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Joint association of the triglyceride–glucose index and stress hyperglycemia ratio with incidence and mortality risks of new-onset atrial fibrillation during sepsis: a retrospective cohort study

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Abstract

Background The triglyceride–glucose (TyG) index and stress hyperglycemia ratio (SHR) have been linked to the cardiovascular risks in critical ill patients. However, little is known about the predictive power of the TyG index, SHR and their combination on the incidence and mortality risks of new-onset atrial fibrillation (NOAF) in patients with sepsis.

Method This retrospective study included patients from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Primary outcomes were defined as the incidence and 360-day mortality of in-hospital NOAF among patients with sepsis. Logistic model, Cox proportional hazard model, Kaplan-Meier analysis and receiver-operating characteristic (ROC) were performed to explore the association between the indices and clinical outcomes. Machine learning approach also was constructed to evaluate and compare the indices in predicting mortality risks.

Results 4276 patients meeting the inclusion criteria were enrolled and 764 individuals developed NOAF during hospitalization. The multivariable adjusted odds ratios (95%, CI) of incidence of NOAF in patients with sepsis in the highest group versus the lowest group were 1.36 (1.10–1.69), 1.35 (1.09–1.67) and 1.58 (1.23–2.02), respectively, for the TyG index, SHR and the TyG index-SHR combination. However, the predictive powers of these indices were relatively low. Among septic patients who developed in-hospital NOAF, those in the highest TyG index group and the highest SHR group exhibited an increased risk of 360-day mortality compared with those with the lowest TyG index and the lowest SHR (the TyG index: hazard ratio [HR] 1.59, 95% CI 1.00–2.62; SHR: HR 1.67, 95% CI 1.03–2.70). Patients with both the highest the TyG index and the highest SHR demonstrated the highest risk of 360-day mortality (HR 1.72, 95% CI 1.08–2.72). The ROC also confirmed the TyG index-SHR combination had more robust predictive power for 360-day

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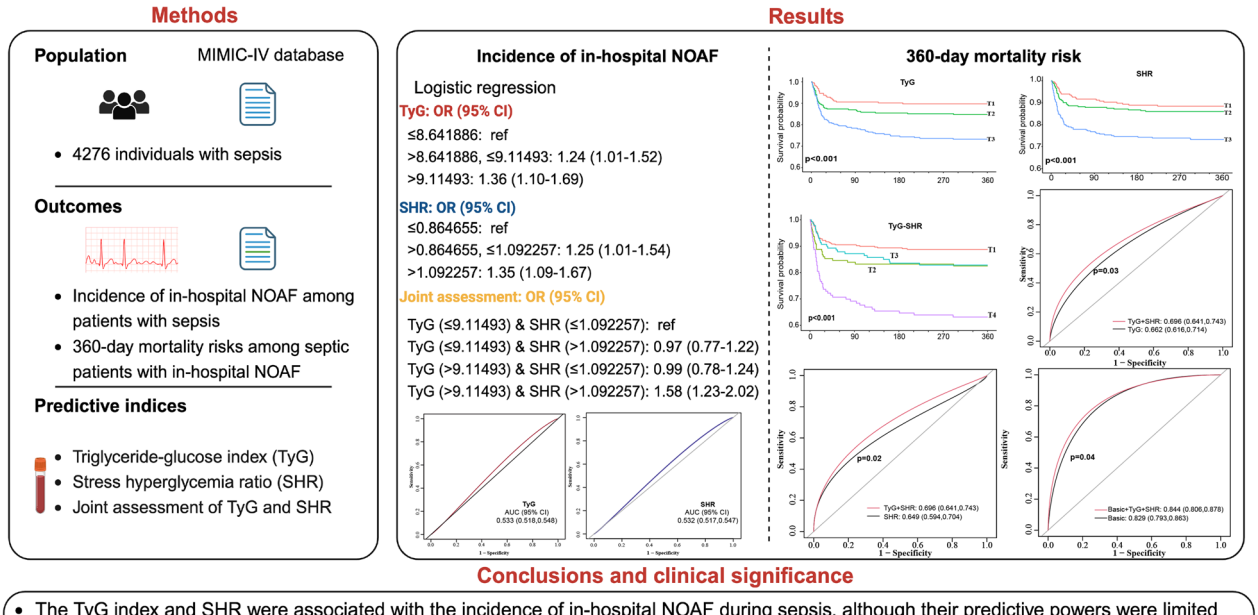
mortality among septic patients with NOAF than the TyG index and SHR itself ($p < 0.05$). The random forest model validated that the predictive capability was significantly enhanced with the integration of the TyG index and SHR.

Conclusion The TyG index and SHR were associated with the incidence of in-hospital NOAF during sepsis, although their predictive powers were limited. In septic patients with in-hospital NOAF, high levels of the TyG index and SHR were significantly associated with increased 360-day mortality risks, with their combination demonstrating superior predictive power. Joint assessments of the TyG index and SHR could help identify individuals at high risks of mortality post-discharge, enabling clinicians to prioritize follow-up care and improve patient management.

Graphical abstract



Keywords Triglyceride–glucose index, Stress hyperglycemia ratio, Mortality risk, New-onset atrial fibrillation, Sepsis

Introduction

Sepsis is a life-threatening host response to infection and is an important cause of mortality and critical illness worldwide [1]. Cardiovascular complications frequently emerging in these patients account for a substantial proportion of the mortality [2]. New-onset atrial fibrillation (NOAF) described as one of the most common complications, which is associated with poor outcomes and higher risk of mortality [3]. The mechanisms of NOAF during sepsis remain unclear and may involve inflammation, oxidative stress, electrolyte disturbance and fluid shifts [4, 5]. According to previous study, NOAF was associated with increased risk of mortality in patients with sepsis [6]. Considering high rates of NOAF in patients with sepsis and its adverse outcomes, it is crucial to explore novel risk factors to identify septic patients at high risk of NOAF and improve their clinical outcomes.

The triglyceride–glucose (TyG) index is proposed as a surrogate marker of insulin resistance (IR), manifesting as elevated insulin levels and reduced sensitivity, which was shown to be associated with the progression of metabolic disorders [7, 8]. At present, numerous studies have proven it might be a favorable indicator for predicting the poor prognosis or death of cardiovascular, cerebrovascular diseases and critical diseases [9, 10]. Patients with sepsis always accompany with IR [11]. Retrospective studies suggested high TyG index indicated an increased in-hospital mortality in critically ill sepsis patients [11, 12]. Previous study demonstrated that the TyG index was an independent predictor for AF among hospitalized patients [13]. Among people without any known cardiovascular diseases, a U - shaped relationship exists between the TyG index and the incidence of AF [14]. However, research investigating the connection between

TyG index and NOAF during sepsis in the literature is lacking. Additionally, the association between the TyG index and mortality risks in septic patients with NOAF is not currently well defined.

Stress hyperglycemia ratio (SHR) is a novel index of stress hyperglycemia and is identified as a marker of actual blood glucose status in critically ill patients [15]. Current studies investigated the association between SHR and the development of AF in acute myocardial infarction (AMI) or post-coronary intervention operation [16–20]. Previous study exhibited a higher SHR was significantly associated with an increased risk of 28-day mortality and in-hospital mortality in patients with sepsis [21, 22]. However, there are relatively few studies on SHR and NOAF during sepsis. The prognostic value of SHR for mortality risks in septic patients with NOAF is still unclear.

Sepsis is a clinical syndrome characterized by high heterogeneity. Previous researches focus on short-term mortality, including in-hospital, 28-day, 30-day mortality. However, in fact, clinicians and researchers have noticed that sepsis is a long-course disease. There is an academic term called "post-sepsis syndrome", which refers to long-term physical, medical, cognitive, and psychological issues. These long-term influences can last from months to years after discharge, which significantly reduce patients' quality of life and increase mortality risks [23, 24]. Additionally, NOAF has been associated with increased long-term mortality of patients in ICU [25]. Therefore, predicting long-term outcomes, such as 360-day mortality, is of great importance. While patients may receive better care during their hospital stay, once discharged, they may lack continuous medical supervision. By identifying patients are at high risks of mortality beyond hospitalization, clinicians can prioritize follow-up care and monitoring strategies to enhance patient management.

Therefore, this retrospective study aimed to investigate the association of the TyG index and SHR with in-hospital NOAF during sepsis. Furthermore, we evaluate the association between these two indices with 360-day mortality risk in septic patients developing NOAF. Importantly, we analyzed the joint association of the TyG index and SHR in predicting 360-day mortality risk in septic patients who developed NOAF.

Method

Study population

The analyzed data in this retrospective study were from the Medical Information Mart for Intensive Care (MIMIC)-IV database upon recruitment between 2008 and 2019. The participants were recruited from the ICU of the Beth Israel Deaconess Medical Center. The original data collection and de-identification process were approved by the Institutional Review Boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. Ting Wu has the access to the database and was responsible for the data extraction. Patients who were diagnosed with sepsis were included in the study. The exclusion criteria were as follows: (1) patients stayed in ICU shorter than 24 h; (2) patients aged less than 18 years old; (3) patients with missing data on fasting blood glucose, HbA1c (%) and triglycerides (TG); (4) patients with multiple admissions, for whom only the initial stay was included; (5) patients with a history of AF or flutter. For incidence of NOAF among patients with sepsis, the required sample size for our analysis was determined to be 1,698.

