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Original Article

Construction of a predictive model for severe hypertriglyceridemia-associated acute pancreatitis using machine learning

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Abstract: Objective: To identify critical risk factors distinguishing severe hypertriglyceridemia-associated acute pancreatitis (SAP-HTG) from its non-severe form (N-SAP-HTG). Machine learning techniques were used to develop predictive models and compare them to conventional scoring systems, aiming to enhance early diagnosis and risk stratification of SAP-HTG. Methods: A retrospective analysis was conducted on 514 patients with acute pancreatitis admitted to HanZhong Central Hospital between August 2018 and June 2024, including 90 SAP-HTG and 424 N-SAP-HTG cases. Key baseline characteristics, scoring indices (APACHE II, Ranson), and laboratory data (fasting blood glucose (FBG), triglycerides (TG), C-reactive protein (CRP)) were collected. LASSO regression was used to identify key predictors, and multivariate logistic regression was applied to assess their associations. Four predictive models - logistic regression, random forest (RF), support vector machine (SVM), and XGBoost - were developed. Model performance was evaluated using the confusion matrix, receiver operating characteristic (ROC) curves, area under the curve (AUC), and SHAP analysis, with comparisons to APACHE II and Ranson scores. Statistical analyses were conducted with SPSS 26.0 and R 4.3.3. Results: Nine predictors were identified: age, diabetes history, FBG, TyG index, amylase (AMY), TG, total cholesterol (TC), CRP, and Ca^{2+}. CRP (OR = 8.787, $P < 0.001$) and TG (OR = 7.548, $P < 0.001$) were significant risk factors, whereas Ca^{2+} and age were protective (OR = 0.258 and 0.290, respectively). Among the models, XGBoost and RF achieved the highest discriminatory power, with AUCs of 0.959 and 0.955, surpassing logistic regression (0.924), SVM (0.926), and traditional scoring systems ($P < 0.002$). SHAP analysis revealed CRP, TG, and TyG index as the most influential factors. Conclusion: Machine learning models effectively identified SAP-HTG risk factors, with XGBoost showing superior performance over conventional scoring systems. These models provide a valuable tool for early diagnosis and risk stratification of SAP-HTG in clinical settings.

Keywords: Severe hypertriglyceridemia-associated acute pancreatitis, machine learning, LASSO regression, XGBoost, SHAP analysis, risk factors, predictive model, ROC curve

Introduction

Hypertriglyceridemia-associated acute pancreatitis (HTG-AP) is a distinct subtype of acute pancreatitis (AP) with a rising global incidence, particularly among individuals with obesity, diabetes, and high-fat dietary habits [1]. Studies show that HTG-AP is more prevalent in patients with obesity and diabetes and is associated with more severe clinical outcomes [2]. Characterized by elevated serum triglyceride (TG) levels, HTG-AP can progress to severe acute pancreatitis with hypertriglyceridemia (SAP-HTG), which is associated with systemic inflammation, multiorgan dysfunction, and increased mortality rate [3]. Hang et al. [4] demonstrated that elevated TG levels, driven by dysregulated lipid metabolism and genetic factors, increase the risk of AP, emphasizing the complex pathophysiological mechanism involved. Compared to non-severe HTG-AP (N-SAP-HTG), SAP-HTG presents distinct clinical and metabolic features, including abnormal lipid metabolism, excessive inflammatory responses, and pancreatic tissue injury [5].

Early identification of high-risk factors for SAP-HTG is critical for timely intervention and improved patient outcomes. However, the heterogeneity and rapid progression of SAP-HTG

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limit the accuracy and specificity of conventional diagnostic and prognostic approaches, underscoring the need for a precise and personalized predictive tool.

Traditional clinical scoring systems for AP severity, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Ranson score, primarily rely on physiological data and laboratory indices, providing only a general estimate of disease severity [6-8]. However, these systems are not fully applicable to SAP-HTG, as they fail to account for the disease-specific features such as elevated TG levels, metabolic disturbances, and inflammatory markers. Moreover, their reliance on linear assumptions limits the ability to capture the complex risk landscape of SAP-HTG, resulting in suboptimal prediction accuracy [9]. Recent evidence further indicates that conventional treatment and prognostic methods are often insufficient for HTG-AP, highlighting the need for more accurate diagnostic tools [10].

To address this gap, predictive models tailored specifically to SAP-HTG are required, integrating diverse clinical, biochemical, and hematologic data. Machine learning (ML) techniques have shown substantial potential in disease prediction and risk assessment by handling high-dimensional data, uncovering nonlinear relationships, and improving model accuracy. A review by Lu et al. [11] emphasized the close association between elevated TG levels, inflammatory markers, and HTG-AP severity and recurrence risk, supporting the need for multidimensional feature integration. By leveraging ML methods, it is possible to identify critical predictive variables, thereby enhancing early diagnostic accuracy and facilitating personalized clinical management of SAP-HTG.

This study systematically analyzed the clinical, biochemical, and hematologic characteristics of patients with SAP-HTG and N-SAP-HTG. Least absolute shrinkage and selection operator (LASSO) regression was used to identify key risk factors, followed by the application of various ML techniques, including logistic regression, random forest (RF), support vector machine (SVM), and extreme gradient boosting (XGBoost), to build high-precision predictive models. Notably, this study innovatively integrated multidimensional predictors with SHapley Additive exPlanations (SHAP) analysis, enabling quantitative evaluation of the relative contribution of variables such as CRP and TG. Additionally, model performances were compared to traditional scoring systems (APACHE II and Ranson). Our findings lay the groundwork for future research in precision medicine.

Materials and methods

Sample size calculation

The sample size was estimated according to the reported incidence of SAP-HTG ranging from 10.4% to 23.9%, as noted by Lu et al. [11]. The formula used was: $N = Z^2 \times [P \times (1 - P)]/E^2$, where $Z = 1.96$ (95% confidence level) and $E = 0.05$ (margin of error). When $P = 0.104$, the required sample size was approximately 143; when $P = 0.239$, it increased to around 280. Therefore, the required sample size ranged from 143 to 280 to ensure adequate statistical power at a 95% confidence level and 5% margin of error.

General data

A retrospective analysis was conducted on 514 patients diagnosed with AP who were admitted to HanZhong Central Hospital between August 2018 and June 2024. Among them, 90 cases were diagnosed with HTG-AP and 424 cases with non-HTG-AP. The study protocol was reviewed and approved by the Medical Ethics Committee of HanZhong Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria: Diagnosis of HTG-AP based on clinical symptoms, elevated AMY or lipase levels (≥ 3 times the upper limit of normal), and imaging evidence of pancreatitis (e.g., CT or MRI) [12]; serum TG ≥ 11.3 mmol/L, or TG between 5.65-11.3 mmol/L with concurrent lipemic serum. Patients aged between 18 and 70 years, of any sex; Availability of complete clinical data at admission, including baseline characteristics, biochemical, and hematologic data.

Exclusion criteria: AP due to other causes (e.g., gallstones, alcoholic pancreatitis, autoimmune pancreatitis); severe comorbidities, such as advanced malignancy, end-stage hepatic or renal failure, or acute myocardial infarction; pregnancy or lactation; prior lipid-lowering therapy or plasma exchange before admission, which might have altered serum TG levels.

