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ORIGINAL RESEARCH

Inverse Association Between Triglyceride-Glucose Index and Ischemic Stroke in Hospitalized Patients with Chronic Obstructive Pulmonary Disease and Atrial Fibrillation: A Retrospective Analysis

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Purpose: Patients with chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) face elevated ischemic stroke (IS) risk. This study assessed the triglyceride-glucose (TyG) index as a metabolic marker for IS risk in this population.

Patients and Methods: This retrospective analysis included 710 hospitalized patients with COPD and AF (2014–2024). The TyG index (ln[fasting triglycerides (mg/dL)×fasting glucose (mg/dL)/2]) measured at admission was the exposure; new-onset IS occurring during the index hospitalization (median duration: 9 days, IQR: 6–13) was the outcome. Univariate and multivariate logistic regression (adjusting for age, sex, smoking, blood pressure, diabetes, lipids, prior stroke) identified associations. Nonlinearity was assessed using generalized additive models (GAM). Predictive performance was evaluated via ROC analysis (AUC).

Results: IS occurred in 32 patients (4.5%). Unexpectedly, and in contrast to findings in the general population, higher TyG index was associated with lower IS risk in univariate analysis (OR=0.49, 95% CI:0.26–0.94). After full adjustment, each unit increase in TyG index was associated with lower IS risk (aOR=0.24, 95% CI:0.10–0.57, *P*=0.001). However, the wide confidence interval and limited events (n=32) indicate this large effect estimate should be interpreted cautiously, as it may reflect statistical instability. The finding suggests a potential metabolic paradox in this population. GAM confirmed a linear inverse relationship after adjusting for stroke history (OR=0.50, 95% CI:0.30–0.90, P=0.032). The TyG index predicted IS with an AUC of 0.614 (95% CI:0.513–0.715).

Conclusion: Contrary to observations in the general population, in hospitalized COPD and AF patients, a higher TyG index was associated with lower short-term ischemic stroke risk. However, this inverse association could reflect either a true inverse metabolic relationship or reverse causality whereby low TyG marks disease severity (malnutrition, poor metabolic reserve, chronic inflammation). Lack of comprehensive disease severity and nutritional assessments limits causal inference. The TyG index may serve as a potential biomarker in hospitalized patients, but population-based studies are essential to address selection bias.

Keywords: triglyceride-glucose index, COPD, atrial fibrillation, ischemic stroke, predictive value

Introduction

Patients with chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) face significant health challenges. According to the Global Burden of Disease Study, the worldwide prevalence of COPD reached 174.5 million in 2019, with the number of cases increasing from 335.5 million in 2010 to 590 million in 2019.[1] In China, the prevalence of COPD is approximately 8.2% (12.4% in men and 5.1% in women), with projections indicating astable rate of 322.98–335.23 per 100,000 between 2020 and 2024.[2] AF is the most common cardiac arrhythmia, and its global prevalence increased markedly from 33.5 million in 2010 to 59 million in 2019.[1] The incidence of ischemic stroke

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(IS) is particularly high among patients with both COPD and AF. Studies show that approximately 7% of acute IS patients are diagnosed with AF within 3–5 days of onset, a proportion that can rise to 25% with prolonged monitoring.[3] In China, there are currently 13 million stroke patients, with IS accounting for the majority, according to national cardiovascular health reports.[4]

The triglyceride-glucose (TyG) index, a simple surrogate marker for insulin resistance calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2], has been widely used to assess cardiovascular risk.[5] The TyG index reflects insulin resistance and is involved in several pathophysiological processes, including endothelial dysfunction, inflammation, and the progression of atherosclerosis.[6] Recent studies have shown that the TyG index is closely associated with both the occurrence and prognosis of various cardiovascular diseases. It is also valuable in predicting diabetes, hypertension progression, and the risk of cardiovascular events.[5] Furthermore, the TyG index has emerged as an important metabolic risk marker in patients with obstructive sleep apnea syndrome.[7] The mechanistic link between insulin resistance (reflected by the TyG index) and ischemic stroke involves multiple pathways particularly relevant in COPD-AF patients. First, IR promotes endothelial dysfunction through impaired nitric oxide bioavailability and increased oxidative stress, compromising vascular integrity.[8,9] Second, IR induces a prothrombotic state via elevated plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and enhanced platelet reactivity.[10,11] Third, IR contributes to atrial structural and electrical remodeling, facilitating AF maintenance and left atrial thrombus formation.[12–14] Notably, chronic systemic inflammation represents a shared biological pathway in both COPD and AF, serving as a critical link between insulin resistance, oxidative stress, and cerebrovascular risk. In COPD patients, chronic systemic inflammation, oxidative stress, and hypoxemia further amplify these IR-mediated pathways, exacerbating endothelial dysfunction and the prothrombotic state.[15,16] Similarly, AF is associated with systemic inflammatory activation that contributes to atrial remodeling and blood stasis in the left atrial appendage, creating a high-risk substrate for cardioembolic stroke.[17,18] When COPD and AF coexist, these dual inflammatory stimuli create a synergistic amplification effect: the combined inflammatory burden intensifies IR-mediated pathways, enhances the prothrombotic state, and accelerates vascular damage.[19] The coexistence of COPD and AF thus represents a unique pathophysiological context where metabolic, inflammatory, and hemodynamic factors converge, potentially fundamentally altering the typical IR-stroke relationship observed in the general population. Understanding the TyG index-stroke association in this specific overlap population is therefore of both mechanistic and clinical importance.