All patients enrolled in the study were divided into different groups according to TyG index (T1: ≤ 8.641886; $N = 1423$; T2: > 8.641886, ≤ 9.11493; $N = 1425$; T3: > 9.11493, $N = 1428$) and SHR (T1: ≤ 0.864655; $N = 1429$; T2: > 0.864655, ≤ 1.092257; $N = 1424$; T3: >1.092257, $N = 1423$). For joint assessment, in order to simplify the analysis and enhance statistical power, we used binary categorization of TyG and SHR to form four groups [T1: low TyG (≤ 9.11493) and low SHR (≤ 1.092257); T2: low TyG (≤ 9.11493) and high SHR (> 1.092257); T3: high TyG (> 9.11493) and low SHR (≤ 1.092257); T4: high TyG (> 9.11493) and high SHR (> 1.092257)].

Variable extraction

Demographics, vital signs, comorbidities, laboratory variables and treatments were extracted based on existing literature and medical knowledge regarding variable that may be associated with the outcomes of interest. The extraction was performed using Postgres SQL (v13.7.1) and Navicate Premium (version 15). Demographics encompassed age and gender. Vital signs included mean blood pressure (MBP), respiratory rate (RR), heart rate (HR), temperature (Tm) and (Sequential Organ Failure Assessment) SOFA score. Comorbidities included in the study comprised conditions like cardiomyopathy, endocarditis, coronary heart disease (CHD), AMI, chronic heart failure (CHF), hypertension, diabetes, chronic kidney disease (CKD), acute respiratory failure (ARF), acute kidney failure (AKF) and obesity. Laboratory variables encompassed white blood cell (WBC), red blood cell (RBC), platelet, hemoglobin, HbA1c, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, calcium, magnesium, chloride, base excess, lactate, total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Utility of antibiotics, glucocorticoids and vasopressor within 48 h after hospital admission and mechanical ventilation (MV) was analyzed. Additionally, we utilized directed acyclic graphs (DAG) to illustrate the relationships among these

variables and their potential associations with the outcomes. The value of the SHR was calculated as fasting blood glucose (FBG) (mg/dl)/ [28.7 x HbA1c (%)– 46.7]. The TyG index was calculated as ln [fasting TG (mg/dl) × FBG (mg/dl)]/2.

Outcomes

The primary outcomes were defined as the incidence of in-hospital NOAF among patients with sepsis and 360-day mortality in septic patients with in-hospital NOAF. Secondary outcomes were 90-day mortality and in-hospital mortality in septic patients developing in-hospital NOAF. Deidentified free-text clinical notes for patients, which are an important source of information for understanding a patient's clinical course, were used to define NOAF. To ensure accurate identification of NOAF, we conducted a one-to-one review of the clinical notes for each patient with sepsis and necessary data. Patients with no prior history of AF or atrial flutter (AFL) who developed AF during hospitalization were defined as having NOAF.

Statistical analysis

Continuous variables were exhibited as the mean ± standard deviation, and differences were evaluated using Student's t test and the Wilcoxon rank-sum test. Categorical variables were reported as total counts and percentages, with differences compared using the chi-square (χ^2) test or Fisher's exact test. Variables with more than 10% missing data were excluded from the analysis. For variables with missing values between 5% and 10%, multiple imputation techniques were employed to estimate and fill in the missing values with the most appropriate data. Variables with less than 5% missing values were replaced with their mean. We performed univariate logistic or Cox regression for all potential predictor variables. Variables that yielded a p-value of less than 0.05 were considered significant and were included in the subsequent multivariate analysis. We calculated variance inflation factors (VIFs) to assess multicollinearity and ensure variable independence. For the multivariate logistic or Cox regression, we applied a forward stepwise selection method. A logistic regression model was employed to evaluate the correlation between various indices (TyG index and SHR) and the incidence of in-hospital NOAF in patients with sepsis. Model 1 adjusted for age, CHF, CHD, diabetes, hypertension, HR, and Tm. Model 2 included model 1 variables with additional adjustments for WBC, RBC, platelet, magnesium, sodium, antibiotics, vasopressor and MV. The Cox proportional hazard models were generated to quantify the relationship between the indices and mortality risks. Model 1 adjusted for cardiomyopathy, CHD, AMI, ARF, AKF, HR, RR. Model 2 included model 1 variables with additional adjustments for SOFA score, WBC, AST, creatinine, BUN, potassium, calcium, lactate, chloride, LDL, use of glucocorticoids and MV. Inverse probability of treatment weighting (IPTW) was also conducted to ensure the robustness of our conclusions. The cumulative incidence of mortality was evaluated using the Kaplan-Meier (K-M) survival analysis. The adjusted restricted cubic spline (RCS) was employed to assess the dose-response relationship between the TyG index, SHR and mortality risks. The predictive power of the indices for mortality risks was evaluating using receiver operating characteristic (ROC) curve analysis. For joint assessment, both the TyG index and SHR were treated as continuous variables and included simultaneously in the predictive model. The area under the curve (AUC) was calculated to compare the predictive capacity of the TyG index, SHR and the combined TyG-SHR assessment. Calibration curves were generated to evaluate how well the predicted probabilities match the observed outcomes. Decision curve analysis (DCA) analysis was conducted to evaluate the clinical utility of prediction models. Subgroup analysis was performed based on cardiomyopathy, CHD, AMI, ARF, AKF, use of glucocorticoids and MV. Stata 12 (STATA Corporation, College Station, Texas, USA) was used to analyze all the data.

Establishment and validation of the prediction models

Lasso regression was utilized to identify and retain important features that contribute significantly to the prediction model. The dataset was divided into a training set and a validation set in a 7:3 ratio. The training set was used to build the predictive models, while the validation set was employed for model evaluation. The filtered variables were analyzed using random forest (RF) model, eXtreme gradient boosting (XGBoost) model, and support vector machines (SVM) model to predict the 360-day mortality risk. The performance of each model was assessed using ROC curve. Calibration curves were used to evaluate the accuracy of the model in predicting absolute risk. DCA analysis was conducted to evaluate the clinical utility of prediction models.

Results

Study population and baseline characteristics

According to the inclusion and exclusion criteria, a total of 4276 individuals were analyzed in the study. The selection process of included patients was presented in Fig. 1. These patients were divided into those who developed NOAF during hospitalization (764, 17.87%) and those who did not develop NOAF (3512, 82.13%). Table 1 presented the detailed baseline characteristics of the two groups of patients. Compared with the patients without NOAF, the septic patients who developed NOAF during hospitalization were older, had a higher proportion of males, a lower MBP, and a higher SOFA score. In addition, the septic patients with cardiomyopathy, AMI, CHF,

