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Inverse Association Between Triglyceride-Glucose Index and Ischemic Stroke in critically ill patients with Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia in critically ill patients and is associated with an increased risk of ischemic stroke (IS). The triglyceride–glucose (TyG) index, a simple surrogate for insulin resistance, has been linked to IS in general and diabetic populations, but its association with IS in critically ill patients with AF remains unclear.

Methods: In this retrospective cohort study, we used the Medical Information Mart for Intensive Care IV (MIMIC-IV) database as the internal cohort and the eICU Collaborative Research Database (eICU-CRD) for external validation. Logistic regression, restricted cubic splines (RCS), receiver operating characteristic (ROC)

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curves, least absolute shrinkage and selection operator (LASSO) regression, and subgroup analyses were applied.

Results: Among 1,295 patients, the proportion of IS was 48.72%. After full adjustment, each 1-unit increase in the TyG index was associated with a lower risk of IS (OR, 0.72; 95% CI, 0.58–0.88; $P = 0.002$). Compared with tertile 1, tertile 3 had a lower risk of IS (OR, 0.65; 95% CI, 0.46–0.92; $P = 0.016$). RCS showed a nearly linear relationship (P for nonlinearity = 0.427). The AUC for TyG alone was 0.603, which improved to 0.919 after incorporating LASSO-selected variables. External validation in the eICU-CRD (1,304 patients) reproduced the inverse association (tertile 3 vs. tertile 1: OR, 0.68; 95% CI, 0.48–0.96; $P = 0.027$; continuous: OR, 0.73; 95% CI, 0.59–0.90, $P = 0.003$). Subgroup analyses showed significant inverse associations in male patients, non-White patients, those aged <65 years, those with myocardial infarction, those without diabetes, and those with malignant cancer, with no significant interactions.

Conclusions: In critically ill patients with AF, a higher TyG index was independently associated with a lower risk of IS, and this inverse association was externally validated. The TyG index alone has limited predictive value, but it improves IS prediction when incorporated into a multi-variable model. Its prognostic value appears context-dependent and should be interpreted with caution in critically ill populations.

Keywords: Triglyceride–glucose index; Insulin resistance; Atrial fibrillation; Ischemic stroke; Critically ill; MIMIC-IV database; eICU-CRD database

Background

Atrial fibrillation (AF) is the most prevalent clinical arrhythmia globally, affecting approximately one in four adults during their lifetime. [1] The global prevalence of AF is estimated at 0.51% of the world's population. Over the past two decades, both the incidence and prevalence of AF have risen considerably, and this upward trend is projected to persist over the next three decades.[2]In the intensive care unit (ICU), the prevalence of AF exceeds one-sixth and its presence is associated with a significantly worse outcomes.[3,4] Stroke is recognized as one of the most serious sequelae of AF. AF is a major risk factor for ischemic stroke (IS), conferring a 5-fold increased risk of stroke and a 2-fold increased risk of mortality. [5]Furthermore, growing evidence supports a temporal relationship between AF and IS, particularly within the 30-day period following an AF episode.[6]Although the prevalence of stroke has declined with the use of antithrombotic therapy and left atrial appendage occlusion /exclusion[7], the burden of ischemic stroke attributable to atrial fibrillation remains substantial.

Insulin resistance (IR) is defined as a diminished biological response of target tissues (skeletal muscle, adipose tissue, and liver) to physiological insulin concentrations, leading to decreased insulin-mediated glucose disposal and metabolism.[8] IR constitutes the core pathophysiological basis for a broad spectrum of metabolic disturbances, including type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease. As a novel biomarker for the identification of IR, the triglyceride–glucose (TyG) index has been widely adopted owing to its computational simplicity and lower time and cost burden, and its predictive value is being extensively

investigated across diverse ethnic populations. [9,10]Furthermore, evidence suggests a linear dose–response relationship between the TyG index and the risk of IR.[11,12]

The TyG index is significantly associated with the incidence of various diseases; furthermore, in a large and homogeneous general population, TyG thresholds are predictive of increased mortality risk.[13] A meta-analysis found that AF patients had higher TyG index values than non-AF patients.[14] Shi W et al. reported that among patients with type 2 diabetes mellitus, a higher TyG index was associated with a higher prevalence of AF.[15] Studies have found that the recurrence rate of atrial fibrillation after radiofrequency ablation (RFCA) increases with higher TyG index levels .[16,17] Moreover, in critically ill patients with AF, an elevated TyG index was significantly linearly associated with increased all-cause mortality at 30, 90, and 365 days.[18,19] The relationship between the TyG index and IS has also been extensively studied. And two meta-analyses showed that a higher TyG index was significantly associated with an increased risk of IS.[20,21] Bian K et al. reported that in all glucose metabolism groups, higher TyG-related indices were associated with an increased risk of IS, and the strongest associations were observed in the prediabetes and normoglycemia groups.[22]Studies have demonstrated that elevated TyG index levels are associated with stroke recurrence in patients with IS.[23,24] Furthermore, the TyG index is significantly associated with all-cause mortality in both the hospital and ICU settings among critically ill patients with IS. [25,26]Despite these findings, evidence regarding the association between the TyG index and IS specifically in critically ill patients with AF remains limited.

Based on the current state of research, this study aims to investigate the relationship between the TyG index and IS in critically ill patients with AF using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. We aimed to evaluate the TyG index as a reliable, simplified prognostic marker in this population and to provide evidence for clinical decision-making in intensive care.

Materials and methods

Data source

This retrospective study utilized data from two critical care databases: the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1)[27] and the eICU Collaborative Research Database (eICU-CRD)[28]. The internal cohort was drawn from MIMIC-IV, a publicly accessible, single-center critical care database maintained by the Beth Israel Deaconess Medical Center (Boston, MA, USA). This database contains records for 300,000 individuals and 196,527 adult ICU admissions between 2008 and 2019. The first author (Weiping Wang) completed the Collaborative Institutional Training Initiative (CITI) program and obtained certification (Record ID 46543547) prior to data extraction. For external validation, we used the eICU-CRD, a multicenter ICU database developed by Philips Healthcare. It comprises more than 200,000 ICU admissions from 335 units across 208 hospitals in the United States between 2014 and 2015.

