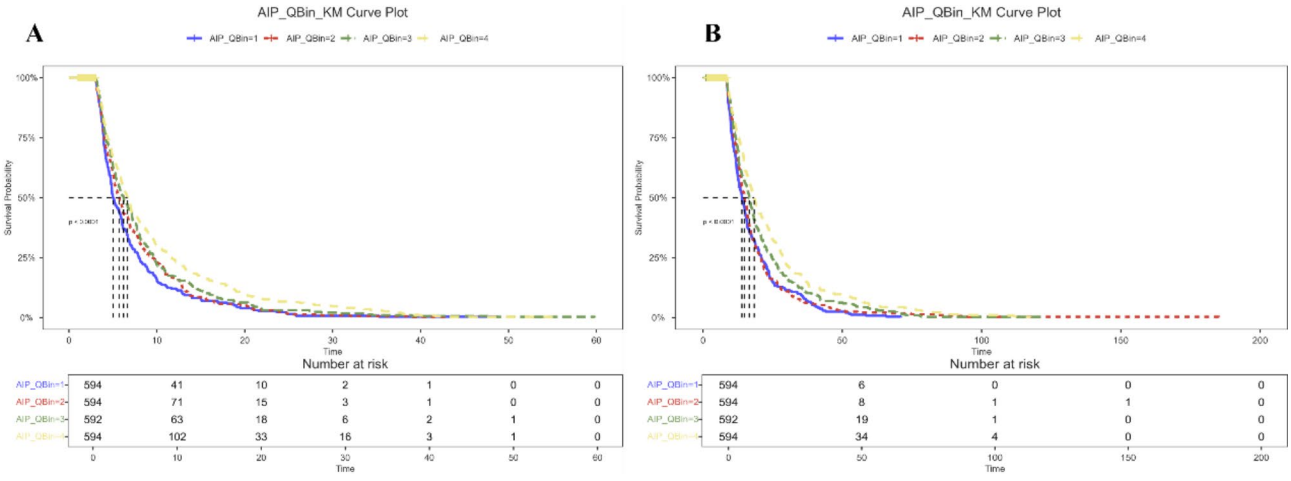

Fig. 2 Kaplan–Meier survival analysis curves of the two cohorts, ICU length of stay (**A**), length of hospitalization (**B**). The horizontal coordinate is the length of hospital stay, the vertical coordinate represents the discharge rate

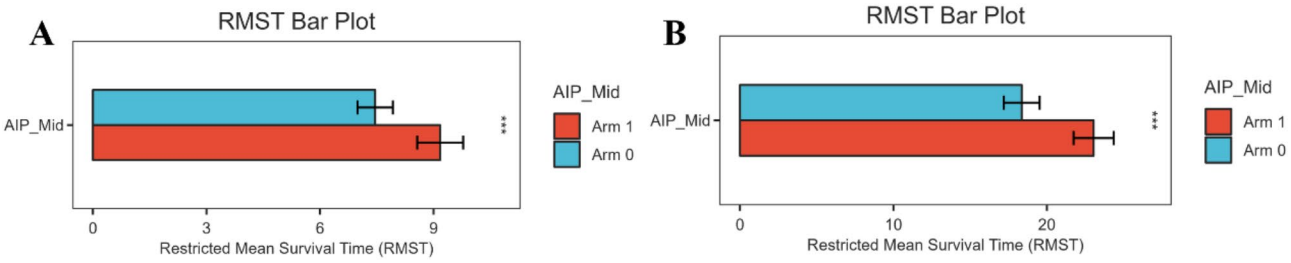

Fig. 3 Restricted mean survival time graph of **A** ICU length of stay and **B** length of hospitalization

Table 1 Relationship between AIP and ICU LOS

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
AIP IQR						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.34 (1.07–1.68)	**0.012**	1.32(1.05 ~ 1.66)	**0.005**	1.28 (1.01–1.61)	**0.038**
Q3	1.23(0.96–1.54)	0.081	1.19(0.95–1.51)	0.133	1.12 (0.88 ~ 1.41)	0.360
Q4	1.78(1.42–2.24)	**< 0.001**	1.69(1.33 ~ 2.15)	**< 0.001**	1.42(1.11 ~ 1.81)	**0.006**
P for trend	1.17 (1.10 ~ 1.27)	**< 0.001**	1.16 (1.07 ~ 1.25)	**< 0.001**	1.09(1.01 ~ 1.18)	**0.025**

P-values have been corrected by Bonferroni.

HR: Hazard Ratio, CI: Confidence Interval

Model1: Crude

Model2: Adjust: age, weight, gender

Model3: Adjust: age, weight, gender, RDW, Sodium, PTT, HLD, AKI, Diabetes, COPD

Table 2 Relationship between AIP and hospital LOS

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
AIP IQR						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.32 (1.05–1.67)	**0.02**	1.33(1.06–1.69)	**< 0.001**	1.26 (0.99–1.61)	0.058
Q3	1.53(1.21–1.92)	**< 0.001**	1.56(1.23–1.96)	**< 0.001**	1.41 (1.10–1.80)	**0.006**
Q4	2.24(1.78–2.82)	**< 0.001**	2.33(1.83–2.97)	**< 0.001**	1.73 (1.34–2.24)	**< 0.001**
P for trend	1.29(1.20–1.39)	**< 0.001**	1.31 (1.21–1.41)	**< 0.001**	1.19(1.10–1.29)	**< 0.001**

P-values have been corrected by Bonferroni.

HR: Hazard Ratio, CI: Confidence Interval

Model1: Crude

Model2: Adjust: age, weight, gender,

Model3: Adjust: age, weight, gender, RDW, Sodium, PTT, HLD, AKI, Diabetes, COPD

age, weight, gender, RDW, Sodium, PTT, HLD, AKI, Diabetes, and COPD. Using model 1 as a reference, the odds ratio (OR) and 95% confidence interval (CI) for the highest quartile subgroup of AIP were 1.69 (1.33–2.15) and 1.42 (1.11–1.81) for models 2 and 3, respectively, suggesting that elevated levels of AIP were significantly associated with ICU LOS, and that, after further adjusting for a wide range of confounders, AIP remained an independent risk factor for prolonged ICU stay. The results of the trend test further suggest a dose-effect relationship between AIP and prolonged ICU stay.

Similarly, we used three multivariate logistic regression analysis models to investigate the relationship between AIP and length of hospitalization. As shown in Table 2, compared with model 1, the OR (95% CI) was 1.56 (1.23–1.96) and 2.33 (1.83–2.97) for Q3 and Q4 in model 2, and 1.41 (1.10–1.80) and 1.73 (1.34–2.24) for Q3 and Q4 in model 3, respectively. All findings were statistically significant with a P-value of less than 0.025. This indicates that as AIP increases, the risk of a longer hospital stay also rises, and this association remained robust after adjusting for various potential confounders. This suggests that AIP could serve as an independent risk factor for the length of hospital stay. Patients in the fourth quartile faced a significantly greater risk of prolonged hospitalization compared to those in the first quartile, highlighting the importance of focusing on this high-risk group.

Detection of linear relationships

RCS curve analysis revealed a linear correlation (p-value < 0.05, non-linear $p > 0.05$) between AIP and ICU LOS as well as the length of hospitalization (Fig. 4A, B). The linear correlation scatterplot shows that AIP was positively correlated with ICU LOS and length of hospitalization ($p < 0.001$, Correlation = 0.124; $p < 0.001$, Correlation = 0.184) (Fig. 4C, D).

Subgroup analysis

We performed subgroup analyses of ICU LOS and hospital LOS, with P-values corrected using Bonferroni (Fig. 5). In the subgroup analysis with ICU LOS as the endpoint, in the age < 65 years, age > 65 years, male, female, with sepsis, with or without AF, with or without mechanical ventilation, with or without hypertension, with or without AKI, without CKD, with or without diabetes, with or without HLD, and with or without HF groups, interquartile group 4 had longer hospital stays (HR > 1, $P < 0.0023$ in each subgroup) (Fig. 5A). In subgroup analyses with hospital LOS as the endpoint, all fourth quartile subgroups had longer hospital stays in the age < 65 years, male, with or without AF, with hypertension, without CKD, without diabetes mellitus, without HLD, and without HF groups (HR > 1, $P < 0.0023$ in each subgroup) (Fig. 5B).