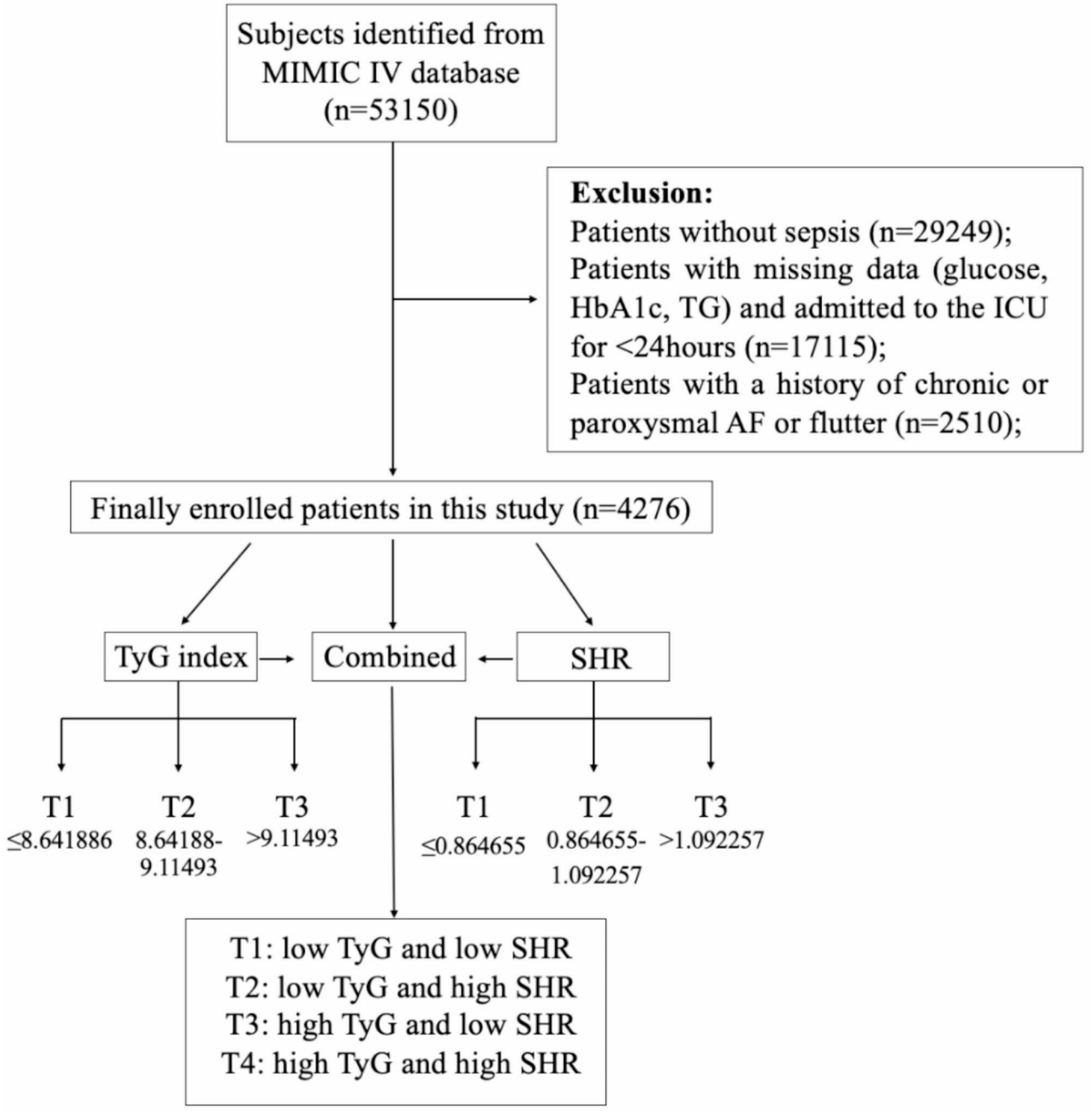


Fig. 1 Patient selection process

CHD and hypertension had a higher risk of developing NOAF. Moreover, high level of WBC, platelets, and magnesium were observed in these patients. Especially, a remarkably higher level of TyG index and SHR was detected among septic patients developing NOAF during hospitalization. Additionally, these patients had a longer length of stay (LOS) and a significantly increased risks of mortality.

The TyG index, SHR and incidence of NOAF in patients with sepsis

When regarded as a continuous variable, TyG was significantly associated with the incidence of NOAF in patients with sepsis both in non-adjusted model (OR 1.19; 95% CI 1.05–1.35) and the adjusted model (Model 1: OR 1.31; 95% CI 1.15–1.51; Model 2: OR 1.30; 95% CI 1.13–1.50). According to the tertile of the TyG level, all patients were divided into three groups (T1: ≤8.641886; $N = 1423$; T2: >8.641886, ≤9.11493; $N = 1425$; T3: >9.11493, $N = 1428$).

Table 1 Baseline characteristics between patients with NOAF and patients without NOAF

Variables (Mean ± SD, *N*, %)	Total (*N* = 4276)	Patients without NOAF (*N* = 3512)	Patients with NOAF (*N* = 764)	*P*
Age, (years)	63.240 ± 14.408	61.870 ± 14.638	69.538 ± 11.347	**< 0.001**
Gender, N (%)				**0.005**
Female	1723 (40.295)	1450 (41.287)	273 (35.733)	
Male	2553 (59.705)	2062 (58.713)	491 (64.267)	
MBP, (mmHg)	77.606 ± 10.452	77.905 ± 10.650	76.229 ± 9.373	**< 0.001**
RR, (rpm)	19.334 ± 3.878	19.343 ± 3.901	19.293 ± 3.771	0.745
HR, (rpm)	85.479 ± 15.210	85.478 ± 15.193	85.483 ± 15.301	0.993
Tm, (°C)	36.922 ± 0.507	36.939 ± 0.510	36.843 ± 0.486	**< 0.001**
SOFA Score	3.579 ± 1.960	3.533 ± 1.933	3.789 ± 2.071	**0.002**
CHF, N (%)				**< 0.001**
No	3195 (74.719)	2696 (76.765)	499 (65.314)	
Yes	1081 (25.281)	816 (23.235)	265 (34.686)	
Cardiomyopathy, N (%)				**0.007**
No	4150 (97.053)	3420 (97.380)	730 (95.550)	
Yes	126 (2.947)	92 (2.620)	34 (4.450)	
Endocarditis, N (%)				0.890
No	4195 (98.106)	3445 (98.092)	750 (98.168)	
Yes	81 (1.894)	67 (1.908)	14 (1.832)	
CHD, N (%)				**< 0.001**
No	2761 (64.570)	2405 (68.479)	356 (46.597)	
Yes	1515 (35.430)	1107 (31.521)	408 (53.403)	
AMI, N (%)				**0.002**
No	4031 (94.270)	3329 (94.789)	702 (91.885)	
Yes	245 (5.730)	183 (5.211)	62 (8.115)	
Hypertension, N (%)				**< 0.001**
No	2211 (51.707)	1888 (53.759)	323 (42.277)	
Yes	2065 (48.293)	1624 (46.241)	441 (57.723)	
Diabetes, N (%)				0.078
No	3189 (74.579)	2600 (74.032)	589 (77.094)	
Yes	1087 (25.421)	912 (25.968)	175 (22.906)	
ARF, N (%)				0.092
No	3176 (74.275)	2627 (74.801)	549 (71.859)	
Yes	1100 (25.725)	885 (25.199)	215 (28.141)	
AKF, N (%)				0.671
No	2665 (62.325)	2194 (62.472)	471 (61.649)	
Yes	1611 (37.675)	1318 (37.528)	293 (38.351)	
CKD, N (%)				0.333
No	3314 (77.502)	2732 (77.790)	582 (76.178)	
Yes	962 (22.498)	780 (22.210)	182 (23.822)	
Obesity, N (%)				0.238
No	3759 (87.909)	3097 (88.183)	662 (86.649)	
Yes	517 (12.091)	415 (11.817)	102 (13.351)	
WBC, (K/UL)	11.157 ± 6.043	11.056 ± 6.041	11.617 ± 6.037	**0.020**
RBC, (K/UL)	3.641 ± 0.800	3.632 ± 0.803	3.678 ± 0.784	0.149
Platelet, (K/UL)	199.740 ± 95.723	201.905 ± 97.687	189.786 ± 85.474	**< 0.001**
Hemoglobin, (g/dl)	10.880 ± 2.324	10.856 ± 2.323	10.993 ± 2.328	0.137
HbA1c, (%)	6.325 ± 1.572	6.334 ± 1.614	6.284 ± 1.362	0.370
Creatinine, (mg/dl)	1.536 ± 1.724	1.540 ± 1.749	1.518 ± 1.601	0.746
BUN, (mg/dl)	26.658 ± 21.131	26.441 ± 21.296	27.656 ± 20.339	0.150
AST, (IU/L)	58.331 ± 135.550	59.522 ± 139.452	52.857 ± 115.862	0.218
ALT, (IU/L)	43.580 ± 87.150	44.330 ± 89.662	40.130 ± 74.480	0.227
Sodium, (mEq/L)	138.009 ± 5.134	138.032 ± 5.219	137.902 ± 4.727	0.524

Table 1 (continued)

Variables (Mean ± SD, *N*, %)	Total (*N* = 4276)	Patients without NOAF (*N* = 3512)	Patients with NOAF (*N* = 764)	*P*
Potassium, (mEq/L)	4.167 ± 0.747	4.167 ± 0.763	4.167 ± 0.667	0.975
Calcium, (mEq/L)	8.110 ± 1.634	8.114 ± 1.602	8.090 ± 1.772	0.714
Magnesium, (mEq/L)	1.967 ± 0.419	1.949 ± 0.407	2.054 ± 0.463	**< 0.001**
Chloride, (mEq/L)	104.301 ± 6.506	104.265 ± 6.557	104.466 ± 6.270	0.438
Base excess, (mEq/L)	-1.034 ± 7.722	-1.020 ± 4.531	-1.101 ± 15.480	0.791
Lactate, (mmol/L)	1.948 ± 1.490	1.957 ± 1.520	1.908 ± 1.346	0.407
TC, (mg/dl)	168.028 ± 50.935	168.779 ± 51.855	164.575 ± 46.347	**0.039**
LDL, (mg/dl)	93.049 ± 38.668	93.440 ± 39.128	91.252 ± 36.450	0.156
HDL, (mg/dl)	49.327 ± 18.199	49.546 ± 18.513	48.323 ± 16.652	0.072
Antibiotics, N (%)				**0.005**
No	647 (15.131)	506 (14.408)	141 (18.455)	
Yes	3629 (84.869)	3006 (85.592)	623 (81.545)	
Vasopressor, N (%)				**< 0.001**
No	3002 (70.206)	2555 (72.751)	447 (58.508)	
Yes	1274 (29.794)	957 (27.249)	317 (41.492)	
Glucocorticoids, N (%)				**0.023**
No	3721 (87.021)	3037 (86.475)	684 (89.529)	
Yes	555 (12.979)	475 (13.525)	80 (10.471)	
MV, N (%)				**< 0.001**
No	2423 (56.665)	2069 (58.912)	354 (46.335)	
Yes	1853 (43.335)	1443 (41.088)	410 (53.665)	
TyG	8.905 ± 0.626	8.893 ± 0.637	8.963 ± 0.574	**0.003**
SHR	1.013 ± 0.330	1.007 ± 0.328	1.042 ± 0.337	**0.007**
Los	5.068 ± 6.811	4.726 ± 6.149	6.638 ± 9.104	**< 0.001**
360-day mortality, N (%)				**< 0.001**
No	3792 (88.681)	3165 (90.120)	627 (82.068)	
Yes	484 (11.319)	347 (9.880)	137 (17.932)	
Hospital mortality, N (%)				**< 0.001**
No	3913 (91.511)	3255 (92.682)	658 (86.126)	
Yes	363 (8.489)	257 (7.318)	106 (13.874)	
90-day mortality, N (%)				**< 0.001**
No	3878 (90.692)	3229 (91.942)	649 (84.948)	
Yes	398 (9.308)	283 (8.058)	115 (15.052)	