Clinical data collection

Patient data were obtained from the hospital's electronic medical record. The clinical characteristics, scoring indices, biochemical, and hematologic data of patients with SAP-HTG and N-SAP-HTG were analyzed and compared. Baseline characteristics included age, sex, body mass index (BMI), smoking history, alcohol consumption, dietary fat intake, and comorbidities (hypertension, diabetes, fatty liver). Clinical scoring indices included APACHE II and the Ranson criteria. Biochemical and hematologic data encompaased fasting blood glucose (FBG), triglyceride-glucose (TyG) index, amylase (AMY), TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), gamma-glutamyl transferase (GGT), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), monocyte count (MON), white blood cell count (WBC), platelet count (PLT), C-reactive protein (CRP), sodium (Na^+), calcium (Ca^{2+}), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), and glomerular filtration rate (GFR).

Machine learning

Four supervised machine learning models - logistic regression, random forest (RF), support vector machine (SVM), and extreme gradient boosting (XGBoost) - were constructed to predict the risk of SAP-HTG. Data preprocessing included median imputation for missing values and factor encoding of categorical variables. The target variable was defined as a binary classification task (SAP-HTG = 1, N-SAP-HTG = 0), and a fixed random seed (2025) was used to ensure reproducibility. Feature selection was conducted using LASSO regression on the *glmnet* package, identifying nine key predictors: age, diabetes history, FBG, TyG index, AMY, TG, TC, CRP, and Ca^{2+}. For the RF and SVM models, recursive feature elimination (RFE) with 10-fold cross-validation was applied to optimize predictor subsets. The RF model was built using the *randomForest* package with *mtry* set to the square root of the number of predictors; The optimal number of trees (228) was determined by minimizing the out-of-bag (OOB) error. The SVM model, constructed from the *svmRadial* method in the *caret* package, used a radial basis function (RBF) kernel. Key hyperparameters (C and σ) were automatically tuned through internal cross-validation grid search. The XGBoost model was implemented using the *xgboost* package with the following parameters: *booster* = "*gbtree*", *objective* = "*binary: logistic*", *eta* = 0.1, *max_depth* = 3, *subsample* = 1, and *colsample_bytree* = 1. The model was trained for 10 boosting rounds and evaluated using log-loss. Model performance was assessed using confusion matrices, receiver operating characteristic (ROC) curves, and area under the curve (AUC), with DeLong's test used to compare predictive power against traditional scoring systems (APACHE II and Ranson). All implementation was conducted in R using the *caret, randomForest, xgboost,* and *pROC* packages.

SHAP (Shapley Additive Explanations) analysis

To enhance the interpretability of the XGBoost model in distinguishing SAP-HTG from N-SAP-HTG, we applied SHAP analysis using the *SHAPforxgboost* package in R. SHAP is a game-theoretic approach that quantifies the contribution of each feature to model predictions by calculating the average marginal effect across all possible feature combinations. In this study, SHAP values were computed for all key predictors to assess their relative effect on disease severity classification. Feature importance was visualized using SHAP beeswarm plots (global importance), waterfall plots (individual prediction explanations), and dependence plots (feature interactions). These analyses provided critical insight into the non-linear and interactive effects of predictors and clarified their role in stratifying patients by disease severity.

Scoring system definitions and comparative rationale

The APACHE II and Ranson scoring systems are widely used to assess the severity of acute pancreatitis [13, 14]. APACHE II incorporates acute physiologic data, age, and chronic health status, with scores ranging from 0 to 71; higher scores indicate greater severity and mortality risk. The Ranson score incorporates clinical and laboratory indicators assessed at admission and after 48 hours, with a maximum score of 11. Higher Ranson scores predict worse outcomes. Both systems are well-established for risk stratification and treatment guidance in clinical practice.

In this study, APACHE II and Ranson scores were used as benchmark references for evaluating the predictive performance of ML models. By comparing AUC values and predictive accuracy, we aimed to determine whether ML-based approaches could outperform traditional scoring systems in identifying patients at risk of SAP-HTG. This comparison provides a clinically relevant framework for interpreting the utility and advantages of ML models in real-world settings.

Outcome measures

Primary outcomes included identification of key risk factors for SAP-HTG, evaluation of model predictive performance (logistic regression, RF, SVM, XGBoost), analysis of variable contributions, and comparison of ML models with traditional scoring systems.

Secondary outcomes included comparison of baseline characteristics, scoring indices, and laboratory findings between SAP-HTG and N-SAP-HTG patients, determination of optimal cut-off values for continuous variables, and validation of model accuracy and consistency.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 and R version 4.3.3. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using independent sample t-tests. Non-normally distributed data were presented as median (P50) and interquartile range (IQR) and compared using Mann-Whitney U tests. Categorical data were expressed as percentages and compared using the chi-square (χ^2) test.

LASSO regression for feature selection was performed using the *glmnet* package. Univariable and multivariable logistic regression analyses (*stats* package) were applied to evaluate independent risk factors. ML models, including SVM (*caret* package), RF (*randomForest* package), and XGBoost (*xgboost* package) were evaluated using confusion matrices (*caret*), ROC curves, and AUCs (*pROC* package). The DeLong test was used to compare AUCs between ML models and traditional scoring systems.

SHAP analysis using the *SHAPforxgboost* package was conducted to quantify variable contributions and explore feature interactions. All statistical tests were two-sided, and $P < 0.05$ was considered significant.

Results

Comparison of patient characteristics between SAP-HTG and N-SAP-HTG groups

Comparison of baseline characteristics between the SAP-HTG and N-SAP-HTG groups revealed significant differences in age ($P < 0.001$) and history of diabetes ($P < 0.001$). Patients with SAP-HTG were younger and had a higher prevalence of diabetes. No significant differences were found between the two groups in terms of sex, BMI, smoking history, alcohol consumption, high-fat diet, history of hypertension, or fatty liver ($P > 0.05$) (**Table 1**).

Comparison of scoring indices between SAP-HTG and N-SAP-HTG groups

Both APACHE II ($P < 0.001$) and RANSON scores ($P < 0.001$) were significantly higher in the SAP-HTG group compared to N-SAP-HTG group, indicating greater disease severe in the SAP-HTG group (**Table 2**).

Comparison of biochemical and hematological indicators

Significant differences were observed in FBG, TyG index, AMY, TG, TC, CRP, and serum Ca^{2+} ($P < 0.001$). Patients with SAP-HTG exhibited higher values for all parameters except Ca^{2+}, which was lower. No significant differences were found in other indicators, including HDLC, LDLC, GGT, RBC, Hb, Hct, MON, WBC, PLT, Na^+, BUN, Cr, UA, and GFR ($P > 0.05$) (**Table 3**).

LASSO regression analysis of characteristic variables in SAP-HTG patients

Nine variables (age, diabetes history, FBG, TyG index, AMY, TG, TC, CRP, Ca^{2+}) were entered into the LASSO regression analysis. Both the 1-standard error (1 se = 0.022) and minimum (min = 0.003) criteria retained all nine variables. Among them, CRP, TG, TyG index, AMY, and FBG showed the strongest associations with SAP-HTG, whereas Ca^{2+} and age were negatively correlated (**Figure 1**).