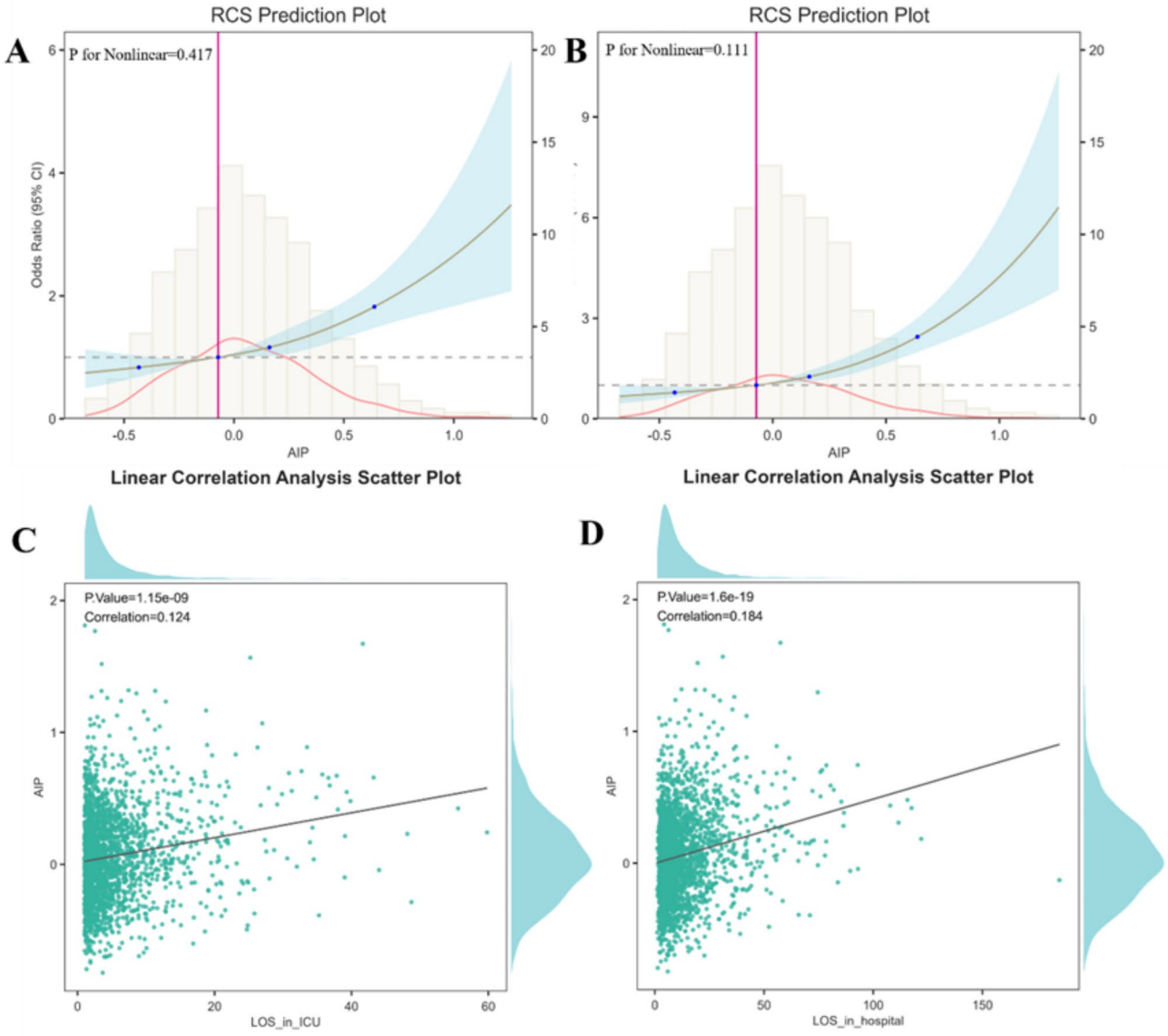

Fig. 4 Restricted cubic spline analysis illustrating AIP with ICU length of stay (**A**), and length of hospitalization (**B**). Linear correlation scatterplot for AIP with ICU length of stay (**C**), and length of hospitalization (**D**)

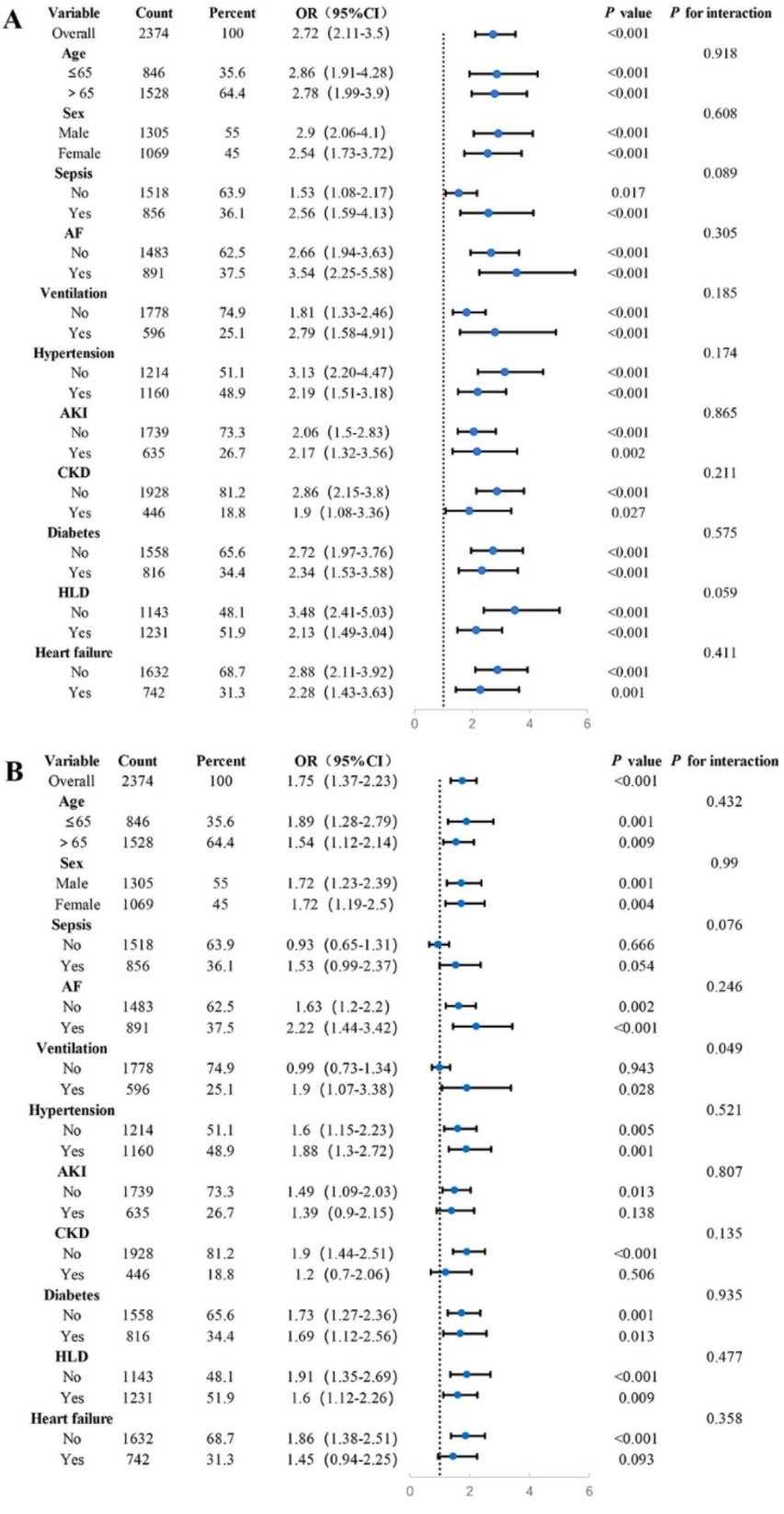

Fig. 5 Forest plots illustrating stratified analyses of the association of AIP and ICU LOS (**A**), and hospital LOS (**B**)

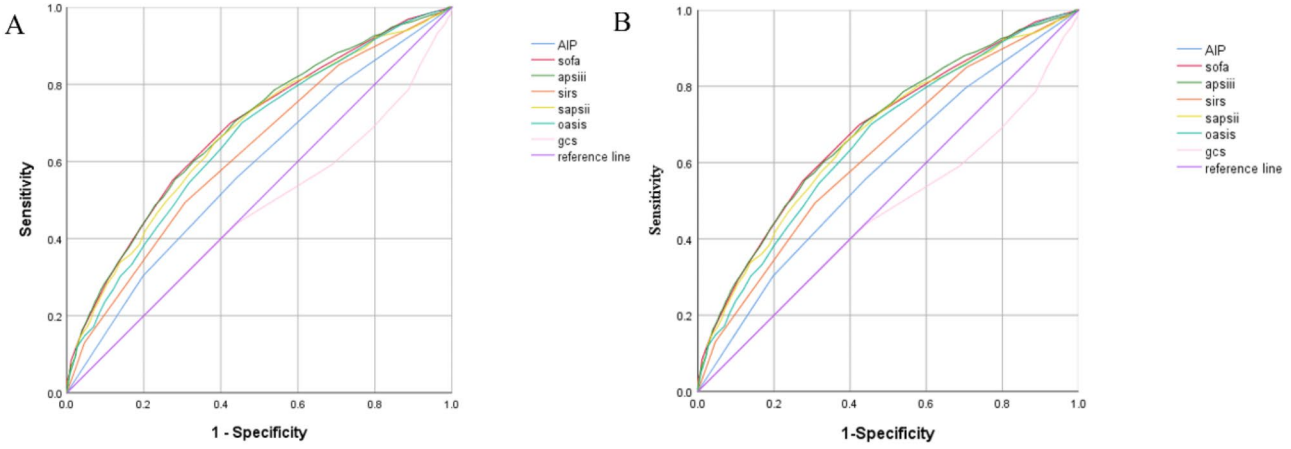

Fig. 6 Comparison of AIP and existing clinical scoring systems **A** ICU LOS **B** Hospital LOS