Study Design and Population

We included 12,276 patients with a first ICU admission for AF. AF and ischemic stroke (IS) were identified using codes from the International Classification of Diseases,

Ninth Revision (ICD-9) and Tenth Revision (ICD-10) (Supplemental Table 1). Exclusion criteria were: (1) multiple hospital admissions; (2) age <18 years; and (3) missing fasting serum triglyceride or glucose data on ICU day 1.

Data Collection

We extracted clinical data using Structured Query Language (SQL) queries in PostgreSQL (version 13.3). Variables included: (1) demographics and vital signs—age, sex, race, weight, heart rate, systolic blood pressure(SBP), diastolic blood pressure(DBP), mean blood pressure(MBP), respiratory rate(RR), and pulse oximetry-derived oxygen saturation; (2) comorbidities—myocardial infarction(MI), congestive heart failure(CHF), hypertension, diabetes, dementia, chronic obstructive pulmonary disease(COPD), cerebrovascular disease(CVD), paraplegia, renal disease, and malignancy; (3) initial laboratory parameters—hematocrit, hemoglobin, platelet count, white blood cell count(WBC), anion gap, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, sodium, potassium, creatinine, international normalized ratio(INR), blood glucose, and triglycerides; (4) treatments—continuous renal replacement therapy, vasoactive drugs, mechanical ventilation, aspirin, heparin, warfarin, clopidogrel, novel oral anticoagulants(NOAS), amiodarone, beta-blockers, statins, and insulin; and (5) illness severity scores—Acute Physiology Score III (APS III) and Oxford Acute Severity of Illness Score (OASIS). All laboratory parameters were recorded on the first day of the first ICU admission.

The triglyceride-glucose (TyG) index was calculated as: TyG index = ln [fasting TG (mg/dL) × fasting glucose (mg/dL) / 2].

Statistical Analysis

Patients with AF were divided into two groups according to the presence or absence of IS. Normally distributed continuous variables are presented as mean ± SD, and skewed continuous variables as median (interquartile range [IQR]). Categorical variables are presented as frequencies (%). Continuous variables were compared using the independent two-sample t-test, and categorical variables were compared using the chi-square or Fisher exact test, as appropriate.

The association between the TyG index and IS was evaluated using binary logistic regression models (odds ratio [OR] and 95% CI), with adjustment for major covariates. Confounders were selected on the basis of clinical interest, previous findings, or a change in the matched OR of more than 10% after addition to the model. Multicollinearity was assessed using the variance inflation factor (VIF), with a VIF ≥5 indicating the presence of multicollinearity (Supplementary Table 2). Four models were used to adjust for potential confounders: Model 1 was unadjusted; Model 2 additionally adjusted for age, sex, weight, race, hypertension, diabetes, myocardial infarction, congestive heart failure, malignant cancer, chronic obstructive pulmonary disease, and renal disease; Model 3 additionally adjusted for heart rate, mean arterial pressure, anion gap, international normalized ratio, creatinine, potassium, and sodium; and Model 4 additionally adjusted for heparin, aspirin, insulin, beta-blockers, statins, and amiodarone. Restricted cubic splines (RCS) were used to explore the dose–response relationship between the TyG index and IS. The predictive value of selected indicators for IS was evaluated using receiver operating characteristic (ROC) curves, with

variables selected by the least absolute shrinkage and selection operator (LASSO).

Subgroup analyses were performed to test for interactions, and forest plots were used to present adjusted ORs and 95% CIs. Subgroup analyses were conducted for age (<65 vs ≥65 years), sex, race, hypertension (yes vs no), diabetes (yes vs no), myocardial infarction (yes vs no), congestive heart failure (yes vs no), chronic obstructive pulmonary disease (yes vs no), malignant cancer (yes vs no), and renal disease (yes vs no).

All analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), Stata MP version 18 (StataCorp, College Station, TX, USA), and Free Statistics software (version 2.3, Beijing, China). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Study Participants

A total of 1,295 patients were included in this analysis, as shown in Figure 1. The proportion of IS was 48.72% (631/1,295). Table 1 (at the end of the article) presents the baseline characteristics of the groups stratified by the presence of IS in critically ill patients with AF. The mean (SD) age in the groups without and with IS was 70.8 (13.1) and 77.3 (10.9) years, respectively. Compared with participants without IS, those with IS had higher SBP, DBP, MBP, SpO_2, hematocrit, hemoglobin, platelet, calcium, chloride, and sodium levels, and lower weight, HR, RR, WBC, anion gap, bicarbonate, BUN, creatinine, INR, glucose, TG, APS III, and OASIS levels. Meanwhile, participants with IS had a lower prevalence of MI, CHF, diabetes, COPD, renal disease,

and malignant cancer, and a higher prevalence of hypertension, dementia, and paraplegia. Furthermore, participants with IS had higher usage rates of aspirin, warfarin, NOACs, beta-blockers, statins, and insulin, and lower usage rates of mechanical ventilation, RRT, heparin, clopidogrel, and amiodarone. Notably, participants with IS had lower TyG index levels compared with those without IS ($P < 0.01$).