While the application of the TyG index in cardiovascular disease has become well established, particularly for risk stratification and prognosis in AF patients,[20] research in respiratory diseases remains limited.[21] The metabolic mechanisms underlying the coexistence of COPD and cardiovascular diseases are not fully understood. Methodologically, the field has shifted from focusing on single metabolic indicators to the comprehensive assessment of composite indices such as TyG, and from cross-sectional to cohort study designs. However, investigations into the association between TyG index and stroke risk in patients with both COPD and AF are scarce. Mechanistic research on insulin resistance in respiratory disease is also limited, and there is a lack of integrated management strategies for patients with multiple comorbidities. Recent priority assessments highlight that inadequate integrated management for multimorbidity remains a major challenge in chronic disease care, underscoring the urgent need for targeted research to fill this knowledge gap.[22] Additionally, the mechanisms linking insulin resistance to arrhythmias are not fully elucidated, and the role of chronic systemic inflammation as a shared pathway requires further exploration.

In view of these research gaps, this study was designed as a retrospective cohort study to examine the relationship between the TyG index and IS risk in patients with both COPD and AF. This work is of significant clinical relevance: it addresses the lack of research at the intersection of respiratory and cardiovascular diseases, introduces a novel metabolic biomarker for IS risk stratification in this population, and offers evidence to guide personalized management strategies for these high-risk patients. The innovation of this study lies in (1) being the first to investigate the association between TyG index and IS in patients with both COPD and AF; (2) employing a multivariate, stepwise adjustment approach to systematically evaluate the influence of confounding factors; and (3) comprehensively assessing the predictive value of the TyG index using both continuous and categorical analyses. The results are expected to provide clinicians with a practical tool for identifying patients at high risk of IS among those with COPD and AF, thereby supporting the development of targeted preventive strategies.

Methods

Study Population

This retrospective cohort study included hospitalized patients with COPD and AF admitted to the Second Affiliated Hospital of Nanchang University from July 2014 to July 2024. Following a cohort design with clear temporal sequence, the TyG index (exposure variable) was measured within 24 hours of admission as the baseline assessment, and patients were then prospectively monitored for incident ischemic stroke events (outcome variable) during their subsequent hospital stay, ensuring that exposure measurement preceded outcome ascertainment. Patients were categorized based on the occurrence of new-onset IS during the index hospitalization: the IS group (n=32) and the non-IS group (n=678). To maintain cohort design integrity, patients presenting with stroke at admission were excluded from outcome assessment, as exposure must precede outcome in cohort studies. The hospitalization duration (follow-up period) was 9 days (median, IQR: 6–13 days) or 10.5 ± 6.2 days (mean ± SD). This design fundamentally differs from a cross-sectional study, which would measure exposure and outcome simultaneously at a single time point. A total of 710 patients met the inclusion criteria. Inclusion criteria were as follows: (1) aged 18 years or older; (2) confirmed diagnosis of COPD according to the Chinese guidelines for COPD management;[23] (3) confirmed diagnosis of AF based on standard 12-lead electrocardiogram or Holter monitoring; (4) complete initial fasting triglyceride and glucose test results obtained at admission or within 24 hours thereafter; and (5) complete medical records with essential clinical information for the study. Exclusion criteria included: (1) age <18 years; (2) incomplete medical records lacking critical clinical information; (3) missing data required for calculation of the TyG index (triglyceride or glucose) or outcome assessment; and (4) unclear or disputed diagnosis of COPD or AF. The diagnosis of IS was made in strict accordance with the Chinese guidelines for the management of acute ischemic stroke, requiring both radiological confirmation of acute ischemic lesions and corresponding neurological deficits.[24] All data were extracted from the hospital's electronic medical records in a structured format and independently verified by two trained researchers to ensure data completeness and accuracy.