AIP vs. existing clinical scoring systems

Furthermore, we performed a comparison between AIP and other traditional scores (Fig. 6), constructing logistic regression models for the comparison [29, 30, 31]. The traditional scores incorporated by the items were SOFA, ASPIII, SIRS, SAPSII, OASIS and GCS scores [32]. For the prediction of ICU LOS(Fig. 6A), the ROC of AIP with the above five scores were 0.578; 0.683; 0.684; 0.624; 0.670; 0.658; and 0.461, respectively. Similarly, for the prediction of hospitalization time (Fig. 6B), they are 0.624; 0.683; 0.684; 0.670; 0.658; and 0.461, respectively.

Machine learning results

ICU LOS

Selection of characteristic variable

The variables characterizing AIP and ICU LOS were selected based on the intersection of the LASSO regression and Boruta algorithm results. After calculation, the Boruta algorithm identified 24 admissible variables, including "sepsis," "mechanical ventilation," "vasopressin," and "OASIS" (Fig. 7A). The path diagrams and crossover curves of the LASSO regression illustrate the included variables (Fig. 7B and C, Supplementary materials Table 4). The combined results of both methods are visualized, with purple feature variables in the feature selection network diagram representing the intersection of the two selection approaches and the variables ultimately used in this study (Fig. 7D).

Model performance comparisons

We constructed five models to predict ICU length of stay for ASCVD: LR, DT, RF, XGB, and LGB. As shown in Fig. 8, the LGB could provide relatively better model fitting performance with an AUC of 0.740 (sensitivity:0.508, specificity:0.879, accuracy:0.678, F1:0.676) compared to the other models, which were DT:0.632; RF:0.737; LR:0.733; and XGBoost:0.739. We performed parameter tuning and prevented model overfitting [33], such as using 5-fold cross-validation, using an independent validation set in cross-validation (not involved in model training and tuning), and using multiple metrics to evaluate the model to ensure that it has good generalization ability (Supplementary Material Table S6, S7). Fig.S1 shows the DCA curves, decision curves, and error histograms for the five models. The sensitivity, specificity, and accuracy of the other models are in the appendix material Table S8. In this study, we chose the LGB model for further investigation.

Model explanation

The SHAP method, a comprehensive interpretation approach suitable for both global and individual sample analysis, was used to interpret the model. For global interpretation, the SHAP means to assess the contribution of features to the model, with the five most important features being sepsis, mechanical ventilation, vasopressin, Charlson score, and age are listed in descending order of importance (Fig. 9A). The direction and role of these five features in the predictive model are visualized, where red indicates high feature values and blue indicates low values (Fig. 9B).

To interpret the prediction results of individual samples, the first sample's data was analyzed, revealing that mechanical ventilation significantly and positively influenced ICU length of stay (+1.28), followed by sepsis (+1.14) (Fig. 8C). Additionally, the model's predictions for two patients—one with a long ICU stay and another with a short ICU stay—are visualized, with red indicating positive contributions to the prediction and blue indicating negative effects. The f(x) values represent the actual SHAP contributions for each factor (Fig. 9D and E).

The LGB model variables predicting ICU LOS for patients with AIP are visualized in a heat map, highlighting the significant impact of sepsis on the model

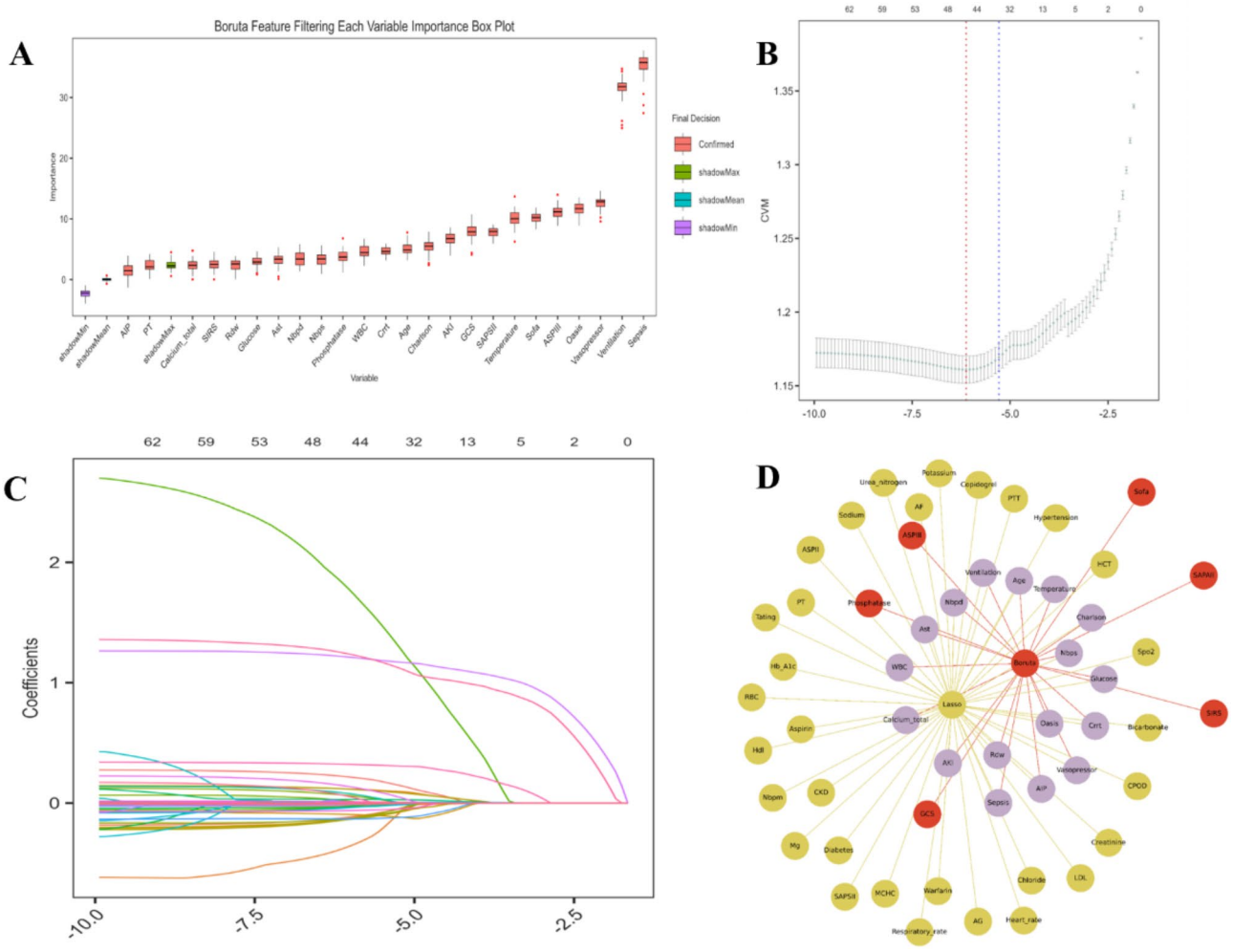

Fig. 7 AIP and ICU LOS Feature Selection Chart (**A**) Feature selection based on the Boruta algorithm. The horizontal axis is the name of each variable, and the vertical axis is the Z value of each variable. The box plot shows the Z value of each variable during model calculation. (**B**, **C**) Path diagrams and cross-validation plots of lasso regression analysis results. (**D**) Feature selection network diagram. The yellow section shows the results of the LASSO regression analysis, the red section shows the results of the Boruta algorithm, and the purple section shows the overlapping variables of the results of the two algorithms

output. Sepsis displays the widest range of colors across all samples and the longest importance bar on the right, indicating its prominent influence (Fig. S2A). Mechanical ventilation shows a notable positive effect in certain samples (darker red areas) while negatively impacting others (darker blue areas). Although vasopressor exhibits a strong influence on specific samples, its overall effect is limited, as reflected by the sporadic distribution of red and blue colors.