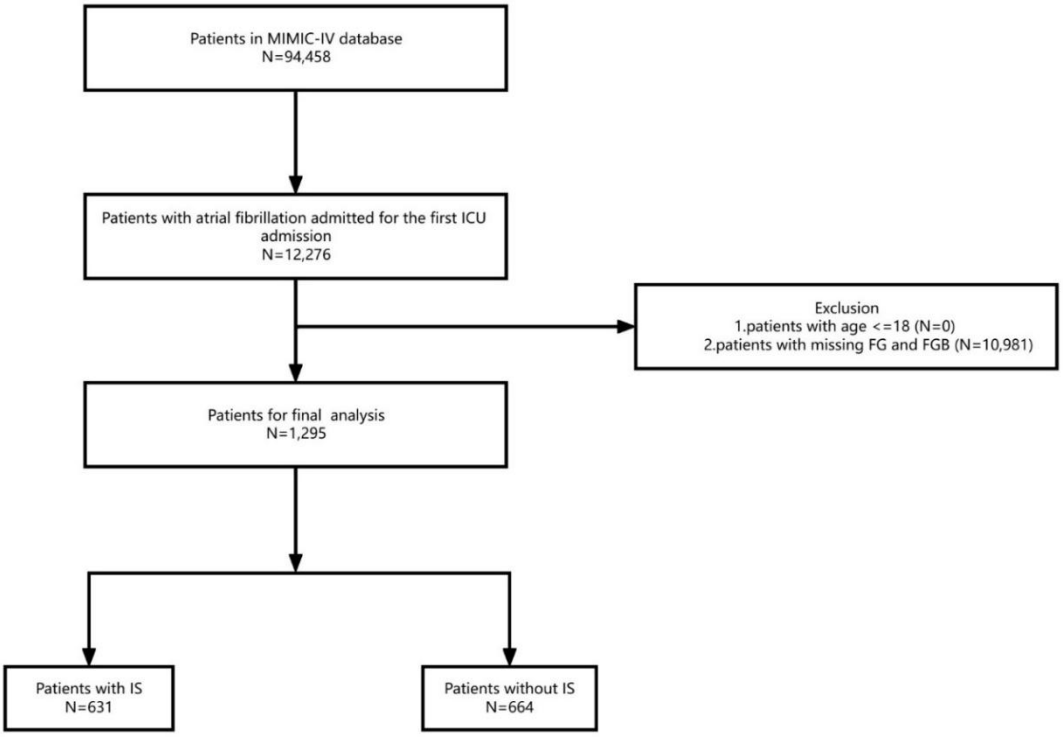


Figure 1 Flowchart of the study cohort.

Abbreviations: *MIMIC-IV*, Medical Information Mart for Intensive Care IV; *ICU*, Intensive Care Unit; *IS*, ischemic stroke.

Participants were stratified into tertiles according to the TyG index: T1 (⩽8.54, n = 432), T2 (8.54–9.09, n = 431), and T3 (>9.09, n = 432). The baseline characteristics of participants by TyG index tertile are presented in Supplementary Table 3. Compared with participants in T1, those in T3 had a greater proportion of males, a younger age, higher body weight, HR, WBC, anion gap, BUN, creatinine, glucose, triglyceride, APS III, and OASIS levels, as well as a higher prevalence of MI, diabetes, and renal disease,

but a lower prevalence of hypertension and IS (P < 0.001).

TyG and Risk of IS

From T1 to T3, the prevalence of IS showed a decreasing trend (Figure 2). A similar trend was observed in the eICU-CRD database (Supplemental Figure 1). We used logistic regression analysis to evaluate the association between the TyG index and the risk of IS (Table 2). As a continuous variable (per 1-unit increase), the TyG index was significantly associated with IS across all models: unadjusted (OR, 0.58; 95% CI, 0.49–0.68; *P* < 0.001) and fully adjusted (OR, 0.72; 95% CI, 0.58–0.88; *P* = 0.002). Similarly, as a categorical variable, compared with patients in tertile 1, those in tertile 3 had a significantly lower risk of IS in both the initial Model 1 (OR, 0.44; 95% CI, 0.33–0.58; *P* < 0.001) and the fully adjusted Model 4 (OR, 0.65; 95% CI, 0.46–0.92; *P* = 0.016). These findings indicate a declining trend in IS risk with higher TyG index levels. Moreover, RCS curves showed a nearly linear relationship between the TyG index and IS (*P* for nonlinearity = 0.427), as shown in Figure 3.

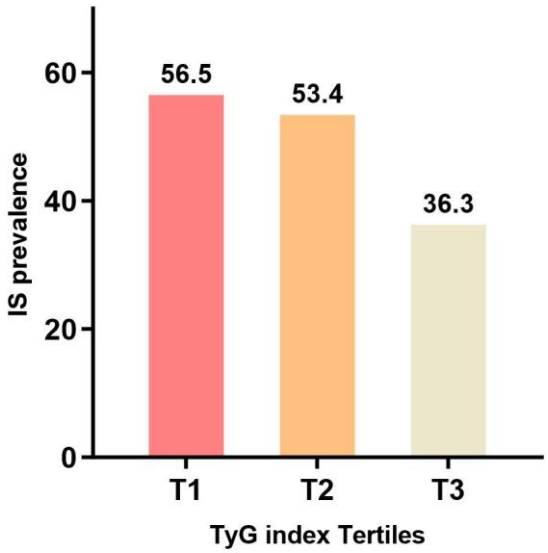


Figure 2 Prevalence of IS based on the tertiles of TyG index. Classification of TyG tertiles: T1

(≤ 8.54), T2 (8.54–9.09), T3 (≥ 9.09)

Abbreviations: *IS*, Ischemic stroke; *TyG index*, Triglyceride-glucose index; *T1*, tertile 1; *T2*, tertile 2; *T3*, tertile 3.