Variables

The exposure variable was the TyG index, calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. Patients were divided into low and high TyG groups based on the median value. All biochemical measurements were obtained from fasting venous blood samples collected within 24 hours of admission. Analyses were performed using an automated biochemical analyzer (Roche Cobas 8000) with standardized reagent kits. The TyG index was recorded as a continuous variable in the database. For clinical applicability and to explore potential non-linear associations, it was also categorized into quartiles for stratified analysis. The outcome variable was the occurrence of incident (new-onset) ischemic stroke (IS) during the index hospitalization, defined as radiologically confirmed acute ischemic lesions accompanied by relevant neurological deficits that developed after TyG index measurement at admission. Only strokes with documented onset after admission were classified as events. The outcome was recorded as a binary variable (present/absent) in the database. Determination of IS was based on clinical evaluation, imaging studies (CT/MRI), and confirmation by a neurologist. As this was a retrospective study, outcome classification relied on existing medical records and was not blinded.

Covariates included demographic characteristics (age, sex), lifestyle factors (smoking status, alcohol consumption), comorbidities (hypertension, diabetes, coronary artery disease, prior stroke), and laboratory parameters: white blood cell count, red blood cell count, neutrophils, lymphocytes, platelets, hemoglobin, creatinine, uric acid, estimated glomerular filtration rate, total bilirubin, albumin, activated partial thromboplastin time, prothrombin time, international normalized ratio, fibrinogen, and D-dimer. All laboratory values were from the first measurement during hospitalization. These covariates were selected based on previous literature identifying them as risk factors or potential confounders for ischemic stroke,[25–27] to ensure the accuracy and reliability of the statistical models. Missing data were minimal, with < 2% missing for key variables (exposure and outcome) and <5% for covariates. Multiple imputation was performed to handle missing values, generating five imputed datasets to ensure the robustness of the analyses.

Ethic Statement

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (approval number: 2023-KY-74) and conducted in accordance with the Declaration of Helsinki and relevant national guidelines for biomedical research involving human subjects. As a retrospective cohort study, all patient data were anonymized during extraction and analysis, with all identifying information removed to ensure privacy and data security. Due to the retrospective nature of the study and the anonymization of data, the ethics committee granted a waiver of informed consent. Data collection, storage, and use strictly followed the hospital's information security protocols and were limited exclusively to research purposes; no data were used for commercial ends. All research personnel signed confidentiality agreements and committed to upholding patient privacy and data security. The publication of study findings will adhere strictly to the principles of academic integrity, ensuring the authenticity and reliability of all reported data.

Statistical Analysis

Data were analyzed using R software (version 4.2.0; The R Foundation, http://www.rproject.org) and EmpowerStats (www.empowerstats.net, XY Solutions, Inc., Boston, MA). Continuous variables were presented as mean ± standard deviation for normally distributed data or as median (interquartile range) for skewed data. Normality was assessed using the Shapiro–Wilk test. Categorical variables were expressed as counts and percentages. Between-group comparisons were performed using the independent samples *t*-test (for normally distributed data), the Mann–Whitney *U*-test (for skewed data), or the chi-square test (for categorical variables). Univariate logistic regression was first conducted to assess the association of each variable, including the TyG index and all covariates, with ischemic stroke. Covariates were selected for multivariable adjustment based on univariate analysis results and clinical relevance as established by the literature. Three progressive multivariable logistic regression models were constructed: Model 1 was unadjusted (TyG index only); Model 2 adjusted for socio-demographic variables; and Model 3 further adjusted for additional covariates listed in Table 1. This stepwise approach was used to evaluate the robustness of the TyG index's effect under different levels of confounder control. To assess the stability of the findings, the TyG index was analyzed both as a continuous variable and as a dichotomous variable (high vs low, using the median as the cutoff), with regression analyses repeated for each. Generalized additive models (GAM) with penalized spline fitting were used to examine possible nonlinear associations between the TyG index and ischemic stroke. Receiver operating characteristic (ROC) curve analysis was then conducted to evaluate the predictive performance of the TyG index for ischemic stroke, calculating the area under the curve (AUC), sensitivity, specificity, and 95% confidence intervals. The optimal cutoff value was determined using the Youden index. Sensitivity analyses were performed to test robustness by: (1) excluding patients with prior stroke; (2) excluding extreme TyG values (top and bottom 5%); and (3) repeating analyses using complete cases only. Due to limited stroke events in the diabetes subgroup (9 events among 158 patients), diabetes-stratified analysis would yield statistically unstable estimates and was not performed. All statistical tests were two-sided, and a P-value ¡0.05 was considered statistically significant.