To illustrate the influence of AIP features on ICU LOS, a SHAP force diagram is presented, showing the direction and magnitude of AIP's contribution to the model predictions. A predominance of red areas with significant magnitude suggests a greater impact of AIP in prolonging LOS, whereas a dominance of blue indicates a tendency to shorten LOS (Fig. S2B).

Hospital LOS

Selection of characteristic variables

The selection of variables characterizing AIP and LOS was based on the overlapping results from the LASSO regression and Boruta's algorithm. The Boruta algorithm identified 38 admissible variables, including "sepsis," "mechanical ventilation," "vasopressin," and "ASPIII" (Fig. 10A). The paths of the LASSO regression and the crossover curves illustrate the included variables, as detailed in previous sections (Fig. 10B and C, Supplementary materials Table 5). The combined results of the two methods are visualized in the feature selection network diagram, where the purple feature variables represent the intersection of both methods and the variables selected by ML in this study, totaling 29 variables (Fig. 10D).

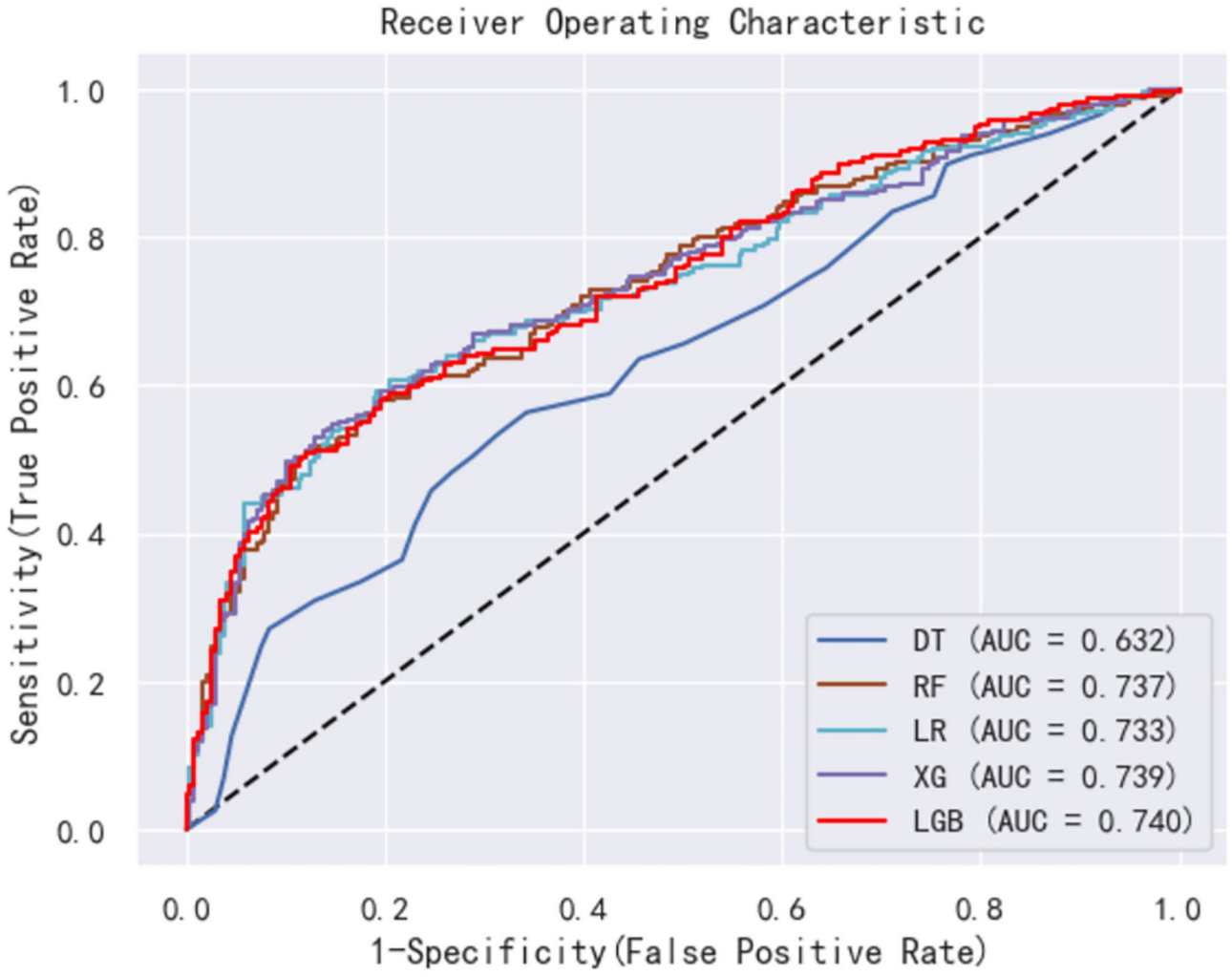

Fig. 8 ROC curves for the machine learning models. LR: logistic regression; DT: decision tree; RF: random forest; XG: extreme gradient boosting; LGB: light gradient boosting machine ROC: receiver operating characteristic; AUC: area under the curve

Building predictive models

As in the previous steps, we constructed five models to predict the hospital LOS for ASCVD patients, as shown in Fig. 11. The LR model can provide relatively better model fitting performance with an AUC of 0.832 compared to the other models (sensitivity:0.802, specificity:0.727, accuracy:0.741, F1:0.74). The AUCs of the other models were DT:0.791; RF:0.813; XGBoost:0.808; and LGB:0.812. We also performed parameter tuning and prevention of model overfitting, etc. Fig. S3 shows the DCA curves, decision curves, and error histograms for the five models. The sensitivity, specificity, and accuracy of the other models are in the appendix material Table S6. In this study, the LR model was chosen for further investigation.

Model explanation

The SHAP means were used to assess the contribution of features to the model, identifying sepsis, vasopressin, mechanical ventilation, SOFA score, and SAPS II as the five most important features in descending order of importance (Fig. 12A). The direction and role of these features in the predictive model are visualized, with red indicating a positive contribution and blue indicating a negative contribution (Fig. 12B).

For individual samples, predictive results are interpreted using graphs that reveal the significant influence of sepsis on hospitalization time, contributing positively (+0.11), while mechanical ventilation was the second most impactful feature, contributing negatively (-1.14) (Fig. 12C). Further, SHAP plots illustrate the in-hospital prognoses for two patients: one with a long hospital stay and another with a short hospital stay, highlighting the contributions of various factors (Fig. 12D and E).