Table 2 Association of the Triglyceride-glucose index with risk of IS

TyG index	Model1		Model2		Model3		Model4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Per1unit increase	0.58 (0.49~0.68)	<0.001	0.68 (0.57~0.82)	<0.001	0.7 (0.58~0.86)	0.001	0.72 (0.58~0.88)	0.002
TyG tertiles								
T1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
T2	0.88 (0.67~1.15)	0.358	1 (0.75~1.34)	0.994	0.99 (0.73~1.34)	0.928	0.95 (0.69~1.3)	0.735
T3	0.44 (0.33~0.58)	<0.001	0.6 (0.44~0.83)	0.002	0.62 (0.44~0.87)	0.005	0.65 (0.46~0.92)	0.016
Trend test		<0.001		0.002		0.007		0.019

TyG index: T1 (TyG index ≤ 8.54), T2 (8.54< TyG index≤ 9.09), T3 (TyG index>9.09).

Abbreviations: *OR*: odds ratio; *CI*: confidential interval; *T1,* tertile 1; *T2,* tertile 2; *T3,* tertile 3.

Model 1: No adjusted

Model 2: adjusted for age, sex, weight, race, hypertension, diabetes, myocardial infarction, congestive heart failure, malignant cancer, chronic obstructive pulmonary disease and renal disease.

Model 3: adjusted for Model 2, heart rate, mean arterial pressure, anion gap, international normalized ratio, creatinine, potassium, and sodium.

Model 4: adjusted for Model 3, heparin, aspirin, insulin, beta-blockers, statins, and amiodarone.

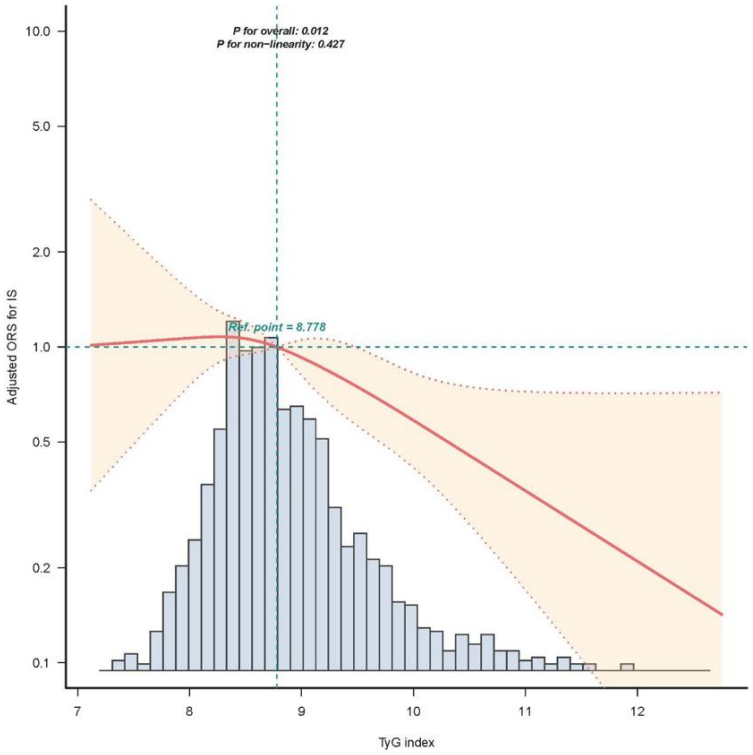


Figure 3 Potential nonlinear association between the TyG index and IS prevalence, assessed using restricted cubic spline regression with 4 knots. The red curve and dashed lines represent predicted values and 95% confidence intervals, respectively. adjustment factors include age, sex, weight, race, hypertension, diabetes, myocardial infarction, congestive heart failure, malignant cancer, chronic obstructive pulmonary disease, renal disease, heart rate, mean arterial pressure, anion gap,

international normalized ratio, creatinine, potassium, sodium, heparin, aspirin, insulin, beta-blockers, statins, and amiodarone.
Abbreviations: *IS*, ischemic stroke; *OR*, odds ratio; *TyG index*, triglyceride–glucose index.

Predictive Performance of the TyG Index

As shown in Figure 4, ROC analysis was performed to evaluate the predictive performance of the TyG index for IS. The AUC for TyG alone was 0.603 (95% CI, 0.572–0.633; $P < 0.001$). After incorporating variables selected by LASSO regression (including age, race, diastolic blood pressure, chloride, potassium, hypertension, cerebrovascular disease, paraplegia, Sepsis-3, aspirin, and statins), the predictive ability improved significantly, with an AUC of 0.919 (95% CI, 0.904–0.934; $P < 0.001$).