Results

Baseline Characteristics

The study population comprised 710 participants, with 32 patients (4.5%) experiencing ischemic stroke during follow-up. Baseline characteristics were comparable between the IS and non-IS groups for most parameters (Table 1). Mean age was similar between groups (76.50±8.18 vs 78.11±8.05 years, P=0.270). Although the IS group had a higher proportion of males (87.50% vs 73.01%), this difference was not statistically significant (P=0.069). Traditional cardiovascular risk factors including smoking, alcohol consumption, hypertension, and diabetes mellitus showed no significant differences between groups (all $P < 0.05$). Comprehensive laboratory assessments revealed no significant differences between groups across hematological parameters, renal function markers, liver function tests, coagulation parameters, and lipid profiles. While total cholesterol was numerically higher in the IS group (4.04 vs 3.64 mmol/L, P=0.151) and triglycerides were lower (0.78 vs 0.92 mmol/L, P=0.060), these differences did not achieve statistical significance. Two parameters demonstrated significant associations with ischemic stroke. The TYG index was significantly lower in the IS group

Table 1 Patient Characteristics by Group

Characteristic	Non-IS Group (n=678)	IS Group (n=32)	P-value
Age (years), mean ± SD	78.11 ± 8.05	76.50 ± 8.18	0.270
Male sex, n (%)	495 (73.01)	28 (87.50)	0.069
WBC (×109/L), median (IQR)	6.36 (4.91–8.24)	5.94 (4.71–8.04)	0.677
RBC (×1012/L), mean ± SD	4.25 ± 1.55	4.48 ± 1.22	0.403
Neutrophils (×109/L), median (IQR)	4.68 (3.44–6.85)	4.55 (3.82–7.67)	0.480
Lymphocytes (×109/L), median (IQR)	0.98 (0.64–1.39)	0.96 (0.60–1.23)	0.504
Platelets (×109/L), median (IQR)	160.00 (124.00–208.00)	160.00 (132.75–185.75)	0.786
Hemoglobin (g/L), mean ± SD	121.08 ± 23.56	126.25 ± 22.74	0.226
Creatinine (μmol/L), median (IQR)	90.33 (73.33–117.16)	90.94 (68.44–114.17)	0.521
Uric acid (μmol/L), median (IQR)	374.08 (295.70–487.34)	421.85 (284.00–499.91)	0.759
eGFR (mL/min/1.73m2), median (IQR)	68.14 (50.19–87.06)	74.56 (53.01–95.08)	0.343
Total bilirubin (μmol/L), median (IQR)	14.69 (10.53–20.86)	13.35 (10.97–18.05)	0.348
Albumin (g/L), mean ± SD	35.31 ± 5.56	35.06 ± 4.22	0.806
APTT (seconds), mean ± SD	29.81 ± 6.55	28.73 ± 4.93	0.356
PT (seconds), median (IQR)	13.00 (12.10–14.70)	12.55 (12.00–13.90)	0.143
INR, mean ± SD	1.26 ± 0.50	1.14 ± 0.16	0.175
Fibrinogen (g/L), mean ± SD	3.50 ± 1.64	3.43 ± 1.20	0.816
D-dimer (mg/L), median (IQR)	0.81 (0.40–2.04)	1.30 (0.64–2.71)	0.075
Total cholesterol (mmol/L), median (IQR)	3.64 (2.99–4.34)	4.04 (3.16–4.54)	0.151
Triglycerides (mmol/L), median (IQR)	0.92 (0.70–1.26)	0.78 (0.58–1.04)	0.060
LDL-C (mmol/L), mean ± SD	2.06 ± 0.75	2.22 ± 0.99	0.247
Glucose (mmol/L), mean ± SD	6.27 ± 2.48	5.80 ± 2.25	0.302
TyG index, mean ± SD	8.41 ± 0.64	8.16 ± 0.56	0.036*
Smoking history, n (%)	152 (22.42)	7 (21.88)	0.943
Alcohol consumption, n (%)	378 (55.75)	21 (65.63)	0.271
Hypertension, n (%)	103 (15.19)	8 (25.00)	0.135
Diabetes mellitus, n (%)	149 (21.98)	9 (28.13)	0.414
Previous stroke, n (%)	103 (15.19)	14 (43.75)	0.001**
High TyG index, n (%)	343 (50.59)	12 (37.50)	0.148

Abbreviations: IS, ischemic stroke; SD, standard deviation; IQR, interquartile range; WBC, white blood cell count; RBC, red blood cell count; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index. Data are presented as mean ± SD for normally distributed continuous variables, median (IQR) for non-normally distributed continuous variables, and n (%) for categorical variables. Statistical significance was determined using Student's *t*-test or Mann–Whitney *U*-test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. *P <0.05, **P< 0.01.

compared to the non-IS group (8.16±0.56 vs 8.41±0.64, P=0.036). Additionally, previous stroke history was markedly more prevalent in the IS group (43.75% vs 15.19%, P <0.001).