Table 1. Comparison of baseline characteristics between SAP-HTG and N-SAP-HTG patients

Variable	Total	SAP-HTG (n = 90)	N-SAP-HTG (n = 424)	Statistic	*P* value
Age				12.499	< 0.001
≥ 45 years	264 (51.36%)	31 (34.44%)	233 (54.95%)		
< 45 years	250 (48.64%)	59 (65.56%)	191 (45.05%)		
Gender				0.110	0.740
Male	322 (62.65%)	55 (61.11%)	267 (62.97%)		
Female	192 (37.35%)	35 (38.89%)	157 (37.03%)		
BMI				0.565	0.452
≥ 25 kg/m^2	315 (61.28%)	52 (57.78%)	263 (62.03%)		
< 25 kg/m^2	199 (38.72%)	38 (42.22%)	161 (37.97%)		
Smoking history				1.806	0.179
Yes	301 (58.56%)	47 (52.22%)	254 (59.91%)		
No	213 (41.44%)	43 (47.78%)	170 (40.09%)		
Alcohol consumption history				0.185	0.667
Yes	239 (46.50%)	40 (44.44%)	199 (46.93%)		
No	275 (53.50%)	50 (55.56%)	225 (53.07%)		
High-fat diet				1.034	0.309
Yes	272 (52.92%)	52 (57.78%)	220 (51.89%)		
No	242 (47.08%)	38 (42.22%)	204 (48.11%)		
Hypertension history				3.378	0.066
Yes	105 (20.43%)	12 (13.33%)	93 (21.93%)		
No	409 (79.57%)	78 (86.67%)	331 (78.07%)		
Diabetes history				10.963	< 0.001
Yes	233 (45.33%)	55 (61.11%)	178 (41.98%)		
No	281 (54.67%)	35 (38.89%)	246 (58.02%)		
Fatty liver				0.605	0.437
Yes	310 (60.31%)	51 (56.67%)	259 (61.08%)		
No	204 (39.69%)	39 (43.33%)	165 (38.92%)		

Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, N-SAP-HTG: Non-Severe Acute Pancreatitis with Hypertriglyceridemia, BMI: Body Mass Index.

Table 2. Comparison of APACHE II and Ranson scores between SAP-HTG and N-SAP-HTG patients

Variable	Total	SAP-HTG (n = 90)	N-SAP-HTG (n = 424)	Statistic	*P* value
APACHE II	3.00 (2.00)	6.00 (4.00)	3.00 (2.00)	12.105	< 0.001
RANSON	1.00 (1.00)	2.00 (4.00)	0.00 (1.00)	12.136	< 0.001

Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, N-SAP-HTG: Non-Severe Acute Pancreatitis with Hypertriglyceridemia, APACHE II: Acute Physiology and Chronic Health Evaluation II, RANSON: Ranson Criteria.

Univariate and multivariate regression analysis of characteristic variables

Univariate analysis showed that FBG, TyG index, AMY, TG, TC, CRP, and diabetes history were significant risk factors for SAP-HTG, with CRP, TG, and AMY having the highest odds ratios (ORs). Conversely, Ca^{2+} and age were protective factors. Multivariate analysis confirmed that CRP (OR = 8.787), TG (OR = 7.548), TyG index (OR = 5.689), AMY (OR = 3.662), FBG (OR = 3.339), TC (OR = 2.873), and diabetes history (OR = 2.541) were independent risk factors for SAP-HTG, while Ca^{2+} (OR = 0.258) and age (OR = 0.290) were protective factors (**Table 4**).

Performance analysis of three machine learning models

To optimize predictive performance, three machine learning models - RF, SVM, and XGBoost - were systematically tuned and evalu-

Table 3. Comparison of biochemical and hematologic data between SAP-HTG and N-SAP-HTG patients

Variable	Total	SAP-HTG (n = 90)	N-SAP-HTG (n = 424)	Statistic	*P* value
FBG (mmol/L)	8.46±2.37	9.47±2.01	8.24±2.39	4.543	< 0.001
TyGindex	3.72±0.44	3.95±0.40	3.68±0.43	5.584	< 0.001
AMY (U/L)	327.00 (397.50)	601.50 (547.25)	292.00 (344.50)	7.283	< 0.001
TG (mmol/L)	10.16 (9.34)	12.09 (5.27)	9.09 (9.96)	4.283	<0.001
TC (mmol/L)	5.89±1.66	6.67±1.61	5.72±1.63	5.027	< 0.001
HDLC (mmol/L)	0.83 (0.80)	0.90 (0.74)	0.81 (0.81)	0.936	0.349
LDLC (mmol/L)	1.22 (1.09)	1.18 (1.25)	1.23 (1.06)	0.630	0.529
GGT (U/L)	30.90 (35.98)	33.35 (46.12)	29.60 (33.57)	1.229	0.219
RBC (×10^12/L)	4.92±0.77	4.88±0.76	4.93±0.77	0.523	0.601
Hb (g/L)	141.00±10.14	141.81±9.80	140.83±10.21	0.832	0.406
Hct (%)	40.26±2.39	40.16±2.91	40.28±2.27	0.438	0.662
MON (×10^9/L)	0.35 (0.25)	0.34 (0.30)	0.36 (0.26)	0.322	0.747
WBC (×10^9/L)	9.77 (3.09)	10.02 (4.52)	9.75 (2.84)	0.938	0.348
PLT (×10^9/L)	151.81±25.29	148.54±27.04	152.50±24.89	1.349	0.178
CRP (mg/L)	47.59±18.67	62.93±28.32	44.34±13.92	5.974	< 0.001
Na^+ (mmol/L)	135.45±5.54	135.61±5.37	135.42±5.58	0.302	0.763
Ca^{2+} (mmol/L)	2.13±0.32	1.98±0.31	2.16±0.31	4.985	< 0.001
BUN (μmol/L)	10.48±1.96	10.37±1.79	10.50±2.00	0.573	0.567
Cr (μmol/L)	45.01±15.13	45.31±14.65	44.95±15.25	0.208	0.835
UA (μmol/L)	369.70±114.43	370.54±118.53	369.53±113.68	0.076	0.939
GFR (mL/min)	105.02±15.37	104.96±16.60	105.03±15.12	0.036	0.971

Note: FBG: Fasting Blood Glucose, TyGindex: TriglycerideGlucose Index, AMY: Amylase, TG: Triglycerides, TC: Total Cholesterol, HDLC: HighDensity Lipoprotein Cholesterol, LDLC: LowDensity Lipoprotein Cholesterol, ApoA1: Apolipoprotein A1, ApoB: Apolipoprotein B, LP: Lipoprotein, ALB: Albumin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, CK: Creatine Kinase, GGT: GammaGlutamyl Transferase, DBil: Direct Bilirubin, IBil: Indirect Bilirubin, RBC: Red Blood Cells, Hb: Hemoglobin, Hct: Hematocrit, MON: Monocytes, WBC: White Blood Cells, NE: Neutrophil Percentage, PLT: Platelets, CRP: CReactive Protein, PCT: Procalcitonin, Na^+: Sodium, Ca^{2+}: Calcium, BUN: Blood Urea Nitrogen, Cr: Creatinine, UA: Uric Acid, GFR: Glomerular Filtration Rate.

ated. For the RF model, the out-of-bag (OOB) error steadily declined as the number of trees increased, achieving optimal performance at 228 trees, beyond which the error stabilized, indicating model convergence and stability (**Figure 2A**). For the SVM model, recursive feature elimination (RFE) selected the most informative predictor subset, with the error rate decreasing as feature count increased, reaching a minimum of 0.107 with eight features, underscoring the effectiveness of RFE in enhancing generalizability (**Figure 2B**). For the XGBoost model, logarithmic loss (log-loss) consistently decreased across 10 boosting iterations, reflecting improved calibration and reduced classification uncertainty, consistent with the principle of progressive optimization in gradient boosting (**Figure 2C**). These tuning procedures ensured each model was trained optimally, enhancing reliability in distinguishing SAP-HTG from N-SAP-HTG.

Confusion matrix evaluation of SAP-HTG predictive models

Confusion matrix analysis demonstrated overall accuracies of 88.91% for logistic regression, 92.02% for RF, 90.47% for SVM, and 91.63% for XGBoost. Among the models, RF achieved the highest accuracy, followed by XGBoost and SVM. Logistic regression had the lowest accuracy, with a notably higher false-positive rate. RF and XGBoost exhibited more balanced sensitivity and specificity, supporting their greater reliability in distinguishing SAP-HTG from N-SAP-HTG (**Figure 3**).