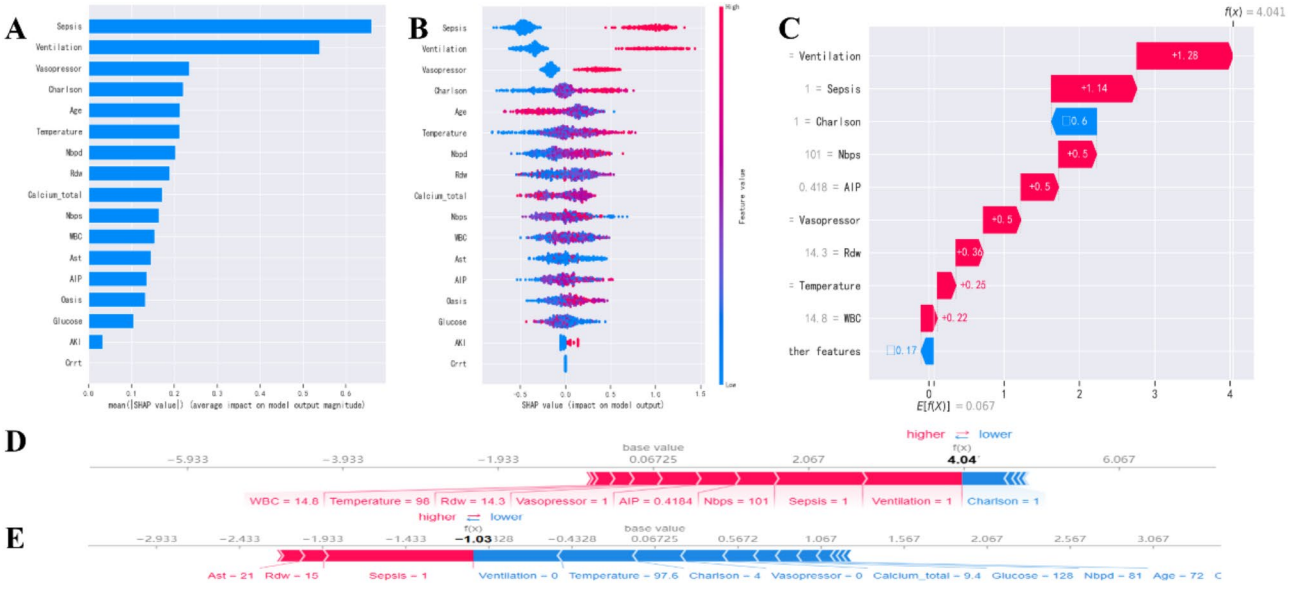

Fig. 9 Global and local model explanation by the SHAP method. **A** SHAP summary bar plot. This plot evaluates the contribution of each feature to the model using mean SHAP values, displayed in descending order. **B** SHAP summary dot plot. The probability of the length of stay in ICU increases with the SHAP values of the features. Each dot represents a patient's SHAP value for a given feature, with red indicating higher feature values and blue indicating lower values. Dots are stacked vertically to show density. **C** SHAP waterfall plot. This plot shows the contribution of each feature to the prediction result of one patient using the LGB(LightGBM) model. Red bars indicate features that contribute positively to the prediction, while blue bars indicate negative contributions. **D**, **E** SHAP force plot. Force diagrams for two different ending patients. RDW: Red blood cell distribution width; Nbps: Noninvasive Blood Pressure; AST: Aspartate transaminase; WBC: White blood cell; AIP: atherogenic index of plasma; AKI: Acute kidney injury; CRRT: Continuous Renal Replacement Therapy

The heat map of the LR model variables predicting hospital LOS for patients with AIP highlights sepsis as the most influential feature in the model output (Fig. S4A). Vasopressin demonstrates a significant positive effect on certain samples (darker red areas) while negatively affecting others (darker blue areas). Mechanical ventilation exerts a strong influence on specific samples, though its overall range of effects remains limited, as reflected by the sporadic distribution of red and blue colors.

A SHAP force diagram illustrates the direction and magnitude of AIP's influence on the length of hospitalization, offering insights into how AIP contributes to model predictions. A predominance of red areas with significant magnitude indicates a greater impact of AIP in lengthening the hospital stay, while a predominance of blue areas suggests a tendency to shorten it (Fig.S4B).

Discussion

In this study, we analyzed data from 2,374 adults and observed a compelling association between the AIP and LOS in both the ICU and overall hospitalization among patients with critically ill ASCVD. Patients in higher quartiles of AIP experienced significantly prolonged ICU and hospital stays compared to those in the lowest quartile. After adjusting for various confounders, the relationship between AIP and LOS remained linear, reinforcing the notion that higher AIP levels are consistently linked to longer stays. For the comparison of AIP with traditional scores, although AIP cannot completely replace traditional scores, it is still relevant in predicting the length of hospitalization. While the traditional score is based on a composite of the patient's multidimensional status, the AIP depends on two blood indicators, but we still hope that the AIP will be a complementary predictor of the length of hospitalization.

To ensure rigorous variable selection, we utilized both LASSO regression and Boruta's algorithm, two widely recognized feature selection methods. AIP was identified as a significant predictor in both methods, a finding that aligns with our logistic regression results. These observations suggest that AIP holds promise as a reliable predictor of hospital and ICU LOS in patients with critically ill ASCVD.

The rapid evolution of artificial intelligence in recent years has led to the widespread adoption of ML algorithms in medical research, particularly for predicting treatment outcomes and patient prognosis. LGB and RF were prioritized for their efficiency in handling high-dimensional data and capturing non-linear interactions, as demonstrated in prior critical care studies [34, 35, 36]. LR, one of the foundational tools in ML, offers not only categorical predictions but also the probability of each outcome, enabling nuanced insights into model confidence. Its interpretable coefficients allow a clear

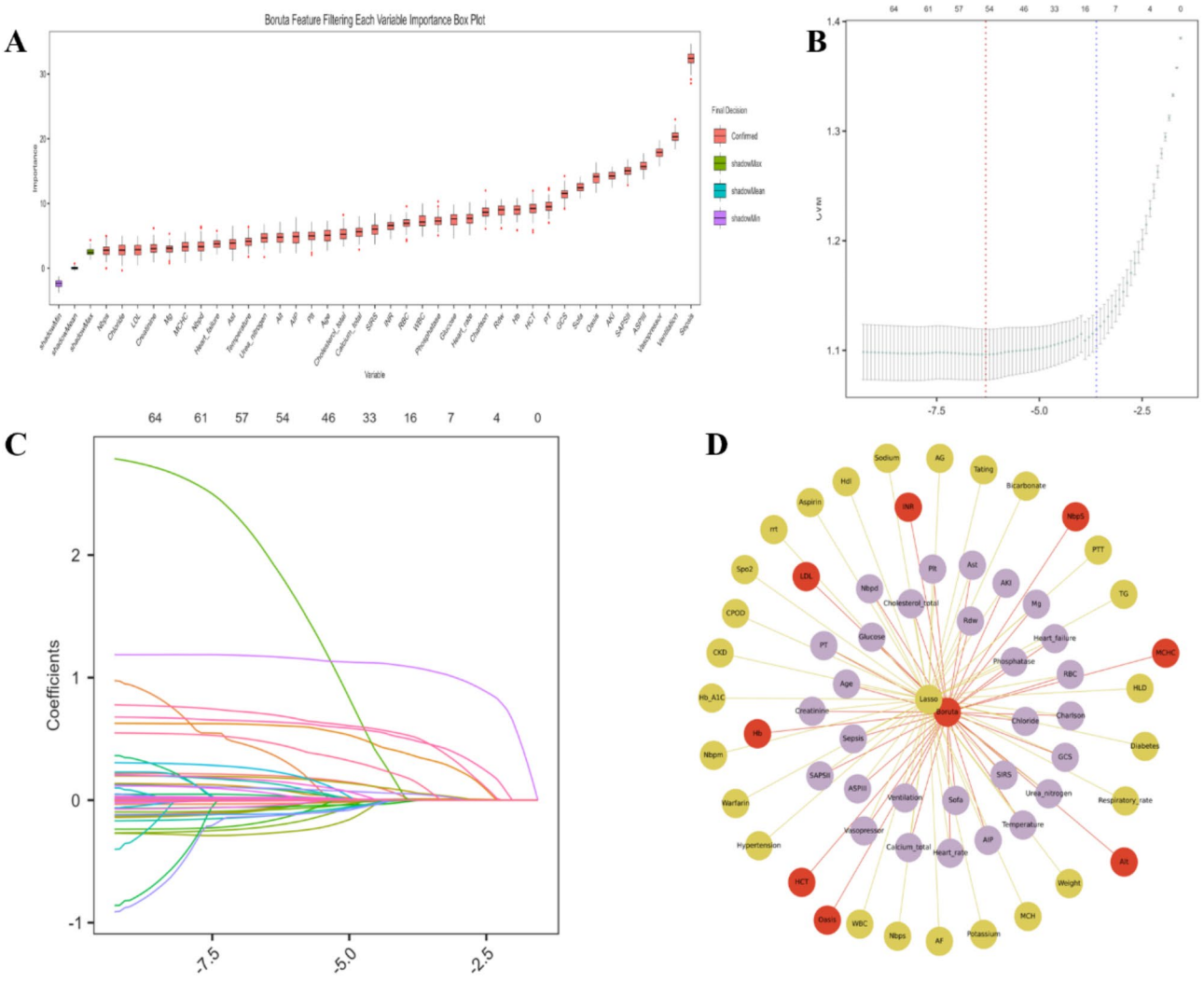

Fig. 10 AIP and hospital LOS Feature Selection Chart **A** Feature selection based on the Boruta algorithm. The horizontal axis is the name of each variable, and the vertical axis is the Z value of each variable. The box plot shows the Z value of each variable during model calculation. **B**, **C** Path diagrams and cross-validation plots of lasso regression analysis results. **D** Feature selection network diagram. The yellow section shows the results of the LASSO regression analysis, the red section shows the results of the Boruta algorithm, and the purple section shows the overlapping variables of the results of the two algorithms

understanding of how individual features influence predictions [37]. Meanwhile, advanced algorithms such as LGB offer significant advantages, including rapid training speeds, low memory consumption, robust handling of high-dimensional datasets, and efficient parallel processing. These attributes make LGB particularly suitable for analyzing large-scale clinical data with intricate feature interactions [27, 34].

From a biological perspective, the role of AIP in atherosclerosis and cardiovascular outcomes is well-supported by prior research. Cholesterol in TG-rich lipoproteins has been identified as a key contributor to atherosclerosis, facilitating plaque formation in arterial walls. Atherogenic Apo B-containing lipoproteins, primarily LDL-C, drive the progression of atherosclerosis by promoting foam cell formation, stimulating immune responses, and producing reactive inflammatory mediators [38, 39, 40, 41]. Observational studies have consistently highlighted a negative correlation between HDL-C and atherosclerotic events, suggesting that HDL-C plays a protective role in vascular health [14, 42].