Bold values indicate significant difference between two groups ($P < 0.05$)

AF: Atrial fibrillation; ALT: Alanine aminotransferase; AMI: Acute myocardial infarction; AKF: Acute kidney failure; ARF: Acute respiratory failure; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CHD: Coronary heart disease; CHF: Chronic heart failure; CKD: Chronic kidney disease; HDL: High density lipoprotein cholesterol; HR: Heart rate; LDL: Low density lipoprotein cholesterol; LOS: Length of stay; MBP: Mean Blood Pressure; MV: Mechanical ventilation; RBC: Red blood cell; RR: Respiratory rate; SHR: Stress hyperglycemia ratio; TC: Total cholesterol; Tm: Temperature; TyG: Triglyceride and glucose index; WBC: White blood cell

When considered as a categorical variable, patients with sepsis with a higher level of TyG index were more likely to develop NOAF during hospitalization, even though after adjusting for all confounding variables (T2 vs. T1 OR 95% CI 1.24 (1.01–1.52); T3 vs. T1: 1.36 (1.10–1.69); *P* for trend: 0.004) (Table 2). Adjusted RCS was performed to evaluate the dose-response relationship of the TyG index on the incidence of NOAF among patients with sepsis, and the results exhibited a non-linear relationship (*P* for nonlinearity = 0.037) (Fig. 2A). The ROC results exhibited a low power of the TyG index to predict the incidence of in-hospital NOAF among patients with sepsis (Fig. 2C and Supplementary Table 1).

When treated as continuous variable, higher level of SHR was significantly correlated with the incidence of NOAF in patients with sepsis (fully adjusted model 2: OR 1.31; 95% CI 1.02–1.69). Similarly, all patients were categorized into three groups: T1.

(≤ 0.864655; *N* = 1429); T2: (> 0.864655, ≤ 1.092257; *N* = 1424); T3: (> 1.092257, *N* = 1423). Compared with patients with a low SHR index, those with a high SHR index demonstrated a significantly higher risk of the incidence of NOAF in patients with sepsis (fully adjusted model 2: T2 vs. T1: OR 1.25; 95% CI 1.01–1.54; T3 vs. T1: OR 1.35; 95% CI 1.09–1.67) (Table 2). A non-linear correlation between SHR index and incidence of NOAF was

Table 2 Logistic regression models for the association of TyG index and SHR with the incidence of NOAF in patients with sepsis

Groups	Non-adjusted OR (95% CI) *P*-Value	Model 1 OR (95% CI) *P*-Value	Model 2 OR (95% CI) *P*-Value
TyG index			
Continuous	1.19(1.05–1.35) 0.005	1.31(1.15–1.51) < 0.001	1.30 (1.13–1.50) < 0.001
T1 (≤ 8.641886; *N* = 1423)	ref	ref	ref
T2 (> 8.641886, ≤ 9.11493; *N* = 1425)	1.25 (1.03–1.52) 0.025	1.22 (1.00-1.50) 0.05	1.24 (1.01–1.52) 0.046
T3 (> 9.11493, *N* = 1428)	1.27(1.05–1.55) 0.015	1.38 (1.12–1.70) 0.002	1.36 (1.10–1.69) 0.004
P for trend	0.016	0.002	0.004
SHR			
Continuous	1.37 (1.09–1.72) 0.007	1.43 (1.13–1.83) 0.003	1.31 (1.02–1.69) 0.035
T1 (≤ 0.864655; *N* = 1429)	ref	ref	ref
T2 (> 0.864655, ≤ 1.092257; *N* = 1424)	1.31 (1.08–1.60) 0.006	1.31 (1.07–1.61) 0.009	1.25 (1.01–1.54) 0.039
T3 (> 1.092257, *N* = 1423)	1.35 (1.11–1.64) 0.003	1.41 (1.15–1.74) 0.001	1.35 (1.09–1.67) 0.006
P for trend	0.003	0.001	0.006
Combined			
T1 (Low TyG and low SHR; *N* = 1963)	ref	ref	ref
T2 (Low TyG and high SHR; *N* = 885)	0.89 (0.72–1.11) 0.305	0.99 (0.79–1.24) 0.930	0.97 (0.77–1.22) 0.807
T3 (High TyG and low SHR, *N* = 890)	0.87 (0.70–1.07) < 0.189	1.00 (0.80–1.26) 0.970	0.99 (0.78–1.24) 0.914
T4 (High TyG and high SHR *N* = 538)	1.52 (1.21–1.91) < 0.001	1.62 (1.28–2.06) < 0.001	1.58 (1.23–2.02) < 0.001
P for trend	0.034	0.002	0.007

Model 1: Age, CHF, CHD, Diabetes, Hypertension, HR, Tm

Model 2: Age, CHF, CHD, Diabetes, Hypertension, HR, Tm, WBC, RBC, Platelet, Magnesium, Sodium, Antibiotics, Vasopressor, MV

observed according to adjusted RCS result (*P* for nonlinearity = 0.027) (Fig. 2B). Similarly, the predictive ability of SHR for incidence of NOAF among patients with sepsis was low (Fig. 2D and Supplementary Table 1).

The TyG index-SHR combination and incidence of NOAF in patients with sepsis

After combining the TyG and the SHR, the patients were divided into four groups: T1: low TyG and low SHR; T2: low TyG and high SHR; T3: high TyG and low SHR; T4: high TyG and high SHR. As presented in Table 2, septic patients with high TyG and high SHR (T4) were more likely to develop NOAF during hospitalization in both unadjusted model (OR 1.52; 95% CI 1.21–1.91) and fully adjusted model 2 (OR 1.58; 95% CI 1.23–2.02). Notably, after adjusting for confounding variables, the OR for the combination of high TyG and SRH reached 1.58, surpassing that of individually elevated TyG or SHR. Moreover, in comparison to the patients in the T1 group, those in the T2 or T3 group did not lead to a marked elevation the incidence of NOAF among patients with sepsis. Collectively, these findings suggested patients with concurrent elevations in both TyG and SHR indices bear the highest risk of NOAF incidence compared to the other groups with varying levels of TyG and SHR.

The TyG index, SHR and 360-day mortality risks among septic patients with in-hospital NOAF

The baseline characteristics of the septic patients with NOAF were categorized based on their 360-day mortality (Supplementary Table 2). DAG (Supplementary Fig. 1) illustrated the relationship between all variables and 360-day mortality of NOAF among patients with sepsis. Cox regression analysis indicated that, as a numerical variable, TyG was significantly correlated with the risks of 360-day mortality in crude model (HR, 2.81; 95% CI 2.17–3.65). After fully adjusted for other variables, a statistically significant association was still observed between TyG level and 360-day mortality risk (HR, 1.90; 95% CI 1.41–2.54) (Table 3). Similar relationships were detected in terms of 90-day mortality and in-hospital mortality (Supplementary Tables 3 and Table 4). When treated as a categorical variable, the TyG index in the highest-level group exhibited a significant increased risks of 360-day mortality both in crude model (HR, 2.83; 95% CI 1.77–4.53) and in model 2 (HR, 1.59; 95% CI 1.00–2.62). However, the TyG index in T3 group showed no significant differences in 90-day mortality and in-hospital mortality (Supplementary Tables 3 and Supplementary Table 4). According to K-M analysis, patients with higher TyG levels have a higher 360-day mortality rate ($p < 0.001$) (Fig. 3A). Similarly, patients with higher TyG levels also exhibited higher risks of 90-day mortality and in-hospital mortality (Fig. 3D and G). After adjusted for all factors, there was a non-linear relationship between TyG level and 360-day mortality (p for non-linear = 0.009) (Fig. 4A). A non-linear relationship was also observed between TyG and both the in-hospital mortality (p for non-linear = 0.011) and 90-day mortality (p for non-linear = 0.004). Subgroup analysis demonstrated no significant interactions between cardiomyopathy, CHD, AMI, ARF, AKF, use of glucocorticoids and MV, and the TyG index for 360-day mortality (Supplementary Table 5). To mitigate potential