ROC curve analysis of predictive models

ROC curve analysis showed the following AUC values: Logistic Regression (0.924), RF (0.955), SVM (0.926), and XGBoost (0.959). XGBoost and RF demonstrated the highest predictive

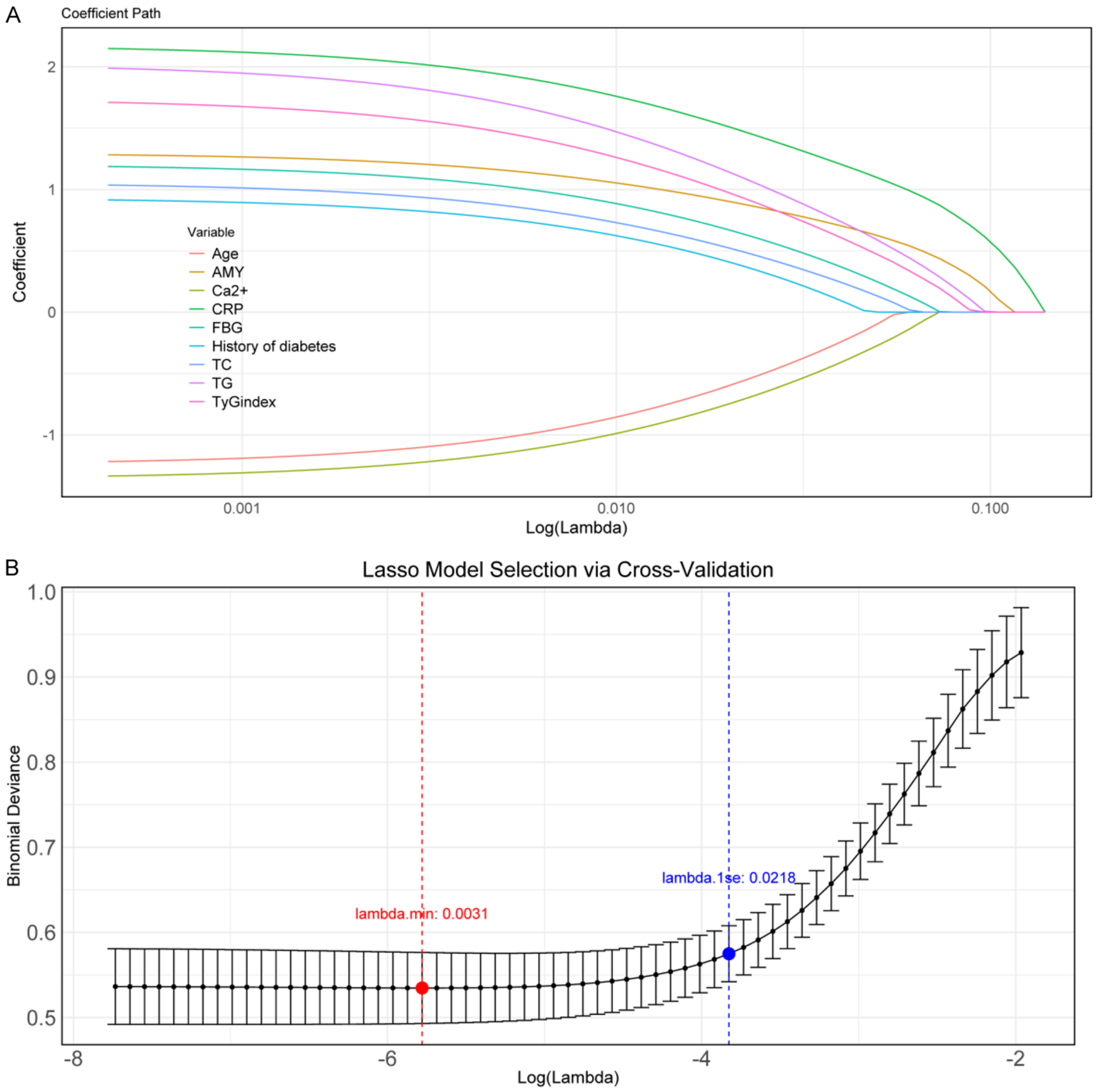

Figure 1. LASSO regression analysis of predictive variables for SAP-HTG. A. LASSO Variable Trace Plot: Shows the trajectory of each variable's coefficient as the penalty parameter (λ) changes, illustrating the variable selection process under different regularization strengths. B. LASSO Coefficient Selection Plot: Displays the predictive variables identified by LASSO regression and their corresponding coefficients, indicating each variable's importance in predicting SAP-HTG. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, FBG: Fasting Blood Glucose, TyGindex: Triglyceride-Glucose Index, AMY: Amylase, TG: Triglyceride, TC: Total Cholesterol, CRP: C-Reactive Protein, Ca^{2+}: Calcium, LASSO: Least Absolute Shrinkage and Selection Operator.

capabilities, followed by SVM, with logistic regression performing least well. Pairwise comparisons using DeLong's test revealed significant differences between logistic regression and RF ($P < 0.001$), logistic regression and XGBoost ($P < 0.001$), RF and SVM ($P = 0.003$), and SVM and XGBoost ($P < 0.001$). No significant differences were observed between RF and XGBoost ($P = 0.58$) or between logistic regression and SVM ($P = 0.816$). The details are shown in **Figure 4**.

SHAP analysis and feature contribution evaluation

SHAP analysis of the XGBoost model revealed that CRP, TG, and TyG index had the highest SHAP values, indicating strong positive contributions to SAP-HTG prediction. In contrast, Ca^{2+}

Table 4. Univariate and multivariate regression analysis of SAP-HTG risk factors

Characteristic	Total (N)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
FBG	514				
< 8.05	297	Reference		Reference	
≥ 8.05	217	3.834 (2.187-6.720)	< 0.001	3.339 (1.608-6.936)	0.001
TyG index	514				
< 3.645	283	Reference		Reference	
≥ 3.645	231	4.758 (2.683-8.438)	< 0.001	5.689 (2.643-12.243)	< 0.001
AMY	514				
< 443	184	Reference		Reference	
≥ 443	330	5.147 (3.156-8.397)	< 0.001	3.662 (1.909-7.027)	< 0.001
TG	514				
< 8.81	297	Reference		Reference	
≥ 8.81	217	6.084 (3.218-11.503)	< 0.001	7.548 (3.295-17.288)	< 0.001
TC	514				
< 6.145	226	Reference		Reference	
≥ 6.145	288	2.929 (1.819-4.716)	< 0.001	2.873 (1.482-5.570)	0.002
CRP	514				
< 57.35	122	Reference		Reference	
≥ 57.35	392	6.920 (4.237-11.303)	< 0.001	8.787 (4.454-17.337)	< 0.001
Ca^{2+}	514				
< 2.085	286	Reference		Reference	
≥ 2.085	228	0.328 (0.203-0.530)	< 0.001	0.258 (0.133-0.500)	< 0.001
Age	514				
< 45	264	Reference		Reference	
≥ 45	250	0.431 (0.268-0.693)	< 0.001	0.290 (0.148-0.565)	< 0.001
History of diabetes	514				
No	233	Reference		Reference	
Yes	281	2.172 (1.363-3.460)	0.001	2.541 (1.335-4.838)	0.005

Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, N-SAP-HTG: Non-Severe Acute Pancreatitis with Hypertriglyceridemia, FBG: Fasting Blood Glucose, TyGindex: Triglyceride-Glucose Index, AMY: Amylase, TG: Triglyceride, TC: Total Cholesterol, CRP: C-Reactive Protein, Ca^{2+}: Calcium, OR: Odds Ratio, CI: Confidence Interval.

and age were associated with negative SHAP values, suggesting protective effects (**Figure 5A**). Waterfall plots of representative cases (patients 12, 26, and 38) revealed that predictions for patients 12 and 26 were primarily influenced by CRP and TG, whereas the prediction for patient 38 was affected by old age and high AMY, with Ca^{2+} showing a notable protective effect (**Figure 5B-D**).