AIP, which encapsulates the balance between TG and HDL-C, has been linked to adverse outcomes across a spectrum of conditions, including diabetes, stroke, cardiovascular disease, and kidney disease [43]. For example, You et al. reported a significant linear association between elevated AIP and increased mortality from diabetes in a healthy population [44]. A cross-sectional study examining blood samples from Mexican women found that AIP could be used as a potential biomarker

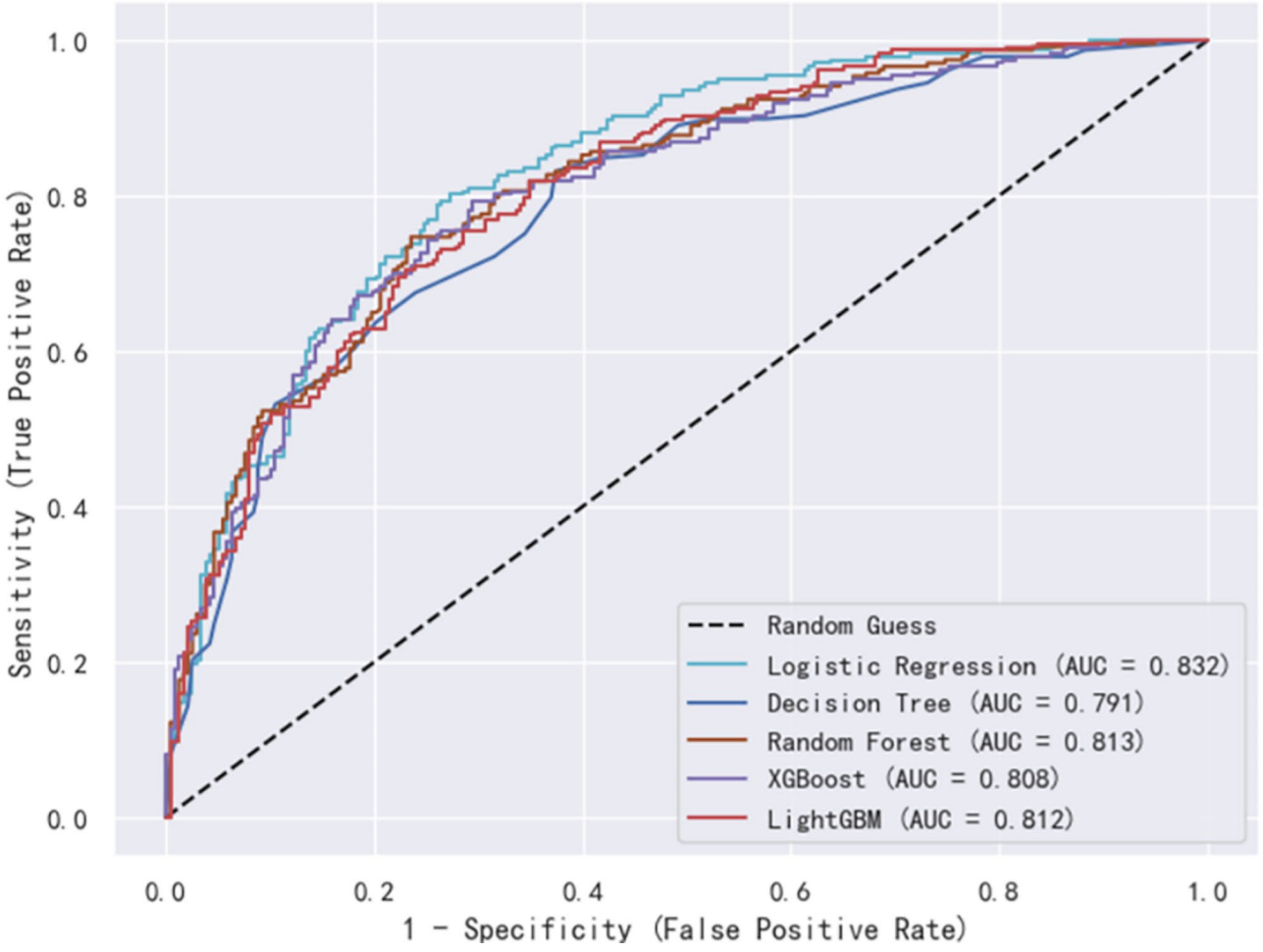

Fig. 11 ROC curves for the machine learning models. LR: logistic regression; DT: decision tree; RF: random forest; XG: extreme gradient boosting; LGB: light gradient boosting machine ROC: receiver operating characteristic; AUC: area under the curve

for the early diagnosis of cardiovascular disease in developing countries [10]. Zheng et al. found that high levels of cumulative AIP were associated with a higher risk of ischemic stroke in the Kailuan Study of 54,123 participants [45]. Furthermore, elevated AIP levels have been associated with worse clinical outcomes and longer hospital stays in patients with acute myocardial infarction [46]. Building on this foundation, our study is the first to specifically investigate the relationship between AIP and ICU LOS as well as overall hospitalization duration in critically ill ASCVD, highlighting the potential value of AIP as a marker of disease severity and prognosis.

The mechanisms by which elevated AIP prolongs hospitalization are multifaceted, with inflammation likely playing a central role. Elevated AIP reflects not only lipid metabolism disturbances but also heightened systemic inflammation, both of which are intimately linked to the pathophysiology of ASCVD [47, 48, 49]. Inflammatory responses drive atherosclerotic plaque formation, rupture, and thrombosis, with HDL-C playing a crucial protective role by facilitating reverse cholesterol transport, reducing vascular lipid deposits, and modulating the inflammatory response [50, 51, 52]. However, elevated AIP is often accompanied by reduced HDL-C levels, which diminishes its anti-inflammatory and antioxidant functions. This reduction hampers the clearance of oxidized LDL and weakens the regulation of inflammatory pathways, potentially exacerbating vascular damage [53, 54].

AIP, therefore, serves as a biomarker that integrates lipid metabolism and inflammatory status, reflecting the dual pathways contributing to ASCVD progression. The interplay between chronic inflammation and lipid abnormalities leads to endothelial damage, increased plaque instability, and heightened cardiovascular risk [55, 56]. AIP, as a crossroads of lipid metabolism and inflammatory responses may be a valuable biomarker for predicting length of hospitalization and clinical outcomes in patients with ASCVD.

This study also has some limitations. Firstly, we only used a single-center database for the study, which may result in the regional, healthcare setting, and patient