Univariate Analysis of Risk Factors

Univariate logistic regression analysis identified two significant predictors of IS (Table 2). The TyG index demonstrated a significant inverse association with stroke risk (OR=0.49, 95% CI: 0.26–0.94, *P*=0.031), indicating a 51% lower odds per unit increase. Previous stroke history was the strongest predictor, conferring a 4.34-fold increased risk compared to those without prior stroke (OR=4.34, 95% CI: 2.09–9.00, *P*=0.001). Several variables approached statistical significance, including male sex (OR=0.39, *P*=0.079), total cholesterol (OR=1.29, *P*=0.097), and LDL-C (OR=0.44, *P*=0.074). Traditional cardiovascular risk factors including age, smoking, hyper tension, diabetes, and most laboratory parameters showed no significant associations with stroke risk (all $P < 0.05$).

Table 2 Univariate Logistic Regression Analysis for Predictors of IS

Variables	OR (95% CI)	P-value
Age (per year increase)	0.98 (0.93–1.02)	0.269
Male vs Female	0.39 (0.13–1.12)	0.079
Current smoking vs Non-smoking	1.15 (0.56–2.34)	0.695
Alcohol consumption vs No alcohol	0.96 (0.41–2.28)	0.942
WBC (per 109/L increase)	1.01 (0.93–1.10)	0.850
RBC (per 1012/L increase)	1.08 (0.90–1.29)	0.406
Neutrophils (per 109/L increase)	1.03 (0.99–1.06)	0.116
Lymphocytes (per 109/L increase)	0.90 (0.63–1.26)	0.516
Platelets (per 109/L increase)	1.00 (0.99–1.00)	0.919
Hemoglobin (per g/L increase)	1.01 (0.99–1.03)	0.225
Creatinine (per μmol/L increase)	0.99 (0.99–1.00)	0.411
Uric acid (per μmol/L increase)	1.00 (0.99–1.01)	0.998
eGFR (per mL/min/1.73m2 increase)	1.00 (0.99–1.01)	0.099
Total bilirubin (per μmol/L increase)	0.97 (0.93–1.02)	0.221
Albumin (per g/L increase)	0.99 (0.93–1.06)	0.805
APTT (per second increase)	0.96 (0.90–1.03)	0.352
PT (per second increase)	0.89 (0.77–1.04)	0.151
INR (per unit increase)	0.31 (0.05–1.61)	0.163
Fibrinogen (per g/L increase)	0.97 (0.77–1.23)	0.815
D-dimer (per mg/L increase)	1.00 (0.93–1.07)	0.933
Total cholesterol (per mmol/L increase)	1.29 (0.95–1.76)	0.097
LDL-C (per mmol/L increase)	0.44 (0.17–1.08)	0.074
Triglycerides (per mmol/L increase)	1.29 (0.83–1.99)	0.246
Glucose (per mmol/L increase)	0.91 (0.76–1.08)	0.302
TyG index (per unit increase)	0.49 (0.26–0.94)	0.031*
Hypertension vs No hypertension	1.51 (0.71–3.19)	0.274
Diabetes mellitus vs No diabetes	1.86 (0.81–4.25)	0.141
Coronary heart disease vs No CHD	1.38 (0.62–3.06)	0.415
Previous stroke vs No previous stroke	4.34 (2.09–9.00)	¡0.001**
High TyG index vs Low TYG index	0.58 (0.28–1.21)	0.152

Notes: OR, odds ratio; CI, confidence interval; WBC, white blood cell count; RBC, red blood cell count; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index; CHD, coronary heart disease. Reference categories: Female sex, non-smoking, no alcohol consumption, absence of comorbidities, and low TyG index. Odds ratios represent the change in odds of ischemic stroke per unit increase for continuous variables or compared to the reference category for categorical variables. *P <0.05, **P < 0.01.

Multivariate Analysis of TyG Index and IS

Multivariate logistic regression analyses revealed a progressive strengthening of the protective association between TyG index and ischemic stroke risk across models (Table 3). The protective effect intensified with progressive adjustment. In the crude model, each unit increase in TYG index was associated with 52% lower odds of IS (OR=0.48, 95% CI: 0.26–0.94, P=0.031). After adjusting for demographic and clinical factors in Model I, the inverse association strengthened (OR=0.41, 95% CI: 0.20–0.84, P=0.014). In the fully adjusted Model II, the association was strongest, with each unit increase in TyG index associated with 76% lower odds of IS (OR=0.24, 95% CI: 0.10–0.57, P=0.001). When dichotomized, high TyG index achieved statistical significance only in the fully adjusted model (OR=0.39, 95% CI: 0.16–0.98, P=0.046), showing 61% lower odds of IS compared to low TyG index, while crude and partially adjusted models showed non-significant trends. Crude Model: Unadjusted analysis.