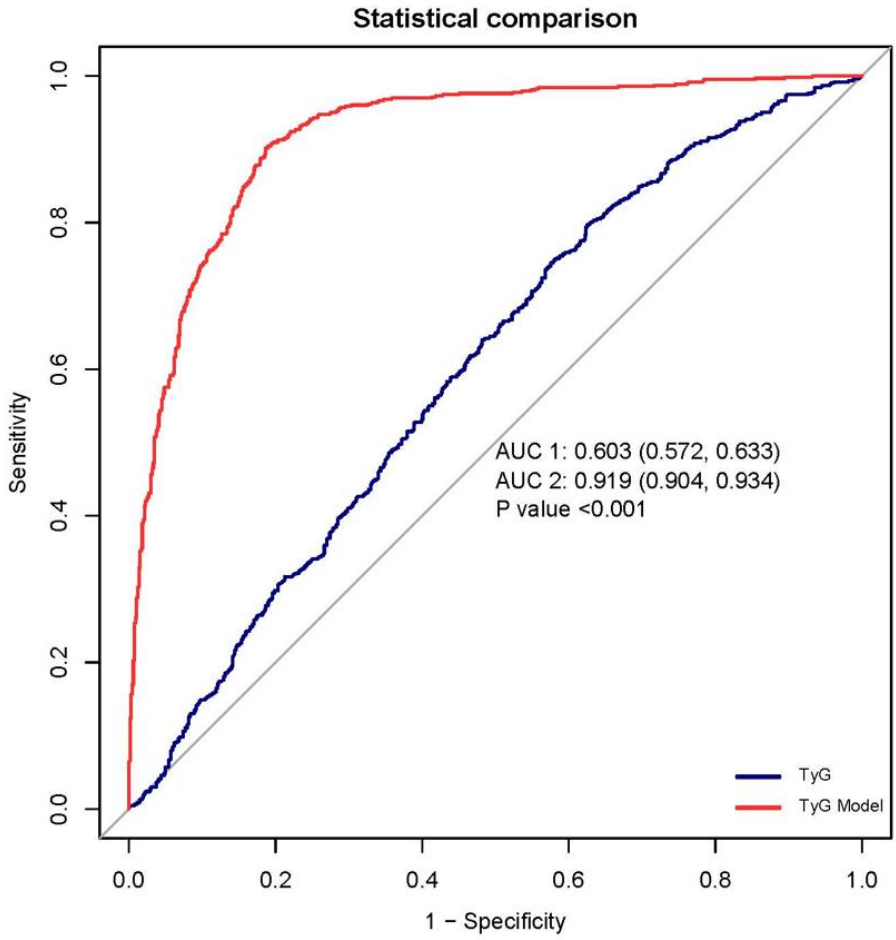


Figure 4 Receiver operating characteristic (ROC) curve analysis of the predictive power of the triglyceride–glucose (TyG) index for ischemic stroke (IS). The new model integrates risk factors selected by LASSO regression, including age, race, diastolic blood pressure, chloride, potassium,

hypertension, cerebrovascular disease, paraplegia, Sepsis-3, aspirin, and statins.
Abbreviations: *AUC*, area under the curve; *IS*, ischemic stroke; *LASSO*, least absolute shrinkage and selection operator; *ROC*, receiver operating characteristic; *TyG index*, triglyceride–glucose index.

External Validation

In the external validation using the eICU-CRD, 1,304 patients were included (Supplementary Figure 2). Compared with patients in tertile 1, those in tertile 3 had a lower risk of IS (T3 vs. T1: OR, 0.68; 95% CI, 0.48–0.96; *P* = 0.027; *P* for trend = 0.031). When modeled as a continuous variable (per 1-unit increase), a higher TyG index remained associated with a lower risk of IS (OR, 0.73; 95% CI, 0.59–0.90; *P* = 0.003), as shown in Table 3.

Table 3 Association of the Triglyceride-glucose index with risk of IS

TyG index	Model1		Model2		Model3		Model4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Per1unit increase	0.73 (0.59~0.9)	0.003	0.83 (0.66~1.05)	0.114	0.92 (0.72~1.18)	0.511	0.84 (0.65~1.09)	0.188
TyG tertiles								
T1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
T2	0.92 (0.67~1.27)	0.613	0.96 (0.68~1.35)	0.818	1.03 (0.72~1.48)	0.854	1 (0.69~1.44)	0.992
T3	0.68 (0.48~0.96)	0.027	0.85 (0.58~1.24)	0.395	1.04 (0.69~1.56)	0.855	0.94 (0.61~1.43)	0.757
Trend test		0.031		0.411		0.843		0.777

TyG index: T1 (TyG index ≤ 8.54), T2 (8.54< TyG index≤ 9.09, T3 (TyG index>9.09).
Abbreviations: *OR*: odds ratio; *CI*: confidential interval; *T1,* tertile 1; *T2,* tertile 2; *T3,* tertile 3.
Model 1: No adjusted
Model 2: adjusted for age, sex, weight, race, hypertension, diabetes, myocardial infarction, congestive heart failure, malignant cancer, chronic obstructive pulmonary disease and renal disease.
Model 3: adjusted for Model 2, heart rate, mean arterial pressure, anion gap, international normalized ratio, creatinine, potassium, and sodium.
Model 4: adjusted for Model 3, heparin, aspirin, insulin, beta-blockers, statins, and amiodarone.

Subgroup Analysis

Subgroup analyses were performed to evaluate the association between the TyG index and IS across various conditions. The TyG index was significantly associated with a lower risk of IS in the following subgroups: male patients (OR, 0.47; 95% CI, 0.28–0.81), non-White patients (OR, 0.45; 95% CI, 0.26–0.80), patients aged <65 years (OR, 0.31; 95% CI, 0.11–0.90), patients with myocardial infarction (OR, 0.34; 95% CI, 0.14–0.83), patients without diabetes (OR, 0.52; 95% CI, 0.34–0.80), and patients with

malignant cancer (OR, 0.64; 95% CI, 0.44–0.93) , as shown in Figure 5. No significant interactions were observed (all *P* for interaction > 0.05).