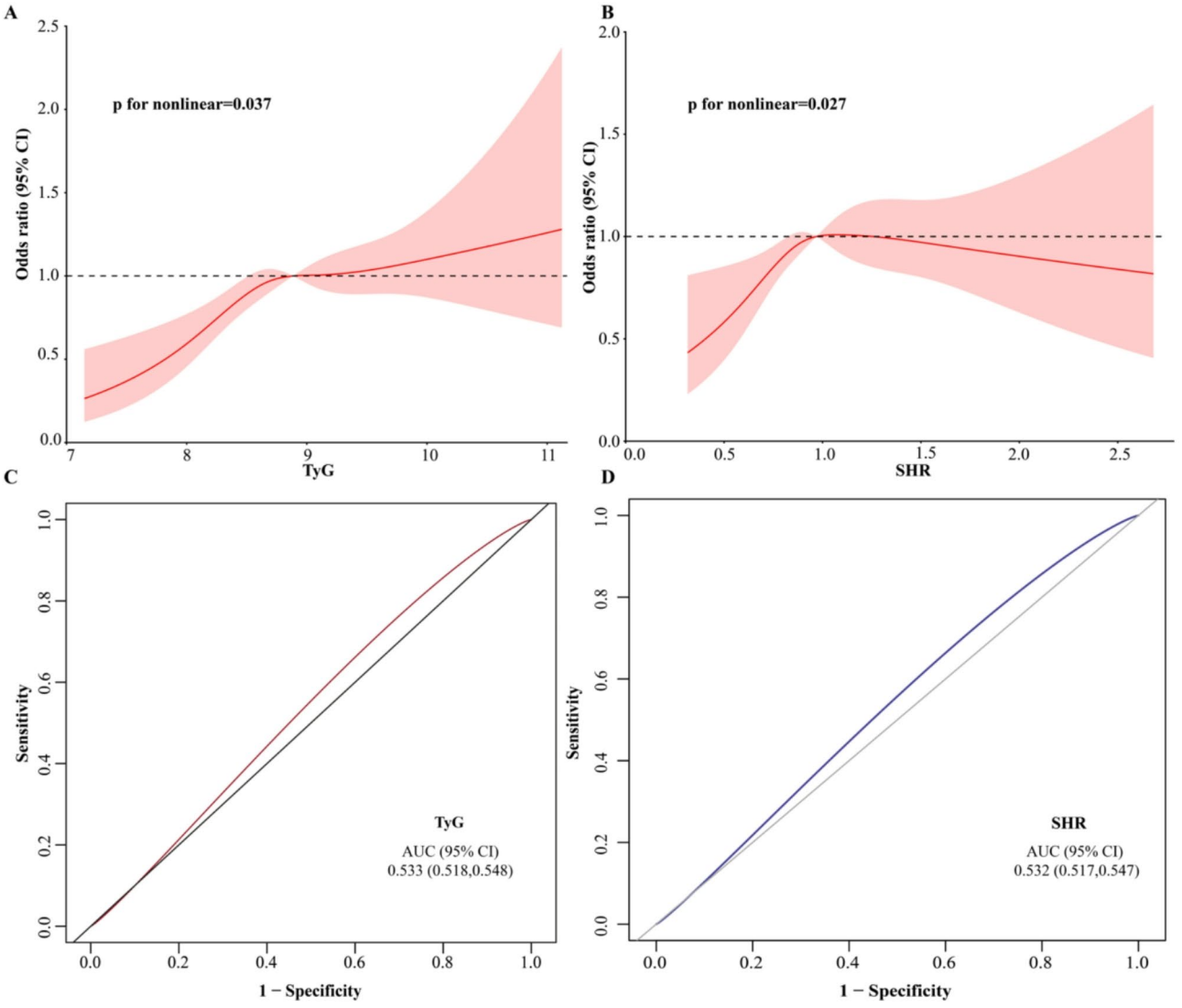


Fig. 2 **A** RCS analysis of the TyG index for incidence of in-hospital NOAF among patients with sepsis; **B** RCS analysis of SHR for incidence of in-hospital NOAF among patients with sepsis; **C** The ROC curves of the TyG index as a marker to predict incidence of in-hospital NOAF among patients with sepsis; **D** The ROC curves of SHR as a marker to predict incidence of in-hospital NOAF among patients with sepsis

confounders and enhance the robust of our results, we further performed IPTW analysis. The TyG was divided at 9.11493, as Cox model indicated that the T3 group of the TyG index was significantly associated with 360-day mortality. The baseline characteristics after matched have been listed in Supplementary Table 6. The results demonstrated that elevated TyG was stably associated with increased 360-day mortality among septic patients with in-hospital NOAF ($p < 0.001$).

As shown Table 3, when the SHR index was regarded as a numerical variable, SHR was closely related to the 360-day mortality risk among septic patients with NOAF in fully adjusted model (model 2: HR, 2.63; 95% CI 1.78–3.89). As a nominal variable, the highest level of SHR exhibited a statistically significant association with the risk of 360-day mortality risk both in unadjusted model (HR, 2.59; 95% CI 1.65–4.08) and fully adjusted model (HR, 1.67; 95% CI 1.03–2.70). Similar relationships were detected in terms of 90-day mortality and in-hospital mortality (Supplementary Tables 3 and Supplementary Table 4). According to K-M analysis, the cumulative incidence of mortality risks, including 360-day mortality, 90-day mortality and in-hospital mortality, was significantly increased in the T3 group compared with the T1 and T2 groups (Fig. 3). Adjusted RCS was employed to visualize the associations between SHR and 360-day mortality. After adjusting for all covariates, a linear relationship was detected between SHR and mortality risks (Fig. 4D–F). The results of subgroup analysis were presented in Supplementary Table 7. The SHR was divided at 1.092257. The baseline characteristics after IPTW-adjusted have been listed in Supplementary Table 8. The

Table 3 COX regression models for the association of the TyG index and SHR with 360-day mortality in sepsis patients with NOAF

Groups	Non-adjusted HR (95% CI) *P*-value	Model 1 HR (95% CI) *P*-value	Model 2 HR (95% CI) *P*-value
TyG index			
Continuous	2.81 (2.17–3.65) < 0.001	2.08 (1.57–2.74) < 0.001	1.90 (1.41–2.54) < 0.001
T1 (≤ 8.641886; *N* = 223)	ref	ref	ref
T2 (> 8.641886, ≤ 9.11493; *N* = 268)	1.55 (0.93–2.58) 0.092	1.27 (0.76–2.12) 0.371	1.27 (0.75–2.15) 0.375
T3 (> 9.11493, *N* = 273)	2.83 (1.77–4.53) < 0.001	1.87 (1.15–3.03) 0.011	1.59 (1.00-2.62) 0.05
P for trend	< 0.001	0.006	0.062
SHR			
Continuous	4.04 (3.05–5.35) < 0.001	3.18 (2.19–4.62) < 0.001	2.63 (1.78–3.89) < 0.001
T1 (≤ 0.864655; *N* = 216)	ref	ref	ref
T2 (> 0.864655, ≤ 1.092257; *N* = 272)	1.24 (0.75–2.05) 0.405	1.19 (0.72–1.98) 0.500	1.30 (0.78–2.19) 0.318
T3 (> 1.092257, *N* = 276)	2.59 (1.65–4.08) < 0.001	1.64 (1.02–2.62) 0.040	1.67 (1.03–2.70) 0.036
P for trend	< 0.001	0.028	0.031
Combined			
T1 (Low TyG and low SHR; *N* = 348)	ref	ref	ref
T2 (Low TyG and high SHR; *N* = 143)	1.65 (0.99–2.72) 0.052	1.21 (0.73–2.02) 0.460	1.27 (0.76–2.13) 0.367
T3 (High TyG and low SHR, *N* = 140)	1.55 (0.93–2.58) < 0.091	1.34 (0.80–2.24) 0.262	1.18 (0.69–2.03) 0.544
T4 (High TyG and high SHR *N* = 133)	3.84 (2.52–5.86) < 0.001	2.08 (1.33–3.27) 0.001	1.72 (1.08–2.72) 0.021
P for trend	< 0.001	0.002	0.030

Model 1: Cardiomyopathy, CHD, AMI, ARF, AKF, HR, RR

Model 2: Cardiomyopathy, CHD, AMI, ARF, AKF, HR, RR, SOFA score, AST, WBC, Creatinine, BUN, Potassium, Calcium, Lactate, chloride, LDL, MV, Glucocorticoids

results demonstrated that elevated SHR was stably associated with increased 360-day mortality among septic patients with in-hospital NOAF ($p = 0.039$).