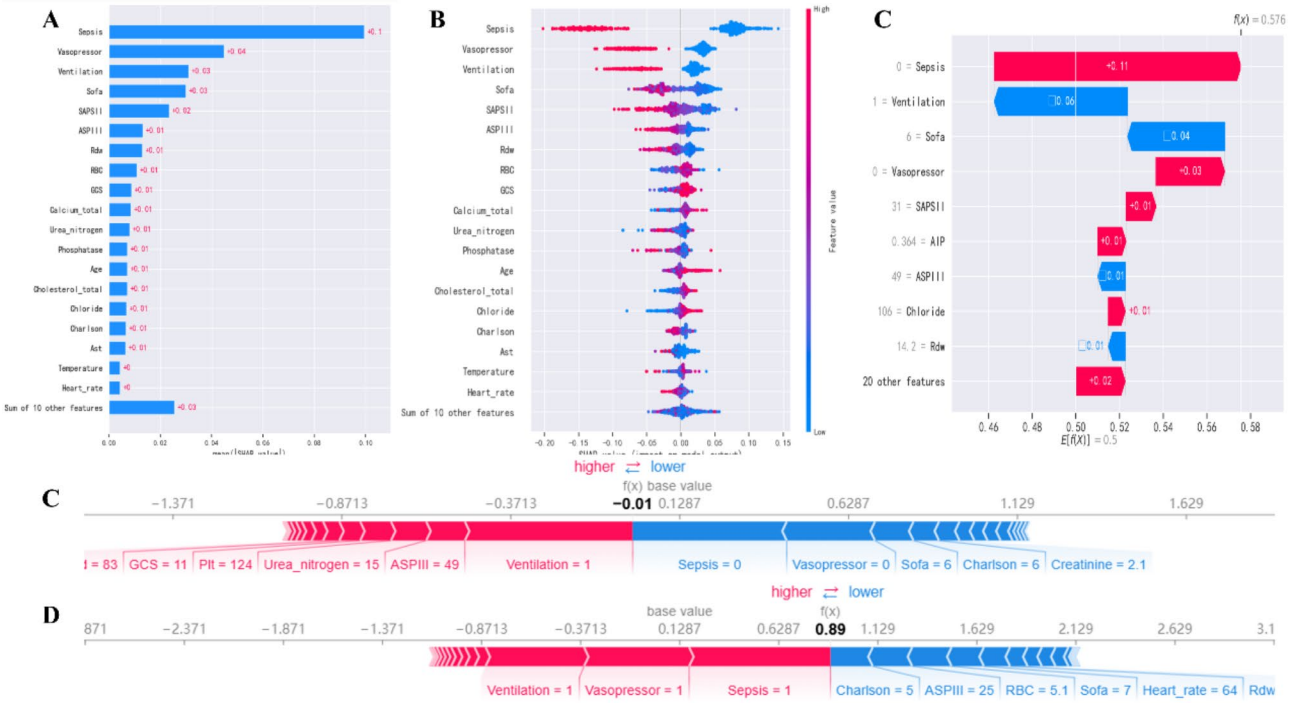

Fig. 12 Global and local model explanation by the SHAP method. **A** SHAP summary bar plot. This plot evaluates the contribution of each feature to the model using mean SHAP values, displayed in descending order. **B** SHAP summary dot plot. The probability of the length of hospitalization increases with the SHAP values of the features. Each dot represents a patient's SHAP value for a given feature, with red indicating higher feature values and blue indicating lower values. Dots are stacked vertically to show density. **C** SHAP waterfall plot. This plot shows the contribution of each feature to the prediction result of one patient using the LR (Logistic Regression) model. Red bars indicate features that contribute positively to the prediction, while blue bars indicate negative contributions. **D**, **E** SHAP force plot. Force diagrams for two different ending patients. RDW: Red blood cell distribution width; RBC: Red blood cell; AST: Aspartate transaminase

population bias, and future studies speak to considering the use of multicenter data to improve external validity. Secondly, there were a large number of missing values in the database, such as height and imaging data, all of which we did not include in the metrics because we considered the effect of missing values. We look forward to further studies as the database is improved. Thirdly, only the baseline AIP index was analyzed in this study. The dynamics of the AIP index were not explored during hospitalization and ICU. Fourthly, despite the inclusion of many potential confounders, due to the limitations of the database, there may still be some unconsidered factors such as patient lifestyle (diet, exercise), treatment regimen, family history, and psychological factors. This will be explored in greater depth as the database is refined.

Conclusion

AIP is an important influence on the length of ICU stay and hospitalization in patients with critically ill ASCVD. Early detection and intervention of AIP can be clinically used as a prognostic assessment tool and play an important role in future treatment strategies. Future studies, particularly those employing prospective designs and external validation cohorts, are needed to confirm and extend these findings.

Abbreviations

AIP	Atherogenic index of plasma
LOS	Length of stay
ASCVD	Atherosclerotic cardiovascular disease
MIMIC	Medical Information Mart for Intensive Care
RCS	Restricted cubic spline
ML	Machine learning
LR	Logistic regression
DT	Decision tree
RF	Random forest
XGB	Extreme gradient boosting
LGB	Light gradient boosting machine
SHAP	Shapley additive explanation (SHAP)
OR	Odds ratio
NBP	Non-invasive blood pressure
CI	Confidence interval
CVD	Cardiovascular disease
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
ICD	International Classification of Diseases
AKI	Acute kidney injury
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
HLD	Hyperlipidemia
RF	Respiratory failure
HF	Heart failure

AF	Atrial fibrillation
Hp	Hypertension
RBD	Red blood cell
WBC	White blood cell
RDW	Red blood cell width of distribution
MCHC	Mean corpuscular hemoglobin concentration
MCH	Mean corpuscular hemoglobin
PLT	Platelet
Hb	Hemoglobin
HCT	Hematocrit
TB	Total bilirubin
ALT	Alanine transferase
AST	Alanine transferase
PT	Prothrombin time
Cr	Serum creatinine
BUN	Blood urea nitrogen
AG	Anion gap
INR	International normalized ratio
SOFA	Sequential Organ Failure Estimate
APS III	Acute Physiology Score III
SIRS	Systemic Inflammatory Response Syndrome Score
SAPS II	Simplified Acute Physiology Score II
OASIS	Oxford Acute Severity of Illness Score
GCS	Glasgow Coma Score
CCI	Charlson Comorbidity Index
AUROC	Area under the receiver operating characteristic
DCA	Decision curve analysis
RMST	Restricted mean survival time
CRRT	Continuous renal replacement therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02654-3 .

Supplementary Material 1

Acknowledgements
None.

Author contributions
YG. FXW and SYM came up with the article concept and design ideas and wrote the initial draft. ZM. SMZ and LTS performed the statistical analysis. CCJ carried out the drawing of the picture and table parts. RGL. XYZ and XDP were pivotal in revising the manuscript. The final manuscript was reviewed and approved by all study contributors.

Funding
The project was supported by the National Natural Science Foundation of China (No. 82171299).

Data availability
No datasets were generated or analysed during the current study.

Declarations

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

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao, China
[2]Department of Critical Care Medicine, The Affiliated Hospital of Qingdao University, Qingdao, China
[3]Department of Critical Care Medicine, The First Medical Center of PLA General Hospital, Beijing, China
[4]Medical Innovation Research Department, Chinese PLA General Hospital, Beijing, China

Received: 13 January 2025 / Accepted: 18 February 2025
Published online: 28 February 2025

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Balakumar P, Maung UK, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacol Res. 2016;113(Pt A):600–9.
3. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(8):631–9.
4. Hu P, Dharmayat KI, Stevens CAT, Sharabiani MTA, Jones RS, Watts GF, Genest J, Ray KK, Vallejo-Vaz AJ. Prevalence of Familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation. 2020;141(22):1742–59.
5. Mostofsky E, Chahal HS, Mukamal KJ, Rimm EB, Mittleman MA. Alcohol and immediate risk of cardiovascular events: a systematic review and dose-response meta-analysis. Circulation. 2016;133(10):979–87.
6. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. Nat Rev Cardiol. 2019;16(4):203–12.
7. Shi Y, Wen M. Sex-specific differences in the effect of the atherogenic index of plasma on prediabetes and diabetes in the NHANES 2011–2018 population. Cardiovasc Diabetol. 2023;22(1):19.
8. Wu TT, Gao Y, Zheng YY, Ma YT, Xie X. Atherogenic index of plasma (AIP): a novel predictive indicator for the coronary artery disease in postmenopausal women. Lipids Health Dis. 2018;17(1):197.
9. Dobiásová M. AIP–atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. Vnitr Lek. 2006;52(1):64–71.
10. Fernández-Macías JC, Ochoa-Martínez AC, Varela-Silva JA, Pérez-Maldonado IN. Atherogenic index of plasma: novel predictive biomarker for cardiovascular illnesses. Arch Med Res. 2019;50(5):285–94.
11. Min Q, Wu Z, Yao J, Wang S, Duan L, Liu S, Zhang M, Luo Y, Ye D, Huang Y, et al. Association between atherogenic index of plasma control level and incident cardiovascular disease in middle-aged and elderly Chinese individuals with abnormal glucose metabolism. Cardiovasc Diabetol. 2024;23(1):54.
12. Yin B, Wu Z, Xia Y, Xiao S, Chen L, Li Y. Non-linear association of atherogenic index of plasma with insulin resistance and type 2 diabetes: a cross-sectional study. Cardiovasc Diabetol. 2023;22(1):157.
13. Duiyimuhan G, Maimaiti N. The association between atherogenic index of plasma and all-cause mortality and cardiovascular disease-specific mortality in hypertension patients: a retrospective cohort study of NHANES. BMC Cardiovasc Disord. 2023;23(1):452.
14. Ito F, Ito T. High-Density lipoprotein (HDL) triglyceride and oxidized HDL: new lipid biomarkers of lipoprotein-Related atherosclerotic cardiovascular disease. Antioxid (Basel). 2020;9(5).
15. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr. 2003;22(3):235–9.
16. Gruenberg DA, Shelton W, Rose SL, Rutter AE, Socaris S, McGee G. Factors influencing length of stay in the intensive care unit. Am J Crit Care. 2006;15(5):502–9.
17. Toptas M, Sengul Samanci N, Akkoc İ, Yucetas E, Cebeci E, Sen O, Can MM, Ozturk S. Factors affecting the length of stay in the intensive care unit: our clinical experience. Biomed Res Int. 2018;2018:9438046.
18. Johnson AEW, Bulgarelli L, Shen L, Gayles A, Shammout A, Horng S, Pollard TJ, Hao S, Moody B, Gow B, et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data. 2023;10(1):1.
19. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al. Development and validation