SHAP dependence plot analysis

The SHAP dependence plots illustrated that CRP, TG, and TyG index exhibited increasing SHAP values with higher feature levels, reinforcing their strong positive contributions to SAP-HTG risk. AMY and FBG also contributed positively but with smaller SHAP gradients. Conversely, Ca^{2+} and age displayed decreasing SHAP values as their values increased, reinforcing their protective roles. A history of diabetes was also associated with a positive contribution, particularly in patients with a history of diabetes (**Figure 6**).

Comparative ROC analysis of predictive models with conventional scoring systems

When compared to traditional scoring systems, the XGBoost achieved the highest AUC (0.959), followed by APACHE II (0.893) and RANSON (0.878). Statistically significant differences in AUC were found between XGBoost and APACHE II (P = 0.002) and between XGBoost

Figure 2. Model optimization analysis for SAP-HTG prediction. A. Error Rate vs. Number of Trees in the RF Model. B. Error Rate vs. Number of Features in the SVM Model. C. Log Loss vs. Number of Iterations in the XGBoost Model. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, RF: Random Forest, SVM: Support Vector Machine, XGBoost: Extreme Gradient Boosting, MIN error: Minimum Error.

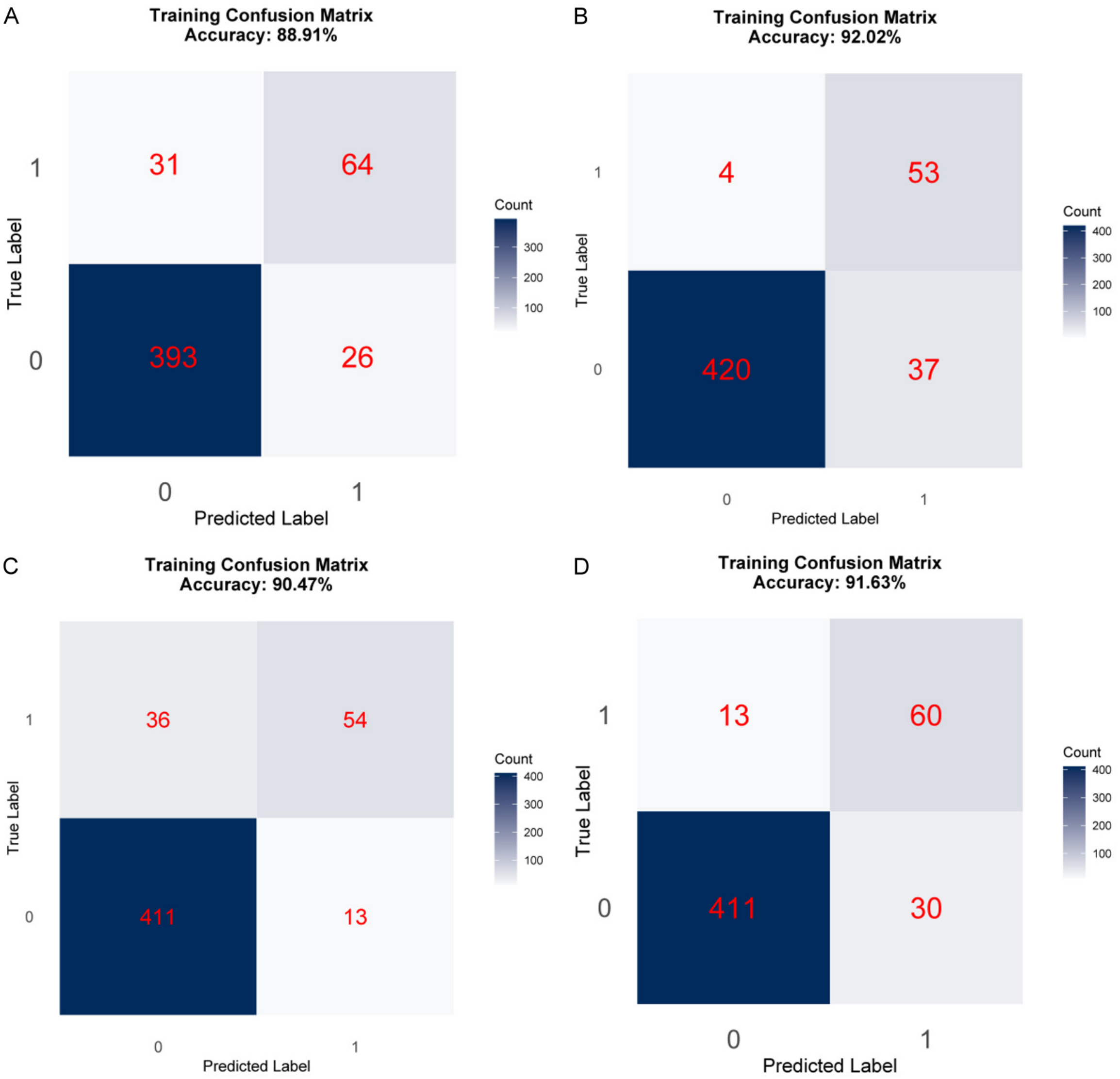

Figure 3. Confusion matrices of SAP-HTG prediction models. A. Logistic Regression Confusion Matrix. B. RF Confusion Matrix. C. SVM Confusion Matrix. D. XGBoost Confusion Matrix. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, RF: Random Forest, SVM: Support Vector Machine, XGBoost: Extreme Gradient Boosting.

and RANSON (P < 0.001). No significant difference was found between APACHE II and RANSON (P = 0.567) (**Figure 7**).

Discussion

Severe hypertriglyceridemia-associated acute pancreatitis (SAP-HTG) has garnered increasing attention due to its rapid progression and high mortality. Its incidence is rising in parallel with the growing prevalence of obesity, diabetes, and high-fat diets. SAP-HTG demonstrates more severe inflammatory responses and metabolic disturbances compared to N-SAP-HTG, highlighting a critical need for early identification of high-risk patients [15]. Traditional scoring systems, including APACHE II and Ranson scores, exhibit limited predictive capacity as they fail to integrate lipid metabolism and inflammatory markers. In contrast, ML techniques enable the recognition of nonlinear relationships and allow the construction of high-precision predictive models [15].