The TyG index-SHR combination and 360-day mortality risks among septic patients with NOAF

After adjusted potential confounding factors, patients with both a high TyG index and high SHR (quartile T4) exhibited a significantly higher risk of 360-day mortality in sepsis patients with NOAF (HR, 1.72; 95% CI 1.08–2.72) when compared with those with low levels (Table 3). Similar relationships were detected in terms of 90-day mortality and in-hospital mortality (Supplementary Tables 3 and Supplementary Table 4). The K-M analysis demonstrated patients in T4 group had higher mortality risks during the period of follow up (Fig. 3C, F, I). Then, the TyG index -SHR combination was divide into two groups: T2 group with TyG > 9.11493 and SHR > 1.092257, and T1 group with the remaining individuals. The baseline characteristics after IPTW-adjusted have been listed in Supplementary Table 9. The result of IPTW also showed that individuals with both high TyG and high SHR had a higher risk of 360-day mortality (HR, 2.31; 95% CI 1.43–3.72, $p < 0.001$).

ROC curve analysis of TyG, SHR and the TyG index-SHR combination

Comparison of predictive power of the TyG Index, SHR, and TyG index-SHR combination for 360-day mortality risk in sepsis patients occurring NOAF was shown in Fig. 5 and Supplementary Table 10. The TyG index-SHR combination had the highest predictive efficacy (AUC: 0.696, 95% CI 0.641–0.743), followed by TyG index (AUC: 0.662, 95% CI 0.616–0.714). Furthermore, whether the TyG index-SHR combination would further increase the predictive ability of the basic model (include confounding factors in adjusted model 2). The results showed significant incremental predictive ability of the TyG index-SHR combination to the basic risk model (0.844 vs. 0.829, $p = 0.04$) (Fig. 5C and Supplementary Table 11). Calibration curves were generated to evaluate how well the predicted probabilities match the observed outcomes. The result indicates that both models have good predictive probabilities (Fig. 5D and E). The results of DCA demonstrated that incorporating TyG and SHR into the basic model could enhance its utility (Fig. 5F).

Machine learning-based models predicting the mortality risks

Lasso regression was applied to identify and retain important features that contribute significantly to the prediction model. The variation characteristics of the coefficient of these variables were shown in Supplementary Fig. 2. The final variables selected via Lasso regression encompassed TyG, SHR, age, CHF, hypertension, CKD, cardiomyopathy, CHD, AMI, AKF, diabetes, platelet, hemoglobin, BUN, ALT, sodium, potassium, MBP, RR, Tm, SOFA score, lactate, TC, LDL, chloride, the utility of glucocorticoids and MV. The dataset was divided into a training set and a validation set in a 7:3 ratio. The filtered variables were analyzed using RF, XGBoost, and SVM models to predict the 360-day mortality risk. The

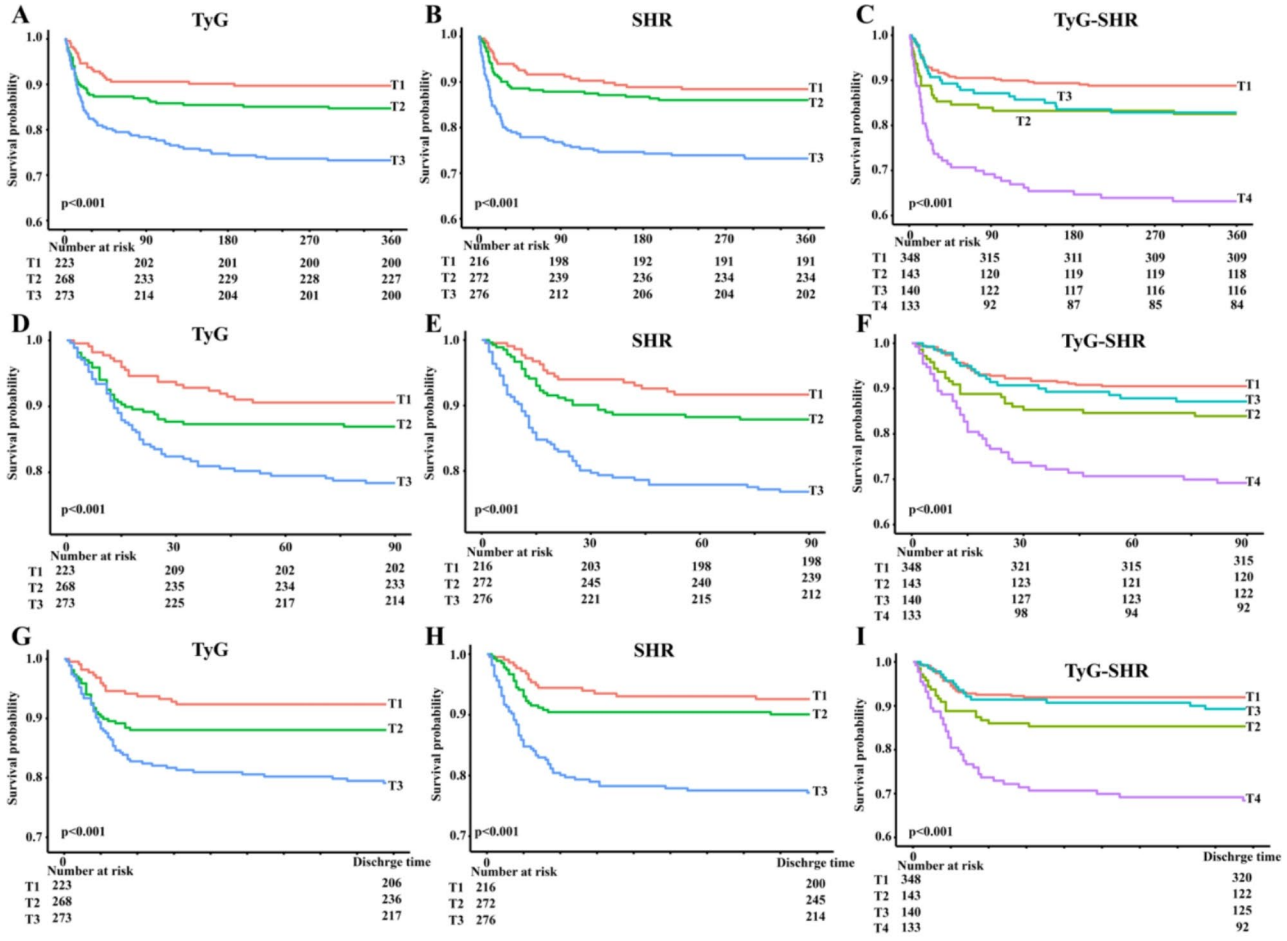


Fig. 3 K–M survival analysis curves for mortality risks in in septic patients with in-hospital NOAF. **A**–**C**. The TyG index, SHR and the TyG index-SHR combination for 360-day mortality risks; **D**–**F**. The TyG index, SHR and the TyG index-SHR combination for 90-day mortality risks; **G**–**I**. The TyG index, SHR and the TyG index-SHR combination for in-hospital mortality risks

RF model demonstrated the highest AUC (0.807), outperforming XGBoost (0.794) and SVM (0.789) (Fig. 6A). Further analysis with RF model evaluated the predictive power of other included variables + TyG or SHR. The results showed that the combined TyG and SHR model possessed superior predictive ability (Fig. 6B and C). Calibration curves (Fig. 6D–F) and DCA (Supplementary Fig. 3) confirmed that the RF model incorporating both TyG and SHR offered superior predictive accuracy and clinical utility, while models using TyG or SHR alone deviated noticeably from the diagonal line.

Discussion

In this study, we investigated the predictive capacity of the TyG index and SHR, both individually and in combination, for assessing incidence and 360-day mortality risk of in-hospital NOAF among patients with sepsis. The results found that elevated the TyG index and SHR were associated with a higher risk of incidence of in-hospital NOAF among patients with sepsis. The study suggested patients with concurrent elevations in both TyG and SHR at the highest risk of NOAF incidence. However, the individual and combined predictive power of TyG index, SHR and their combination for NOAF incidence during hospitalization was limited. Furthermore, our findings showed a positive association between the TyG index, SHR, and 360-day mortality in septic patients with NOAF, with higher levels correlating with increased mortality risks. Patients with concurrent elevations in both indices were significantly associated with the highest risk of 360-day mortality. Notably, the predictive power of the TyG index-SHR combination for 360-day mortality was superior to that of the TyG index or SHR alone. The integration of machine learning models, particularly the RF approach, further substantiated our conclusions.