of the American heart association's PREVENT equations. Circulation. 2024;149(6):430–49.
20. Liu D, Ren B, Tian Y, Chang Z, Zou T. Association of the TyG index with prognosis in surgical intensive care patients: data from the MIMIC-IV. Cardiovasc Diabetol. 2024;23(1):193.
21. Cheng L, Zhang F, Xue W, Yu P, Wang X, Wang H, Wang J, Hu T, Gong H, Lin L. Association of dynamic change of triglyceride-glucose index during hospital stay with all-cause mortality in critically ill patients: a retrospective cohort study from MIMIC IV2.0. Cardiovasc Diabetol. 2023;22(1):142.
22. Wang J, Li H, Luo H, Shi R, Chen S, Hu J, Luo H, Yang P, Cai X, Wang Y, et al. Association between serum creatinine to albumin ratio and short- and long-term all-cause mortality in patients with acute pancreatitis admitted to the intensive care unit: a retrospective analysis based on the MIMIC-IV database. Front Immunol. 2024;15:1373371.
23. Onat A, Can G, Kaya H, Hergenç G. Atherogenic index of plasma (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010;4(2):89–98.
24. Austin PC, White IR, Lee DS, van Buuren S. Missing data in clinical research: a tutorial on multiple imputation. Can J Cardiol. 2021;37(9):1322–31.
25. Yue S, Li S, Huang X, Liu J, Hou X, Zhao Y, Niu D, Wang Y, Tan W, Wu J. Machine learning for the prediction of acute kidney injury in patients with sepsis. J Transl Med. 2022;20(1):215.
26. Swanson K, Wu E, Zhang A, Alizadeh AA, Zou J. From patterns to patients: advances in clinical machine learning for cancer diagnosis, prognosis, and treatment. Cell. 2023;186(8):1772–91.
27. Handelman GS, Kok HK, Chandra RV, Razavi AH, Lee MJ, Asadi H. eDoctor: machine learning and the future of medicine. J Intern Med. 2018;284(6):603–19.
28. Dong Z, Wang Q, Ke Y, Zhang W, Hong Q, Liu C, Liu X, Yang J, Xi Y, Shi J, et al. Prediction of 3-year risk of diabetic kidney disease using machine learning based on electronic medical records. J Transl Med. 2022;20(1):143.
29. Rahmatinejad Z, Tohidinezhad F, Reihani H, Rahmatinejad F, Pourmand A, Abu-Hanna A, Eslami S. Prognostic utilization of models based on the APACHE II, APACHE IV, and SAPS II scores for predicting in-hospital mortality in emergency department. Am J Emerg Med. 2020;38(9):1841–6.
30. Rahmatinejad Z, Dehghani T, Hoseini B, Rahmatinejad F, Lotfata A, Reihani H, Eslami S. A comparative study of explainable ensemble learning and logistic regression for predicting in-hospital mortality in the emergency department. Sci Rep. 2024;14(1):3406.
31. Rahmatinejad Z, Reihani H, Tohidinezhad F, Rahmatinejad F, Peyravi S, Pourmand A, Abu-Hanna A, Eslami S. Predictive performance of the SOFA and mSOFA scoring systems for predicting in-hospital mortality in the emergency department. Am J Emerg Med. 2019;37(7):1237–41.
32. Rahmatinejad Z, Peiravi S, Hoseini B, Rahmatinejad F, Eslami S, Abu-Hanna A, Reihani H. Comparing in-hospital mortality prediction by senior emergency resident's judgment and prognostic models in the emergency department. Biomed Res Int. 2023;6042762.
33. Jiang T, Gradus JL, Rosellini AJ. Supervised machine learning: a brief primer. Behav Ther. 2020;51(5):675–87.
34. Li M, Han S, Liang F, Hu C, Zhang B, Hou Q, Zhao S. Machine learning for predicting risk and prognosis of acute kidney disease in critically ill elderly patients during hospitalization: internet-based and interpretable model study. J Med Internet Res. 2024;26:e51354.
35. Raita Y, Goto T, Faridi MK, Brown DFM, Camargo CA Jr., Hasegawa K. Emergency department triage prediction of clinical outcomes using machine learning models. Crit Care. 2019;23(1):64.
36. Kalimouttou A, Lerner I, Cheurfa C, Jannot AS, Pirracchio R. Machine-learning-derived sepsis bundle of care. Intensive Care Med. 2023;49(1):26–36.
37. Choi RY, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to machine learning, neural networks, and deep learning. Transl Vis Sci Technol. 2020;9(2):14.
38. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol. 2006;47(8 Suppl):C7–12.
39. Libby P. The changing landscape of atherosclerosis. Nature. 2021;592(7855):524–33.
40. Libby P, Bornfeldt KE, Tall AR. Atherosclerosis: successes, surprises, and future challenges. Circ Res. 2016;118(4):531–4.
41. Nayor M, Brown KJ, Vasan RS. The molecular basis of predicting atherosclerotic cardiovascular disease risk. Circ Res. 2021;128(2):287–303.
42. Rosenson RS, Brewer HB Jr., Barter PJ, Björkegren JLM, Chapman MJ, Gaudet D, Kim DS, Niesor E, Rye KA, Sacks FM, et al. HDL and atherosclerotic cardiovascular disease: genetic insights into complex biology. Nat Rev Cardiol. 2018;15(1):9–19.
43. Huang Q, Liu Z, Wei M, Huang Q, Feng J, Liu Z, Xia J. The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China. Cardiovasc Diabetol. 2023;22(1):125.
44. You FF, Gao J, Gao YN, Li ZH, Shen D, Zhong WF, Yang J, Wang XM, Song WQ, Yan H, et al. Association between atherogenic index of plasma and all-cause mortality and specific-mortality: a nationwide population–based cohort study. Cardiovasc Diabetol. 2024;23(1):276.
45. Zheng H, Wu K, Wu W, Chen G, Chen Z, Cai Z, Cai Z, Lan Y, Wu S, Chen Y. Relationship between the cumulative exposure to atherogenic index of plasma and ischemic stroke: a retrospective cohort study. Cardiovasc Diabetol. 2023;22(1):313.
46. Qin M, Chen B. Association of atherogenic index of plasma with cardiovascular disease mortality and all-cause mortality in the general US adult population: results from NHANES 2005–2018. Cardiovasc Diabetol. 2024;23(1):255.
47. Lan Y, Wu D, Cai Z, Xu Y, Ding X, Wu W, Lan S, Chen L, Guo Z, Balmer L, et al. Supra-additive effect of chronic inflammation and atherogenic dyslipidemia on developing type 2 diabetes among young adults: a prospective cohort study. Cardiovasc Diabetol. 2023;22(1):181.
48. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Association of ideal cardiovascular health metrics with serum uric acid, inflammation and atherogenic index of plasma: a population-based survey. Atherosclerosis. 2019;284:44–9.
49. Xiao S, Wang X, Zhang G, Tong M, Chen J, Zhou Y, Ji Q, Liu N. Association of systemic immune inflammation index with estimated pulse wave velocity, atherogenic index of plasma, triglyceride-glucose index, and cardiovascular disease: a large cross-sectional study. Mediators Inflamm. 2023;1966680.
50. Kowara M, Cudnoch-Jedrzejewska A. Pathophysiology of atherosclerotic plaque Development-Contemporary experience and new directions in research. Int J Mol Sci. 2021;22(7).
51. Nurmohamed NS, van Rosendael AR, Danad I, Ngo-Metzger Q, Taub PR, Ray KK, Figtree G, Bonaca MP, Hsia J, Rodriguez F, et al. Atherosclerosis evaluation and cardiovascular risk Estimation using coronary computed tomography angiography. Eur Heart J. 2024;45(20):1783–800.
52. Severino P, D'Amato A, Pucci M, Infusino F, Adamo F, Birtolo LI, Netti L, Montefusco G, Chimenti C, Lavalle C et al. Ischemic heart disease pathophysiology paradigms overview: from plaque activation to microvascular dysfunction. Int J Mol Sci. 2020;21(21).
53. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res. 2004;95(8):764–72.
54. Navab M, Reddy ST, Van Lenten BJ, Fogelman AM. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol. 2011;8(4):222–32.
55. Ibanez B, Fernández-Ortiz A, Fernández-Friera L, García-Lunar I, Andrés V, Fuster V. Progression of early subclinical atherosclerosis (PESA) study: JACC focus seminar 7/8. J Am Coll Cardiol. 2021;78(2):156–79.
56. Mendieta G, Pocock S, Mass V, Moreno A, Owen R, García-Lunar I, López-Melgar B, Fuster JJ, Andres V, Pérez-Herreras C, et al. Determinants of progression and regression of subclinical atherosclerosis over 6 years. J Am Coll Cardiol. 2023;82(22):2069–83.

Publisher's note