In this study, key risk factors were selected through LASSO regression, and predictive models were developed using logistic regression, RF, SVM, and XGBoost algorithms. Among them, XGBoost demonstrated the best performance (AUC = 0.959), significantly outperform-

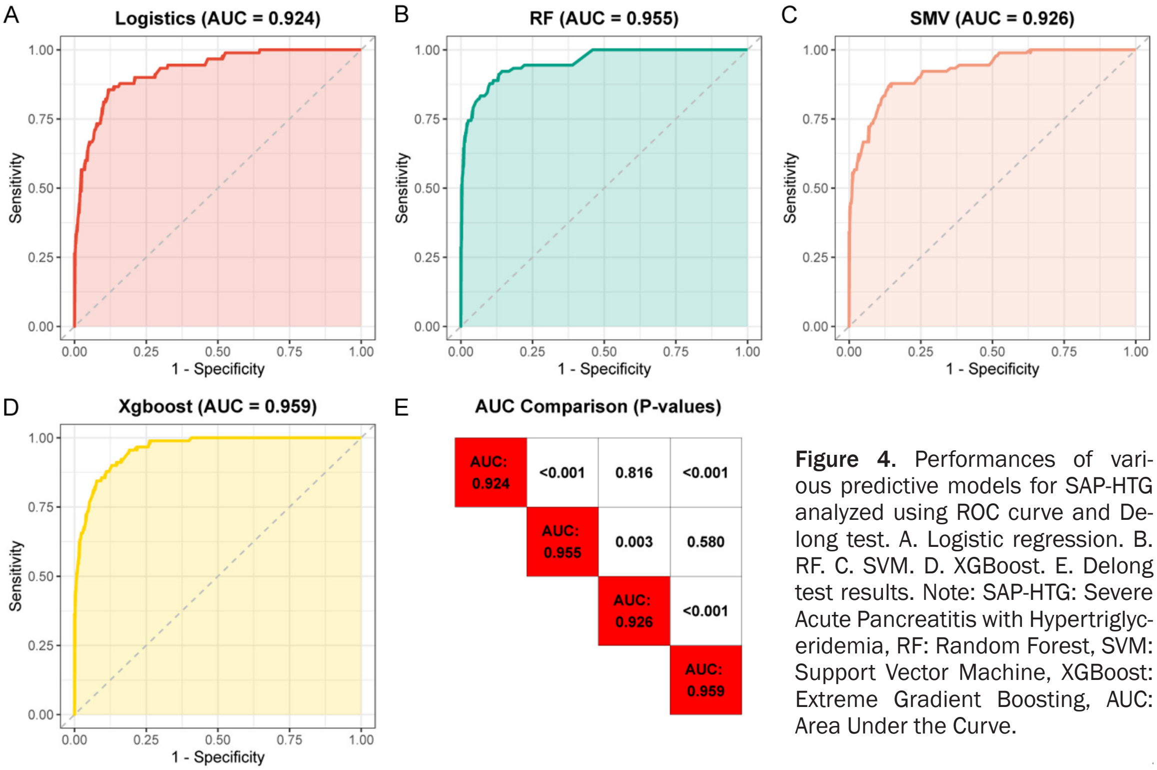

Figure 4. Performances of various predictive models for SAP-HTG analyzed using ROC curve and Delong test. A. Logistic regression. B. RF. C. SVM. D. XGBoost. E. Delong test results. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, RF: Random Forest, SVM: Support Vector Machine, XGBoost: Extreme Gradient Boosting, AUC: Area Under the Curve.

ing APACHE II (AUC = 0.893) and Ranson (AUC = 0.878). SHAP analysis further identified CRP, TG, and TyG index as core predictors, providing valuable tools for early diagnosis and risk stratification. These findings help address current limitations in SAP-HTG prediction and support the advancement of precision medication.

LASSO regression identified seven critical risk factors (CRP, TG, TyG index, AMY, FBG, TC, and diabetes history) and two protective factors (age and Ca) for SAP-HTG. These factors demonstrate strong associations with the disease's underlying pathophysiology and offer important clinical guidance. CRP (OR = 8.787), as an inflammatory marker, reflects intense systemic inflammatory responses in SAP-HTG. This response is likely mediated by proinflammatory cytokines such as IL-6 and TNF-α, which exacerbate pancreatic necrosis and contribute to multi-organ damage. Literature indicates that CRP correlates with HTG-AP severity and recurrence risk [11], suggesting that close CRP monitoring may provide a reliable measure of inflammatory status and guide timely anti-inflammatory or supportive interventions, including fluid resuscitation.

TG (OR = 7.548) represents a hallmark feature of SAP-HTG, inducing microcirculatory dysfunction through chylomicron deposition and free fatty acid (FFA) toxicity, directly damaging acinar cells and amplifying inflammation via the TLR4 pathway. Tan et al. [16] documented significantly higher TG levels in HTG-AP patients, emphasizing the urgency of lipid-lowering interventions. TG-derived non-esterified fatty acids (NEFA) have been linked to multiple organ failure, supporting the necessity of rapid TG reduction [17]. Clinically, insulin infusion and plasmapheresis are effective strategies, and Zhou et al. [18] reported improved outcomes with insulin combined with low-molecular-weight heparin (LMWH).

TyG index (OR = 5.689) reflects insulin resistance, which may aggravate disease progression by promoting lipolysis, increasing FFA levels, and triggering oxidative stress. Wang et al. [19] demonstrated significant correlations between TyG index and SAP-HTG severity. When combined with systemic immune-inflammation index (SII) and nutritional risk index (NRI), the model achieved an AUC of 0.705, highlighting the importance of comprehensive glucose and metabolic syndrome management.

AMY (OR = 3.662) and FBG (OR = 3.339) reflect enzymatic and glucose metabolic disturbances. These abnormalities likely result from local

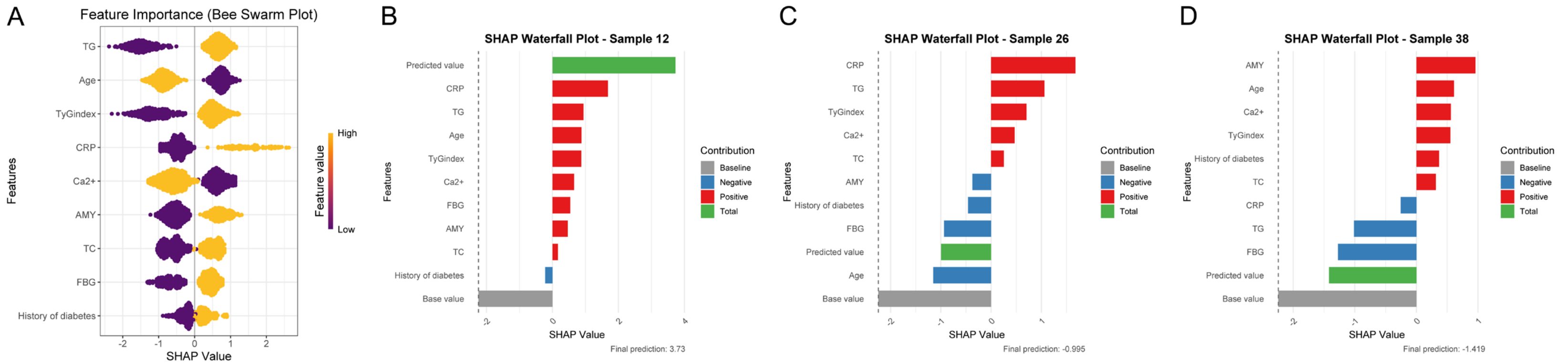

Figure 5. SHAP waterfall analysis of SAP-HTG prediction model. A. SHAP beeswarm plot of feature variables. B-D. SHAP waterfall force plots for samples 12, 26, and 38. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, CRP: C-Reactive Protein, TG: Triglyceride, TyGindex: Triglyceride-Glucose Index, AMY: Amylase, FBG: Fasting Blood Glucose, Ca^{2+}: Calcium, XGBoost: Extreme Gradient Boosting, SHAP: Shapley Additive Explanations.