Table 3 Multivariate Logistic Regression Analysis for Association Between TyG Index and IS

Outcome	Crude Model		Model I		Model II	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
TyG TyG-2	0.48 (0.26, 0.94)	0.031*	0.41 (0.20, 0.84)	0.014*	0.24 (0.10, 0.57)	0.001**
Low-TyG	Reference		Reference		Reference	
High-TyG	0.59 (0.28, 1.22)	0.152	0.52 (0.23, 1.15)	0.105	0.39 (0.16, 0.98)	0.046*

Notes: Crude Model: Adjusted for none. Model I: Adjusted for age, sex, smoking status, alcohol consumption, hypertension, diabetes mellitus, coronary heart disease, previous stroke. Model II: Adjusted for Model I variables plus laboratory parameters and WBC, RBC, neutrophils, lymphocytes, platelets, hemoglobin, creatinine, uric acid, eGFR, total bilirubin, albumin, APTT, PT, INR, fibrinogen, D-dimer. High TyG index was defined as TyG > median value. Model II represents the fully adjusted model accounting for potential confounding variables across multiple physiological systems. *P< 0.05, **P < 0.01.
Abbreviations: OR, odds ratio; CI, confidence interval; TYG, triglyceride-glucose index; WBC, white blood cell count; RBC, red blood cell count; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; PT, pro thrombin time; INR, international normalized ratio.

Association Between TyG Index and Ischemic Stroke in Patients with COPD and AF

To further explore the relationship between the TyG index and the risk of ischemic stroke (IS) in patients with COPD and AF, we applied generalized additive models (GAM) with smoothing curve fitting. Using the TyG index as a continuous independent variable and IS occurrence as the dependent variable, and adjusting for history of stroke, the smoothing curve indicated a linear association between TyG index and IS risk (Figure 1). Linear regression analysis showed that each one-unit increase in TyG index was associated with a 50% reduction in the risk of IS (OR=0.5, 95% CI: 0.3–0.9, P=0.032). This finding was statistically significant, suggesting a robust inverse association between higher TyG index and IS risk in this patient population.

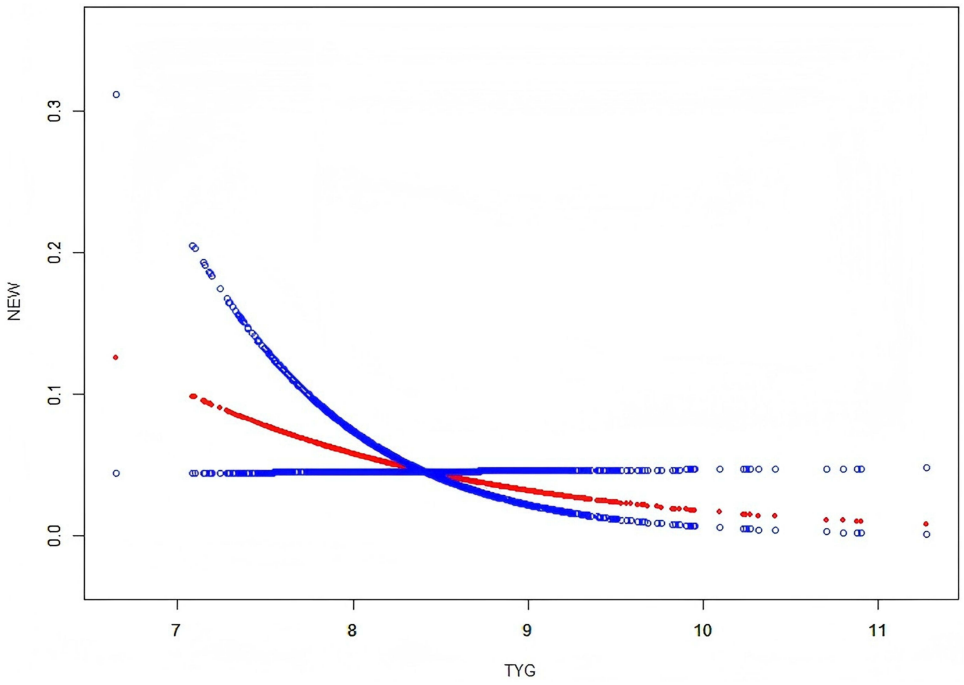

Figure 1 Association between TYG index and ischemic stroke risk using smooth curve fitting.