As mentioned, TyG index reflects IR during the metabolic process. Several investigations suggested that TyG index was a reliable risk predictor of all-cause mortality in ICU patients and critically ill stroke [11, 26]. A retrospective study showed a correlation between TyG

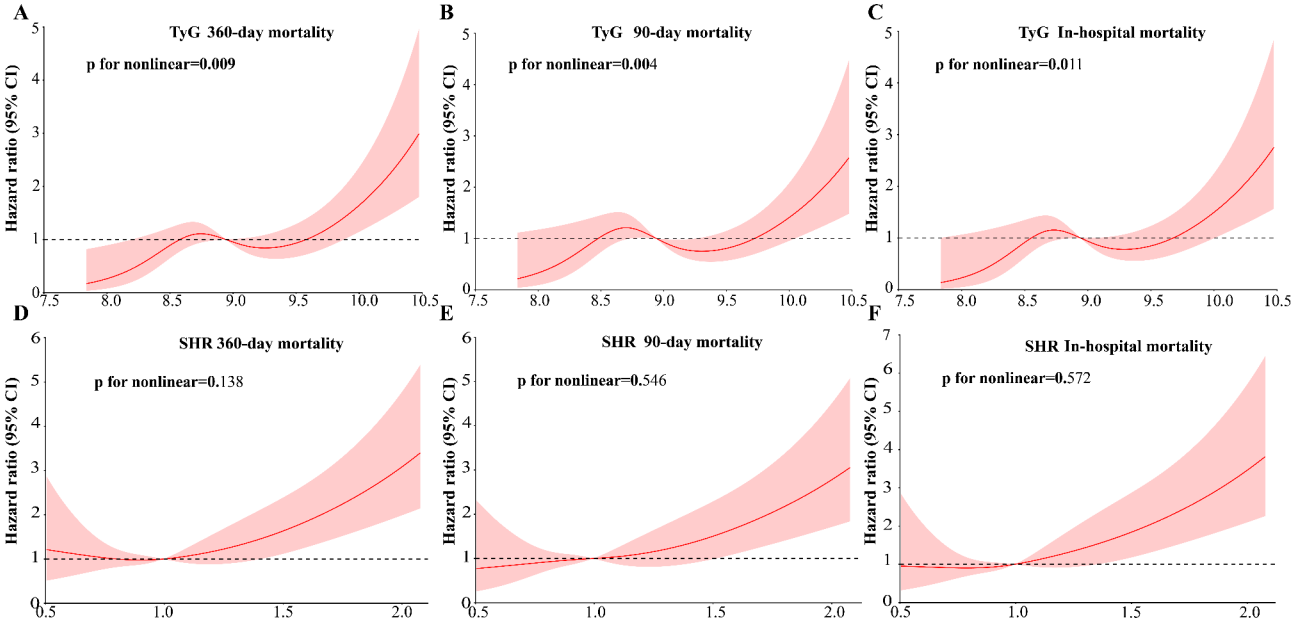


Fig. 4 **A**–**C** RCS analysis of the TyG index for 360-day mortality, 90-day mortality and in-hospital mortality in septic patients with in-hospital NOAF; **D**–**E** RCS analysis of SHR for 360-day mortality, 90-day mortality and in-hospital mortality in septic patients with in-hospital NOAF

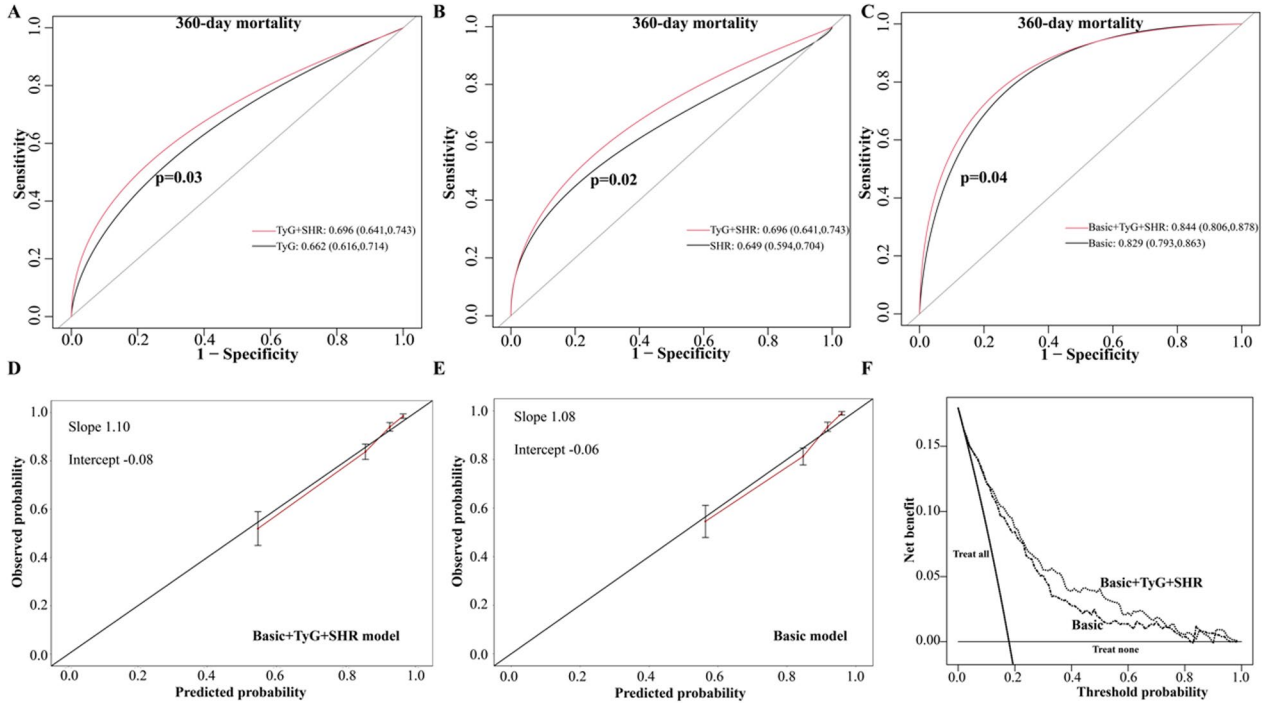


Fig. 5 **A** The ROC curves of the TyG index-SHR combination vs. the TyG index as a marker to predict 360-day mortality risks in sepsis patients with NOAF; **B** The ROC curves of the TyG index-SHR combination vs. SHR as a marker to predict 360-day mortality risks in sepsis patients with NOAF; **C** The ROC curves of basic risk model vs. + the TyG index-SHR combination to predict 360-day mortality risks. **D** Calibration curves of basic + TyG + SHR model; **E** Calibration curves of basic risk model; **F** DCA of basic risk model vs. + the TyG index-SHR combination

index and the mortality of sepsis [27], which supplemented the correlation between the TyG index and the poor prognosis of critically ill diseases. Among populations without known cardiovascular disease, U-shaped association between the TyG index and AF incidence was founded [14]. Among non-diabetic hospitalized patients, increased TyG index was closely associated with AF incidence [13]. Importantly, our study newly evaluated the