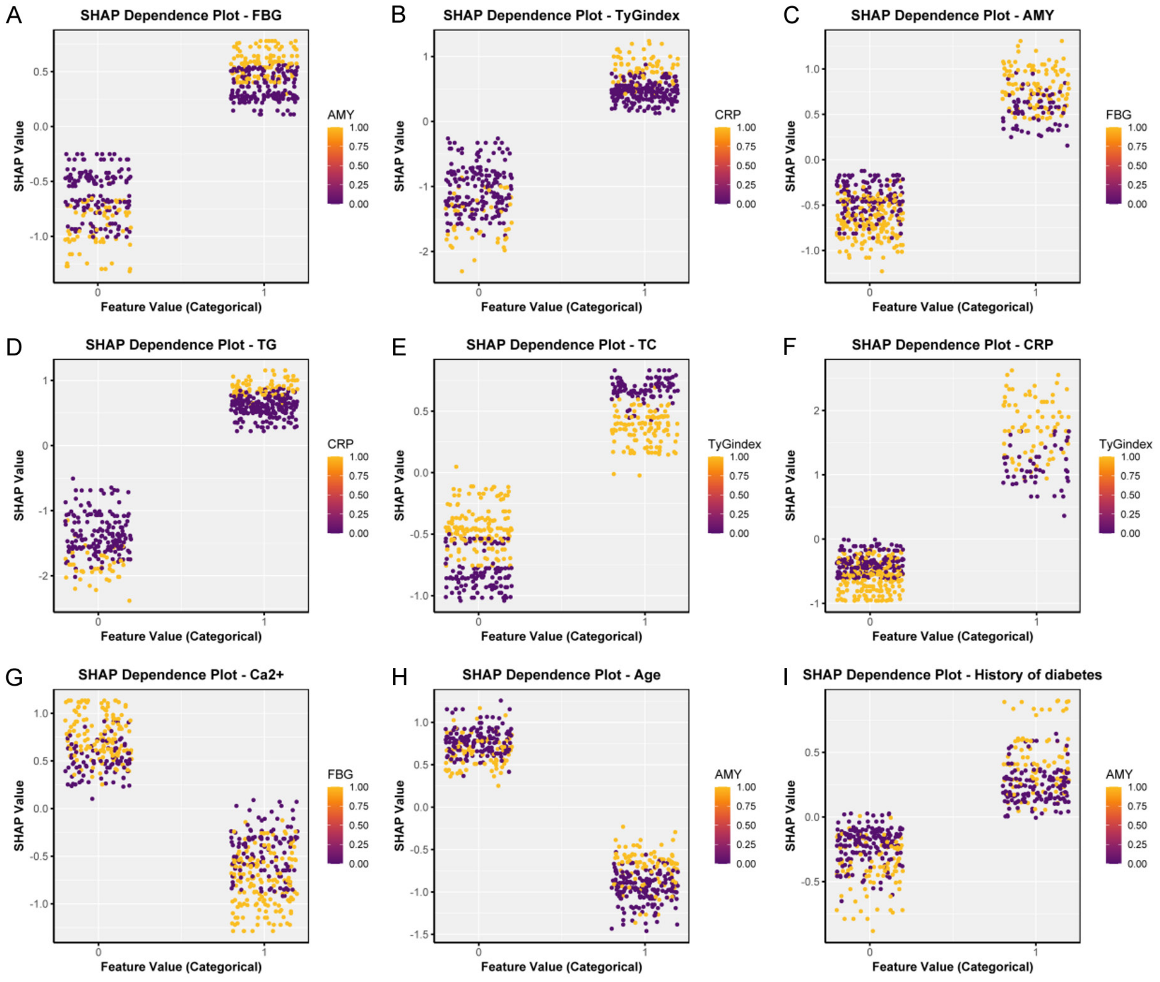

Figure 6. SHAP dependence plots for SAP-HTG prediction model. A. SHAP dependence plot: CRP vs. TG. B. SHAP dependence plot: TG vs. Ca^{2+}. C. SHAP dependence plot: AMY vs. Diabetes. D. SHAP dependence plot: Ca^{2+} vs. TG. E. SHAP dependence plot: TyG Index vs. AMY. F. SHAP dependence plot: FBG vs. TG. G. SHAP dependence plot: Age vs. Ca^{2+}. H. SHAP dependence plot: TC vs. CRP. I. SHAP dependence plot: Diabetes vs. AMY. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, CRP: C-Reactive Protein, TG: Triglyceride, TyGindex: Triglyceride-Glucose Index, AMY: Amylase, FBG: Fasting Blood Glucose, TC: Total Cholesterol, Ca^{2+}: Calcium, XGBoost: Extreme Gradient Boosting, SHAP: Shapley Additive Explanations.

pancreatic inflammation and stress hyperglycemia triggered by TG elevation. Literature has confirmed FBG as an independent risk factor for SAP-HTG [20], supporting the role of insulin therapy and nutritional support in management. TC (OR = 2.873) and diabetes history (OR = 2.541) indicate long-term lipid metabolic disorders and metabolic syndrome, which predispose the pancreas to TG-induced injury. Ding et al. [21] identified diabetes history as a predictor of HTG-AP recurrence, emphasizing the importance of chronic metabolic control. Shafiq et al. [22] found that HTG-AP patients exhibit higher BMI and increased clinical severity, further supporting a need for comprehensive metabolic syndrome management.

These risk factors may act synergistically to exacerbate disease severity. For example, TG and CRP may establish a vicious cycle of inflammation and lipotoxicity. Literature supports insulin infusion as an effective strategy for rapidly lowering TG and improving HTG-AP prognosis [1]. Clinically, CRP and TG should be prioritized for monitoring, in combination with TyG index and FBG, to guide comprehensive strategies including lipid-lowering, anti-inflammatory, and glycemic control measures aimed at reducing the risk of SAP-HTG onset and progression.

Serum Ca^{2+} (OR = 0.258, ≥ 2.085 mmol/L as a protective factor) and age (OR = 0.290, ≥ 45 years as a protective factor) demonstrated neg-