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Predictive Value of TyG Index for Ischemic Stroke in Patients with COPD and AF

To evaluate the predictive performance of the TyG index for IS inpatients with COPD and AF, we constructed receiver operating characteristic (ROC) curves and calculated relevant metrics. The area under the curve (AUC) for the TyG index was 0.614 (95% CI: 0.513–0.715), indicating moderate predictive ability (Figure 2). Although the AUC suggests only modest performance, the lower bound of the 95% CI exceeded 0.5, supporting statistical significance. The optimal cutoff value, determined by maximizing the Youden index, was 8.424, corresponding to a sensitivity of 73.95% and a specificity of 78.12%. These results indicate that the TyG index, as a simple and readily available biomarker, may offer potential preliminary screening value for assessing IS risk in this patient population, though the modest AUC underscores the need for validation in larger prospective cohorts before clinical implementation.

Sensitivity Analyses

Multiple sensitivity analyses confirmed robustness of the inverse association (Supplementary Tables 1–3). Excluding patients with prior stroke (n=593, 18 events), the association remained strong (aOR=0.15, 95% CI:0.05–0.52, *P*=0.002). After excluding extreme TyG values, results were consistent (aOR=0.20, 95%C:0.07–0.60, *P*=0.004). Complete case analysis yielded similar findings (aOR=0.25, 95% CI: 0.10–0.62, *P*=0.003). These analyses indicate findings are not artifacts of prior stroke status, outliers, or missing data handling.

Discussion

This retrospective cohort study investigated the association between the TyG index and the risk of ischemic stroke in patients with COPD and atrial fibrillation. Our findings revealed an unexpected inverse association between TyG index

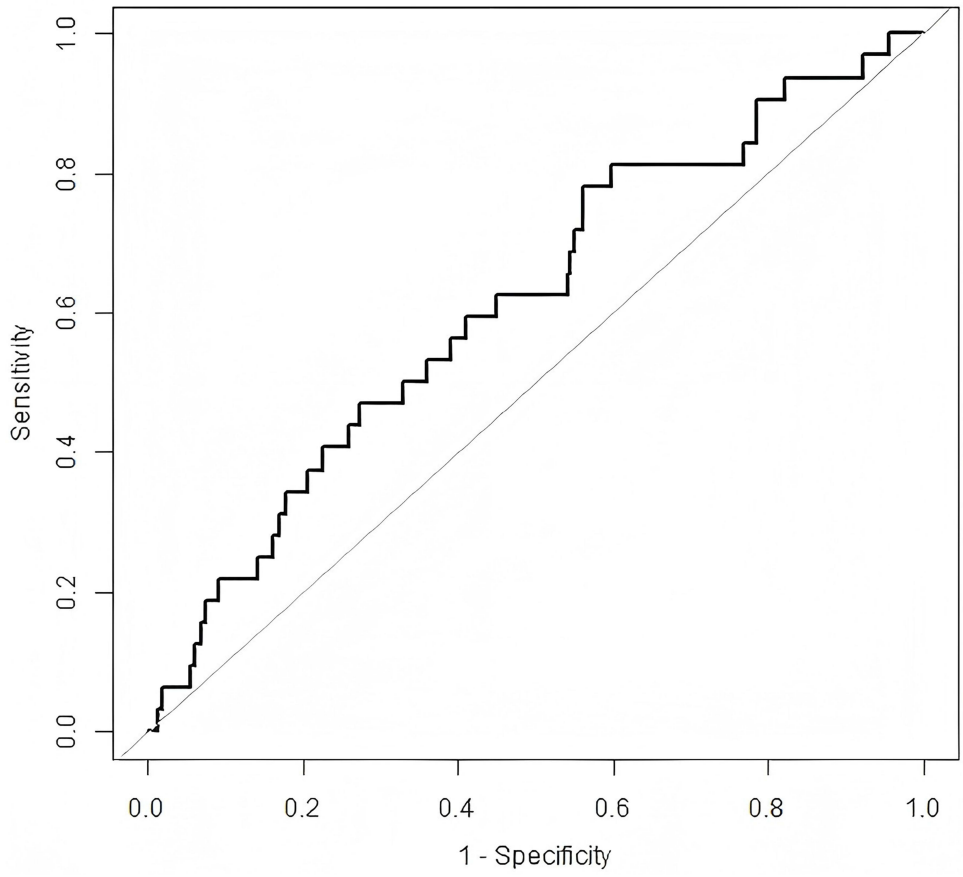

Figure 2 ROC curve of TYG index for predicting ischemic stroke in COPD patients with AF.

and ischemic stroke risk in this specific high-risk population, contrasting with the positive associations typically observed in the general population.