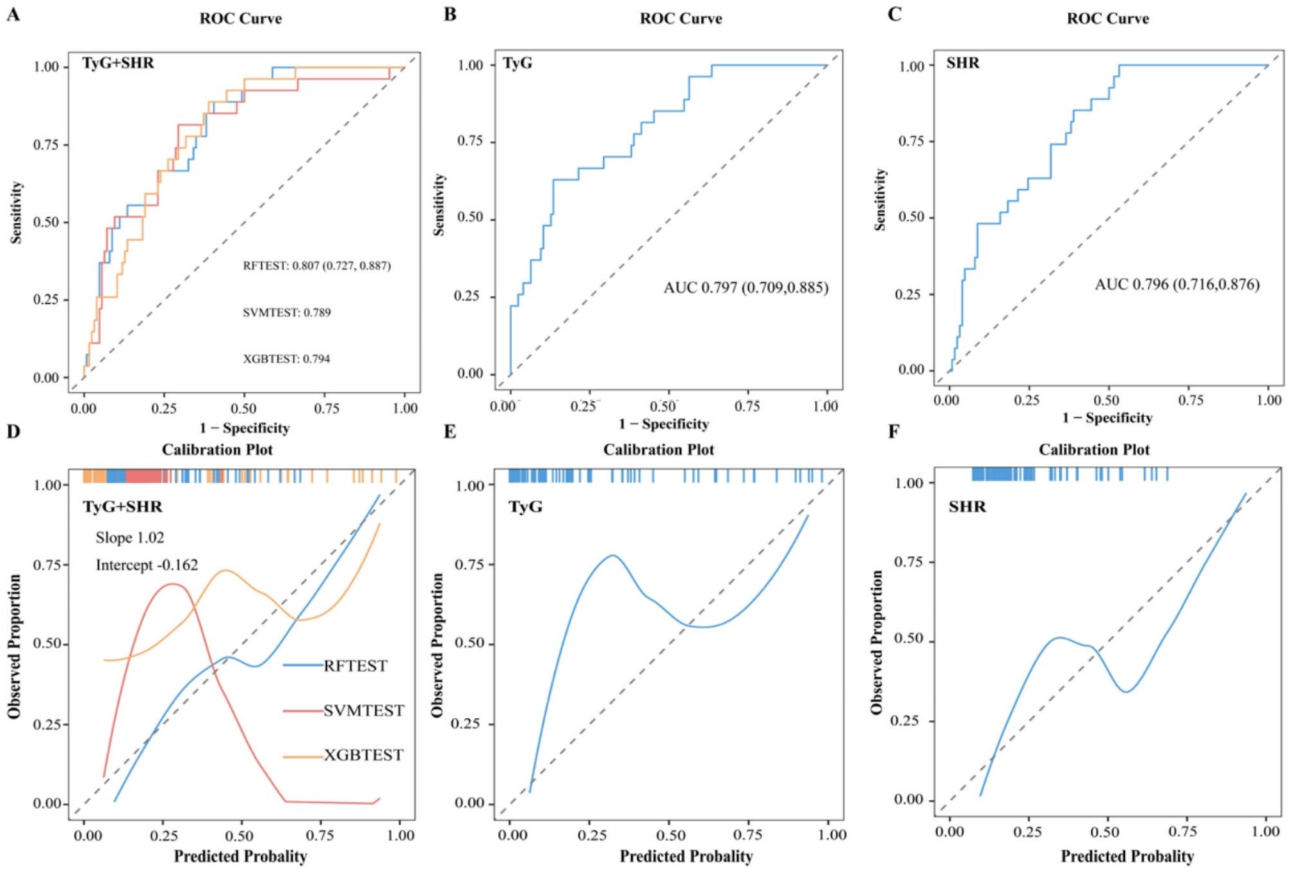


Fig. 6 **A** The ROC curves for RF, XGBoost, and SVM models incorporating other selected variables, TyG and SHR; **B** The ROC curves for RF model incorporating other selected variables and TyG; **C** The ROC curves for RF model incorporating other selected variables and SHR; **D** Calibration curves for RF, XGBoost, and SVM models incorporating other selected variables, TyG and SHR; **E** Calibration curve for RF model incorporating other selected variables and TyG; **F** Calibration curve for RF model incorporating other selected variables and SHR

predicative power of the TyG index for incidence and mortality risks of NOAF during sepsis. According to our results, the TyG index was closely associated with the incidence of NOAF during sepsis. Furthermore, the TyG index was an independent risk factor of 360-day mortality among septic patients with NOAF. However, when treated as a categorical variable, the TyG index did not exhibit significant associations with in-hospital and 90-day mortality. Firstly, the RCS analysis revealed the relationship between the TyG index and mortality outcomes was nonlinear, displaying a complex pattern. In the T3 group, higher TyG levels initially appeared to correlate with a reduction in mortality risk, but beyond a certain threshold, the risk increased. Categorizing TyG could mask these non-liner relationships, resulting in a lack of statistical significance in mortality outcomes. More importantly, the TyG index primarily reflects chronic metabolic dysfunction and IR, which were associated with long-term cardiovascular and metabolic risks [28]. In the acute phase and short-term of sepsis, acute stress response may overshadow the effects of chronic conditions, leading to a diminished role of the TyG index when categorized.

The positive association between the TyG index and NOAF may be due to IR. A state of IR could induce a condition termed "cardiac lipotoxicity", which means an over-accumulation of lipids in cardiomyocytes. Cardiac lipotoxicity triggers dysfunction and apoptosis of cardiomyocytes, and impaired myocardial metabolism, followed by functional and structural changes in cardiomyocytes, thereby inducing the incidence of AF [29]. Elevated TyG levels reflected significant metabolic dysfunction characterized by disrupted glucose and lipid metabolism. In the context of sepsis, this dysregulation could exacerbate inflammatory response, leading to endothelial dysfunction and increased vascular permeability [30, 31]. This dysfunction could lead to complications such as acute respiratory distress syndrome and renal failure, ultimately increasing mortality risk [2]. In the presence of NOAF, the combination of metabolic derangements and arrhythmias intensifies cardiovascular stress, further elevating mortality risks. In addition, IR was commonly accompanied by chronic inflammatory

response [32]. In a setting where sepsis already triggers dysregulated inflammation, the additional inflammatory response linked to IR may predispose to life-threatening events. IR was also linked with autonomic dysregulation. Specifically, increased sympathetic nervous system activity and reduced parasympathetic tone have been observed in such metabolic states. This disturbance could lead to structural remodeling, including atrial fibrosis and hypertrophy, resulting in higher mortality risks [33, 34].

SHR often is regarded as a novel index to assess stress-induced hyperglycemia regardless of past blood glucose levels and has been confirmed in the critical ill field to be a risk factor of patient's mortality. According to previous studies, patients with an elevated SHR were more likely to have a higher risk of 28-day mortality and in-hospital mortality in patients with sepsis [21]. The similar conclusion was drawn from two center retrospective cohort study [35]. Regarding cardiovascular diseases, a significant association between high SHR and long-term mortality was observed [19]. Among patients with AMI, elevated SHR was significantly associated with long- and short-term all-cause mortality [36]. In critically ill patients with AF, the mortality risks at 30-days, 90-days, 180-days and 365-days were significantly higher in the highest SHR group [37]. To our knowledge, it is the first study to evaluate the effects of SHR on NOAF during sepsis and mortality risk of septic patients with NOAF. Our findings exhibited elevated SHR was positively associated with higher incidence of NOAF in patients with sepsis and higher 360-day mortality risks among these patients, suggesting an adverse effects of increased SHR on cardiovascular complications of sepsis.

An elevated SHR serves as an indicator that the body's stress response remains unresolved, accompanied by the persistence of autonomic nervous dysfunction. During the process, sympathetic nervous system is overly activated and the parasympathetic nervous system is inhibited, resulting in shortened atrial action potential duration and accelerated depolarization. These electrophysiological modifications lead to a shortening of the atrial effective refractory period. As a result, the atrial tissue becomes more susceptible to local reentrant electrical activity, leading to the development of AF [38]. Moreover, the metabolic disruptions induced by sympathetic stimulation offer a setting propitious to the occurrence of AF [39]. Regarding all-cause mortality among septic patients with NOAF, an elevated SHR had a detrimental impact on cardiomyocyte function and myocardial energy generation. This not only exacerbates AF but also heightens the risk of death [40, 41]. Additionally, glycosylation end products can trigger fibrosis, causing an increase in atrial stiffness [42]. A higher SHR level induces an adrenergic response, which is linked to left atrial dilatation [43]. Significantly, the augmented atrial stiffness and left atrial remodeling are likely to lead to the progression of AF and an increase in mortality.

This is the first study to construct model to predict the mortality risks in septic patients with NOAF post-discharge. Our finding suggested patients with both an elevated the TyG index and elevated SHR exhibited a high risk of incidence and 360-day mortality risk of NOAF during sepsis. Notably, the predictive power of the TyG index-SHR combination for 360-day mortality was superior to that of the TyG index or SHR alone. Understanding the synergistic association of TyG and SHR help clinicians identify septic patients at a higher risk of developing NOAF and adverse outcomes. Elevated levels of the TyG index and SHR together indicates a state of both chronic and acute metabolic stress. This combination amplifies inflammatory signaling pathways, while the inflammation is a key driver of atrial remodeling and increases the incidence of life-threatening events [39]. Additionally, both IR and acute hyperglycemia are associated with heightened sympathetic nervous system activity, which contributing to increased heart rate and reduced heart rate variability, creating an electrophysiological environment conducive to AF and resulting in higher mortality risks [38]. The combined metabolic disturbances associated with high TyG and SHR levels can impair myocardial energy metabolism, contributing to increased myocardial oxygen demand and ischemia, known triggers for AF and adverse outcomes [40, 41].

This study still has several limitations. Firstly, it is a retrospective analysis from a single center, the observation bias and confounding bias were supposed to limit the generalizability of results. Secondly, confounding factors not included in the database may also affect the results. Therefore, we used multifaceted and rigorous statistical methods, and these analyses consistently yielded the same results, which strengthened the validity of our findings. Thirdly, due to the nature of the database, we were unable to ascertain specific causes of death. To enhance the reliability of our results, we adjusted a comprehensive range of confounding factors and applied IPTW to minimize biases and ensure the robustness of our conclusions. Fourthly, although our initial cohort included 4,276 patients, only 764 individuals were used for the analysis of mortality outcomes. This relatively small sample size limits the reliability and generalizability of the mortality predictions. Additionally, false discovery rate (FDR) correction was not applied in our analysis, which may increase the risk of type I errors. Finally, in patients with sepsis, glucose and TG levels could fluctuate significantly during hospitalization. The TyG index and SHR may vary throughout the course of illness. These temporal variations could influence the stability and predictive accuracy of these indices. Future studies should consider serial

measurements to better characterize the relationship between these metabolic indices and clinical outcomes in septic patients.

Conclusion

The TyG index and SHR were associated with the incidence of in-hospital NOAF during sepsis, although their individual and combined predictive powers were limited. Among septic patients with in-hospital NOAF, elevated levels of the TyG index and SHR were significantly associated with increased 360-day mortality risks, with their combination demonstrating superior predictive capability. Joint assessments of the TyG index and SHR could effectively identify individuals at high risks of mortality risk post- discharge, allowing clinicians to prioritize follow-up care and enhance patient management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02709-5.

Supplementary Material 1.

Author contributions

ZH.Z., ZJ.Z., W.X., Q.L., RZ. S., and T.W. contributed to the study conception and design, acquisition of the data, and analysis and interpretation of the.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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