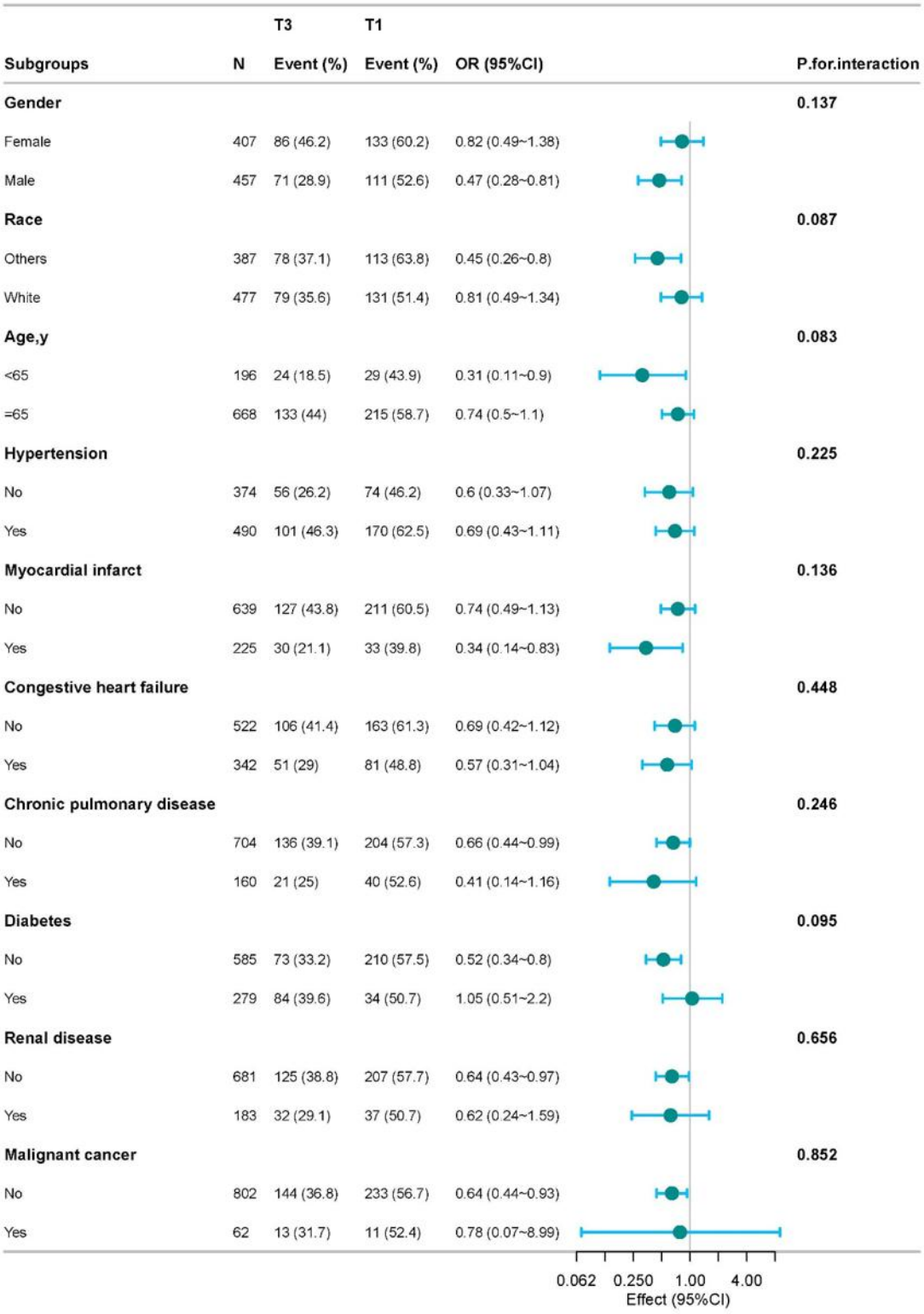


Figure 5 Subgroup analyses of the association between the TyG index (T3 vs. T1) and IS in critically

ill patients with AF. Models were adjusted for age, sex, weight, race, hypertension, diabetes, myocardial infarction, congestive heart failure, malignant cancer, chronic obstructive pulmonary disease, renal disease, heart rate, mean arterial pressure, anion gap, international normalized ratio, creatinine, potassium, sodium, heparin, aspirin, insulin, beta-blockers, statins, and amiodarone.
Abbreviations: *AF,* atrial fibrillation*; IS,* ischemic stroke*; T1,* tertile 1; *T3,* tertile 3; *TyG index,* triglyceride–glucose index.

Discussion

In this retrospective cohort study of critically ill patients with AF, a higher TyG index was independently associated with a lower risk of IS after adjustment for potential confounders. Restricted cubic spline analysis confirmed a nearly linear inverse relationship across the full range of TyG values, and external validation in the eICU-CRD reproduced this association. The consistency of these findings across two independent ICU databases strengthens the robustness of the observed inverse relationship. Our findings therefore raise important questions about the applicability of the TyG index as a prognostic marker in the specific context of critical illness complicated by AF.

The predictive performance of the TyG index was modest when used alone, with an AUC of 0.603. However, after incorporating variables selected by LASSO regression—including age, race, diastolic blood pressure, chloride, potassium, hypertension, cerebrovascular disease, paraplegia, Sepsis-3, aspirin, and statins—the predictive ability improved substantially (AUC, 0.919). This suggests that although the TyG index alone has limited discriminatory value, it contributes meaningfully to a multi-marker prediction model that integrates routine clinical and laboratory variables. Subgroup analyses showed that the inverse association was significant in male patients, non-White patients, those aged <65 years, those with myocardial infarction, those

without diabetes, and those with malignant cancer, with no significant interactions. These findings indicate that the association is consistent across several clinically relevant subgroups, although the absence of interaction should be interpreted with caution given the limited power of subgroup analyses.

The discrepancy between our results and those of prior studies may be explained by several factors unique to critical illness. First, the TyG index comprises fasting triglycerides and fasting plasma glucose, both of which fluctuate substantially in critical illness due to acute stress, fasting status, parenteral nutrition, and vasoactive medications, potentially distorting the relationship with true insulin resistance.[29–31] Second, a lower TyG index in this population may reflect malnutrition, cachexia, or severe systemic illness rather than favorable metabolic health. In critically ill patients, low triglyceride and glucose levels may accompany hepatic dysfunction, poor nutritional reserve, or prolonged fasting—conditions that are themselves associated with worse outcomes, including ischemic stroke. This phenomenon, sometimes described as "reverse epidemiology," has been observed for other metabolic markers (such as lipid levels, body mass index, hemoglobin glycation index, adiponectin biology et al.) in ICU populations. [32–39]Third, reverse causation cannot be excluded: the systemic inflammatory response and hemodynamic instability of critical illness may alter glucose and lipid metabolism in ways that lower the TyG index in patients who are more severely ill and therefore at higher risk of stroke.[40–43] Finally, despite adjustment for available confounders, residual confounding by unmeasured factors—such as the use of anticoagulants, lipid-lowering agents, and vasopressors—may have

contributed to the observed inverse association.