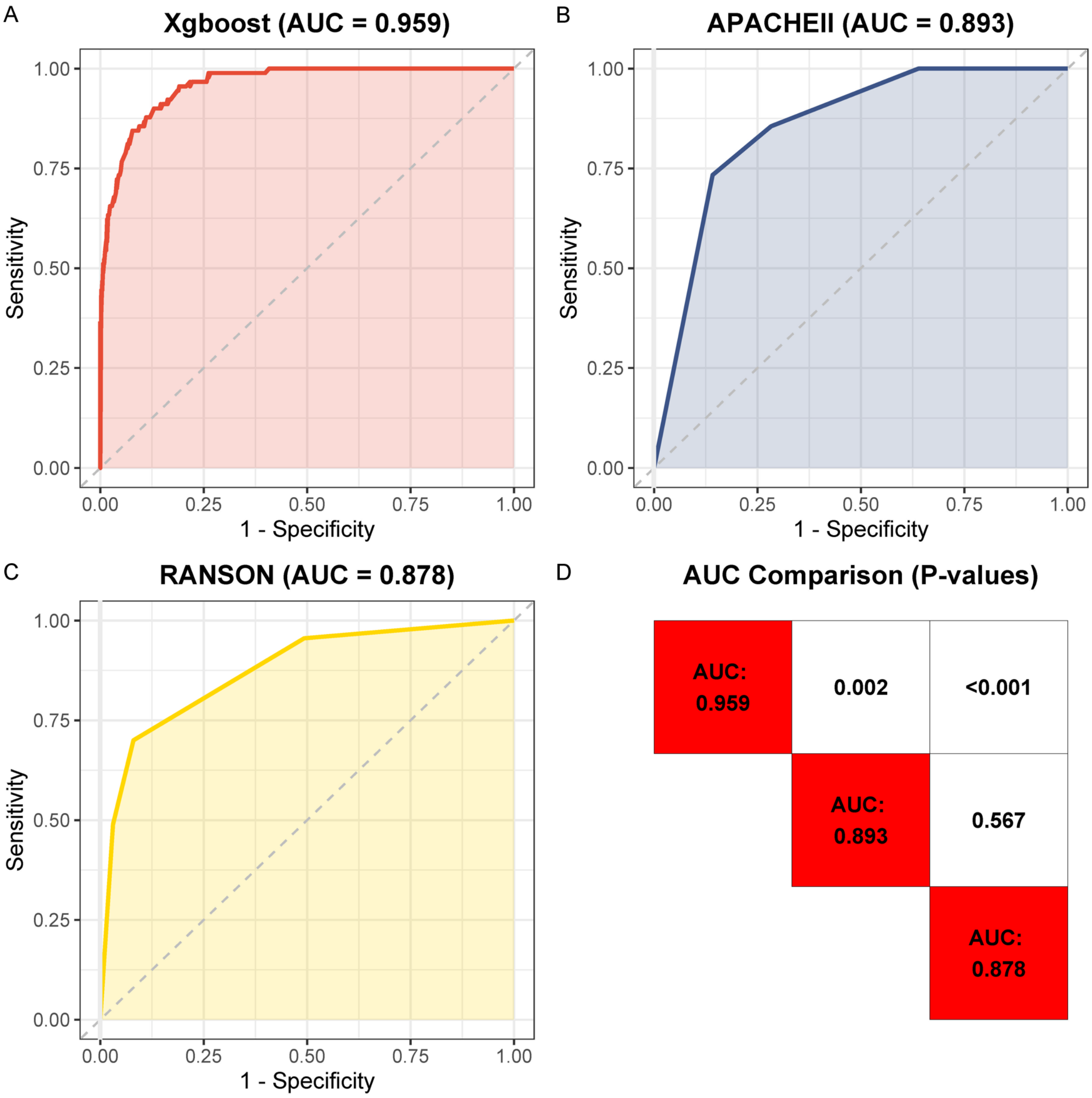

Figure 7. Performances of machine learning predictive models for SAP-HTG analyzed using ROC curve and Delong test. A. XGBoost; B. APACHE II; C. RANSON; D. Delong test results. Note: SAP-HTG: Severe Acute Pancreatitis with Hypertriglyceridemia, XGBoost: Extreme Gradient Boosting, APACHE II: Acute Physiology and Chronic Health Evaluation II, RANSON: Ranson Criteria, AUC: Area Under the Curve.

ative associations with SAP-HTG severity, offering valuable clinical insights. Low Ca^{2+} levels may result from fat saponification due to pancreatic necrosis, inflammation-induced hypoalbuminemia, or multi-organ dysfunction (e.g., renal impairment), and is typically associated with more severe pancreatic injury and systemic inflammation. Dong et al. [23] identified low Ca^{2+} as an independent predictor for SAP-HTG, with an AUC of 0.957 when incorporated into the model. Conversely, maintaining higher serum calcium may alleviate pancreatic damage by stabilizing cellular membranes, suppressing proinflammatory cytokines such as IL-1β, and supporting cardiovascular and neurological function. Clinically, regular calcium monitoring and timely supplementation may improve prognosis.

Interestingly, patients aged ≥ 45 years demonstrated a protective effect, possibly due to decreased metabolic rates or adaptive changes associated with chronic diseases, which reduce rapid accumulation of TG and FFAs.

Previous studies reported that patients < 40 years have a higher HTG-AP recurrence risk [21], supporting that younger individuals may be more susceptible due to active metabolism, obesity, or genetic predisposition. Similarly, Cao et al. [24] observed higher ICU admission rates in younger patients, reinforcing the need for early screening and timely intervention. Both univariate and multivariate analyses in this study confirmed the independent protective role of age. Genetic predisposition has also been implicated in younger patients [25], supporting a need for future studies exploring genetic susceptibility markers.

The protective effects of Ca^{2+} and age may reflect their roles in modulating inflammation and maintaining metabolic homeostasis. For example, high Ca^{2+} may inhibit proinflammatory cytokine release, whereas older patients may exhibit attenuated inflammatory responses due to metabolic adaptation. These findings underscore the importance of targeted early screening and intervention in younger patients and close monitoring of Ca^{2+} levels, to mitigate SAP-HTG complications.

All four ML models (logistic regression, RF, SVM, XGBoost) demonstrated strong predictive performance for SAP-HTG. XGBoost (AUC = 0.959) and RF (AUC = 0.955) outperformed logistic regression (AUC = 0.924), SVM (AUC = 0.926), and traditional scores (APACHE II: 0.893; Ranson: 0.878). DeLong test confirmed the superiority of XGBoost and RF, emphasizing their strength in capturing complex nonlinear relationships and multidimensional feature interactions. RF, using 228 trees, achieved 92.02% accuracy with balanced sensitivity and specificity, while XGBoost, optimized through gradient boosting (eta = 1, max_depth = 3), showed stable log-loss reduction and the highest AUC, highlighting its clinical potential.

Literature has demonstrated the predictive utility of CT- and serum marker-based models incorporating Ca^{2+} and CRP, achieving high accuracy (AUC = 0.930) in SAP-HTG [23], consistent with the advantages observed in our ML models. Compared to APACHE II and Ranson scores, ML models integrate SAP-HTG-specific features such as TG and TyG index, thereby providing enhanced predictive power. Wang et al. [19] reported an AUC of 0.705 for a model combining SII, NRI, and TyG index, supporting the effectiveness of multi-feature integration approaches. In our study, confusion matrix analysis revealed that RF and XGBoost demonstrated fewer false positives than logistic regression, achieving better classification balance.

SHAP analysis enhanced interpretability through summary and waterfall plots, revealing CRP, TG, and TyG index as dominant contributors, particularly in high-value ranges. This highlights the synergistic effects of inflammation and dyslipidemia. For instance, predictions in samples 12 and 26 were driven by high CRP and TG levels, while sample 38 was influenced by age and AMY, with Ca^{2+} exerting a protective effect. SHAP dependence plots illustrated strong positive impacts of CRP and TG at high levels, suggesting shared pathologic pathways in SAP-HTG progression. AMY and diabetes history interactions reflected complex relationships between pancreatic injury and metabolic disorders.

Negative contributions of Ca^{2+} and age further support their protective roles, possibly due to metabolic stability and disease tolerance. Literature supports that insulin infusion can rapidly reduce TG and improve outcomes in HTG-AP [26, 27], aligning with SHAP findings on TG. Wang et al. [28] reported that rapid TG reduction did not significantly shorten the duration of organ failure, suggesting that SHAP can aid in prioritizing treatment timing. Clinically, SHAP provides a basis for monitoring priorities - focus should be on dynamic changes in CRP and TG to guide lipid-lowering and anti-inflammatory therapy, while closely monitoring low Ca^{2+} patients for deterioration risk. These findings offer precise tools for early diagnosis and individualized treatment of SAP-HTG, addressing traditional score limitations and advancing precision medicine.

Nevertheless, several limitations should be acknowledged. First, this was a single-center retrospective study, raising the possibility of sampling bias. Second, data were static and lacked longitudinal dynamics. Future research should include multicenter cohorts for external validation, integrate dynamic clinical and laboratory data, and incorporate imaging features, genetic markers, and development of

XGBoost-based CDSS to evaluate their effect on reducing mortality and improving outcomes. Finally, emerging techniques such as deep learning should also be explored to further optimize SAP-HTG prediction and treatment approaches.

Conclusion

This study identified nine key risk factors for SAP-HTG using LASSO regression and constructed several machine learning models. Among them, the XGBoost model achieved the highest predictive performance. These findings provide a reliable and interpretable tool for early diagnosis and individualized risk stratification of SAP-HTG, thus advancing precision medicine.

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Disclosure of conflict of interest

None.

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