Our findings align with a recent study reporting an inverse association between the TyG index and IS in hospitalized patients with COPD and AF, suggesting that in specific high-risk, inflammation-driven populations, the conventional positive relationship may be attenuated or reversed.[44] In contrast, other studies in critically ill patients with stroke have reported a positive linear association between the TyG index and all-cause mortality, [45,46]although those cohorts were not restricted to patients with AF and focused on mortality rather than incident IS. However, a real-world retrospective cohort found no independent association between the TyG index and IS occurrence or recurrence, and despite a more adverse lipid profile in paroxysmal AF, this did not translate into a greater cerebrovascular burden. [47]Moreover, Huang et al. found that in the general population, estimated glucose disposal rate was inversely associated with the incidence of myocardial infarction, heart failure, atrial fibrillation, and ischemic stroke, and in clinical practice, eGDR may serve as a more valuable predictor of CVD events than TyG and other insulin resistance–related indices.[48] Collectively, these divergent findings underscore that the prognostic value of the TyG index is context-dependent.

From a clinical perspective, our findings suggest that the TyG index should be interpreted with caution as a prognostic marker in critically ill patients with AF. Although the TyG index alone has modest discriminatory ability, its inclusion in a multi-variable model significantly improves IS prediction. Clinicians should consider the patient's nutritional status, severity of illness, and concurrent metabolic

derangements when using this index for risk stratification. The TyG index may not perform uniformly across different ICU subpopulations, and its prognostic value appears to be context-dependent.

This study has several limitations. First, its retrospective design and reliance on the MIMIC-IV and eICU-CRD databases limit generalizability to other ICU populations. Second, the TyG index was calculated from a single measurement at ICU admission, which may not reflect dynamic changes in metabolic status during the ICU stay. Third, although we adjusted for a broad range of covariates and performed external validation, unmeasured confounding cannot be fully excluded. Fourth, the study was conducted in a specific high-risk population (critically ill patients with AF), and the findings should not be extrapolated to other patient groups. Prospective studies with serial metabolic measurements and broader validation are warranted to confirm our findings and to clarify the mechanisms underlying the inverse association observed in this population.

Conclusions

In critically ill patients with AF, a higher TyG index was independently associated with a lower risk of IS, and this inverse association was reproduced in an external cohort. Although the TyG index alone had limited predictive value, its inclusion in a multivariable model substantially improved IS prediction. These findings suggest that the prognostic value of the TyG index is context-dependent and should be interpreted with caution in critically ill populations.

Abbreviations

AF	atrial fibrillation
APS III	Acute Physiology Score III
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	confidence interval
CITI	Collaborative Institutional Training Initiative
COPD	chronic obstructive pulmonary disease
CVD	cerebrovascular disease
DBP	diastolic blood pressure
eGDR	estimated glucose disposal rate
eICU-CRD	eICU Collaborative Research Database
FPG	fasting plasma glucose
HR	hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
ICU	intensive care unit
INR	international normalized ratio
IQR	interquartile range

IR	insulin resistance
IS	ischemic stroke
LASSO	least absolute shrinkage and selection operator
MBP	mean blood pressure
MI	myocardial infarction
MIMIC-IV	Medical Information Mart for Intensive Care IV
NOACs	novel oral anticoagulants
OASIS	Oxford Acute Severity of Illness Score
OR	odds ratio
RCS	restricted cubic splines
ROC	receiver operating characteristic
RR	respiratory rate
RRT	renal replacement therapy
SBP	systolic blood pressure
SD	standard deviation
SpO_2	pulse oximetry-derived oxygen saturation
SQL	Structured Query Language
TG	triglycerides
TyG	triglyceride–glucose
VIF	variance inflation factor

WBC white blood cell

Supplementary Information

Supplementary Table 1. The meaning of ICD-9 and ICD-10 codes for ischemic stroke and atrial fibrillation.

Supplementary Table 2. The variance inflation factor (VIF) of variables.

Supplementary Table 3. Baseline characteristics of participants by the tertiles of TyG index.

Supplementary Figure 1. Prevalence of IS based on the tertiles of TyG index.

Supplementary Figure 2. Flowchart of the study cohort. in eICU-CRD database.

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Author contributions

WP.W. contributed to the study conception and design, data acquisition, statistical analysis, interpretation of data, and drafting of the manuscript. L.W., ZX. L, XB. L, CC.L performed data analysis and reviewed the manuscript. YJ. D. and HM. G. designed the study and reviewed the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version to be published.

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Data availability

The data analyzed in this study are available from the MIMIC-IV (version 3.1) and eICU-CRD databases via PhysioNet (https://physionet.org/). Access requires CITI certification and a data use agreement. The analysis code is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Data were obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1). The Institutional Review Board of the Beth Israel Deaconess Medical Center reviewed the collection of patient information and the creation of the research resource, and granted a waiver of informed consent and approval of the data-sharing initiative.

Consent for publication

Not applicable.

Competing interests

The authors have disclosed that they do not have any potential conflicts of interest.

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Table 1 Baseline characteristics of participants by IS

Characteristics	Total(n=1295)	Without IS(n=664)	IS(n=631)	P
Age, year, Mean ± SD	74.0 ± 12.5	70.8 ± 13.1	77.3 ± 10.9	< 0.001
Gender, Man, n (%)	681 (52.6)	396 (59.6)	285 (45.2)	< 0.001
Race, White, n (%)	714 (55.1)	392 (59)	322 (51)	0.004
Weight, Mean ± SD	83.8 ± 27.8	88.7 ± 31.1	78.7 ± 22.7	< 0.001
Vital signs				
Heart rate, Mean ± SD	105.8 ± 24.7	107.4 ± 25.6	104.1 ± 23.7	0.016
SBP, Mean ± SD	157.4 ± 25.0	150.9 ± 24.8	164.2 ± 23.3	< 0.001
DBP, Mean ± SD	97.9 ± 22.2	92.9 ± 21.5	103.1 ± 21.8	< 0.001
MBP, Mean ± SD	114.8 ± 25.0	111.6 ± 28.0	118.2 ± 20.9	< 0.001
RR, Mean ± SD	28.4 ± 6.1	28.7 ± 6.1	28.2 ± 6.2	0.144
Spo2, Mean ± SD	91.3 ± 6.3	90.7 ± 6.6	91.9 ± 5.9	< 0.001
Laboratory parameters				
Hematocrit, Mean ± SD	37.8 ± 6.3	37.1 ± 6.6	38.6 ± 5.8	< 0.001
Hemoglobin, Mean± SD	11.3 ± 2.3	10.9 ± 2.4	11.7 ± 2.2	< 0.001
Platelets, Mean ± SD	197.3 ± 86.2	193.1 ± 95.8	201.7 ± 74.7	0.072
WBC, Mean ± SD	13.0 ± 7.4	14.5 ± 9.1	11.4± 4.7	< 0.001
Anion gap, Mean ± SD	16.3 ± 4.8	16.9 ± 5.3	15.6 ± 4.1	< 0.001
Bicarbonate, Mean± SD	24.0 ± 3.9	24.2 ± 4.5	23.9 ± 3.1	0.176
BUN, Median (IQR)	22.0(16.0, 34.0)	26.0 (17.0, 43.0)	20.0(15.0, 28.0)	< 0.001
Calcium, Mean ± SD	8.4 ± 0.9	8.2 ± 1.0	8.6 ± 0.7	< 0.001
Chloride, Mean ± SD	101.7 ± 5.6	100.7 ± 6.1	102.7 ± 4.8	< 0.001
Creatinine, Median (IQR)	1.1 (0.8, 1.5)	1.1 (0.9, 2.0)	1.0 (0.8, 1.3)	< 0.001
Sodium, Mean ± SD	137.6 ± 4.8	136.8 ± 5.3	138.3 ± 4.2	< 0.001
Potassium, Mean± SD	3.9 ± 0.6	3.9 ± 0.6	3.9 ± 0.5	0.034
INR, Mean ± SD	1.6 ± 1.0	1.7 ± 1.2	1.4 ± 0.5	< 0.001
Glucose, Mean ± SD	150.8 ± 85.8	163.0 ± 105.4	138.0 ± 55.9	< 0.001
TG, Median (IQR)	98.0(74.0,144.0)	104.0(78.0,167.2)	92.0(70.0,129.0)	< 0.001
Scoring systems				
APS III, Mean ± SD	52.4 ± 27.6	58.8 ± 31.1	45.8 ± 21.3	<0.001
OASIS, Mean ± SD	36.1 ± 9.7	37.6 ± 10.4	34.6 ± 8.7	<0.001
Comorbidities, n (%)				
MI, n (%)	340(26.3)	232(34.9)	108(17.1)	< 0.001
CHF, n (%)	507 (39.2)	305 (45.9)	202 (32)	<0.001
Hypertension, n (%)	746 (57.6)	324 (48.8)	422 (66.9)	< 0.001
Diabetes, n (%)	395 (30.5)	211 (31.8)	184 (29.2)	0.307
Dementia, n (%)	104 (8.0)	43 (6.5)	61 (9.7)	0.035
COPD, n (%)	240 (18.5)	146 (22)	94 (14.9)	0.001
CVD, n (%)	790 (61.0)	188 (28.3)	602 (95.4)	< 0.001
Sepsis3, n (%)	589 (45.5)	382 (57.5)	207 (32.8)	< 0.001

Paraplegia, n (%)	472 (36.4)	71 (10.7)	401 (63.5)	<0.001
Renal disease, n (%)	268 (20.7)	156 (23.5)	112 (17.7)	0.011
Malignant cancer, n (%)	106 (8.2)	62 (9.3)	44 (7)	0.121
Treatment, n (%)				
Ventilation use, n (%)	1014 (78.3)	554 (83.4)	460 (72.9)	<0.001
RRT, n (%)	124 (9.6)	107 (16.1)	17 (2.7)	<0.001
Aspirin, n (%)	395 (30.5)	192 (28.9)	203 (32.2)	0.203
Heparin, n (%)	704 (54.4)	410 (61.7)	294 (46.6)	<0.001
Warfarin, n (%)	38 (2.9)	16 (2.4)	22 (3.5)	0.251
Clopidogrel, n (%)	75 (5.8)	42 (6.3)	33 (5.2)	0.399
NOACs, n (%)	39 (3.0)	19 (2.9)	20 (3.2)	0.746
Amiodarone, n (%)	100 (7.7)	77 (11.6)	23 (3.6)	<0.001
Beta blockers, n (%)	187 (14.4)	61 (9.2)	126 (20)	< 0.001
Statins, n (%)	470 (36.3)	211 (31.8)	259 (41)	<0.001
Insulin, n (%)	793 (61.2)	343 (51.7)	450 (71.3)	<0.001
TyG index, Mean± SD	8.9 ± 0.7	9.0 ± 0.8	8.8 ± 0.6	< 0.001

Continuous variables are presented as mean± SD if normally distributed and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%). Abbreviations: *IS*, Ischemic stroke; *SBP*, Systolic blood pressure; *DBP*, Diastolic blood pressure; *MBP*, Mean blood pressure; *RR*, Respiratory rate; *SpO_2*, Pulse oximetry-derived oxygen saturation; *WBC*, White blood cell count; *BUN*, Blood urea nitrogen; *INR*; International normalized ratio; *TG*, Triglycerides; *APS III*, Acute physiology score III; *OASIS*, Oxford acute severity of illness score; *MI*, Myocardial infarction; *CHF*, Congestive heart failure; *COPD*, Chronic obstructive pulmonary disease; *CVD*, Cerebrovascular disease; *RRT*, Renal replacement therapy; *NOACs*, Novel Oral anticoagulants; *TyG index*, Triglyceride-glucose index

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