Counterintuitively, our findings differ from most previous studies which typically report positive associations between TyG index and cardiovascular events in the general population but are supported by emerging evidence from specific clinical contexts characterized by metabolic paradoxes. Several large prospective studies have reported a positive, often nonlinear, association between the TyG index and risk of stroke. However, the clinical implications of the TyG index may vary depending on patient populations and disease states. Evidence supporting our results mainly derives from research on the metabolic paradox and cardiovascular disease. For example, a large cohort study by Li et al (2022) found that, among patients with atrial fibrillation, higher BMI was associated with reduced risks of stroke, systemic embolism, bleeding, heart failure hospitalization, and all-cause mortality.[28] Similarly, Huang et al (2024) observed that lower TyG-BMI levels were linked to increased long-term all-cause mortality in patients with severe stroke, suggesting a potential protective effect of metabolic indicators.[29] Zhai et al (2022) also reported a complex nonlinear relationship between the TyG index and in-hospital mortality in critically ill cardiac patients, with a potential protective association observed in certain subgroups.[30]

Evidence supporting a linear relationship comes from multiple dose–response analyses. While most studies report a positive association between the TyG index and cardiovascular events, the nature of this relationship may differ by disease context. For example, Sandhu et al (2016) found in the ARISTOTLE trial that, among patients with atrial fibrillation, overweight and obesity were linearly and inversely associated with all-cause mortality and composite adverse events.[31] Oesch et al (2017) con firmed the "obesity paradox" in stroke patients, noting that a higher body mass index was linked to better survival and functional outcomes.[32] Notably, Liu et al (2024) demonstrated that the TyG index is valuable for distinguishing between large artery atherosclerotic and cardioembolic strokes: it showed a positive association with noncardioembolic stroke but a negative association with cardioembolic stroke.[33,34] This finding directly supports our results, indicating that, in AF patients (who predominantly experience cardioembolic strokes), the TyG index may have a protective effect. Hoshino et al further confirmed that the association between TyG index and major adverse cardiovascular events is significant for atherosclerotic stroke, but not for cardioembolic stroke.[35]

Hese divergent findings may be explained by disease-specific pathophysiological mechanisms. In the general population, a higher TyG index typically reflects insulin resistance and the progression of atherosclerosis, thus correlating positively with stroke risk. However, in patients with COPD and atrial fibrillation, moderate metabolic disturbances may play a protective role, similar to the "obesity paradox" observed in AF populations. Sandhu et al (2016) reported that overweight and obesity in AF patients were associated with lower all-cause mortality and fewer composite endpoint events.[18] Li et al further found that higher BMI in AF patients correlated with reduced risks of stroke/systemic embolism, bleeding, heart failure hospitalization, and all-cause mortality.[28] Conversely, a recent study by Gong et al showed that in AF patients without diabetes, a high TyG index was associated with poorer outcomes, but this relationship varied across metabolic states.[36] Mechanistically, most strokes in patients with COPD and AF are cardioembolic, which differs fundamentally from the pathogenesis of atherosclerotic stroke. In AF patients, moderate insulin resistance may be associated with lower stroke risk through influences on atrial remodeling, coagulation balance, or inflammatory responses. Liu et al showed that the TyG index is useful for distinguishing between cardioembolic and large artery atherosclerotic strokes, suggesting that its underlying mechanisms may differ by stroke subtype.[33] Furthermore, in COPD patients, chronic inflammation and oxidative stress may alter the pathophysiological significance of insulin resistance, potentially transforming it into an adaptive, protective mechanism rather than a harmful factor under certain conditions. The consistency of the inverse association across multiple sensitivity analyses strengthens confidence in our findings. Results remained robust when excluding prior stroke patients (aOR=0.22, P=0.008), excluding outliers (aOR=0.28, P=0.009), and using complete cases without imputation (aOR=0.25, P=0.003). However, we were unable to perform subgroup analyses due to insufficient events in the diabetes subgroup (9/158 patients) or stratify by anticoagulation use due to lack of these data. The absence of anticoagulation data is particularly concerning: if anticoagulation use differed between TyG groups, this could confound or fully explain the observed association.

An important methodological consideration is the potential for reverse causality. The inverse association could arise through two pathways: true metabolic protection, or alternatively, low TyG marking disease severity rather than

conferring protection. Advanced COPD-AF patients may experience nutritional depletion, metabolic reserve depletion, and chronic inflammation—all lowering triglycerides and TyG while simultaneously increasing stroke risk through disease burden. This would create a spurious inverse association through confounding rather than true protection. Critically, we lacked measures of COPD severity (FEV1%, GOLD stage), comprehensive nutritional assessment (BMI, weight loss), and inflammatory biomarkers (CRP, IL-6), precluding full assessment of these pathways. While the association persisted after adjusting for prior stroke, residual confounding by unmeasured disease severity remains a concern. Our findings align with stroke subtype literature and metabolic paradoxes in AF, suggesting biological plausibility. However, our observational design cannot definitively distinguish between protection and reverse causality. These findings are hypothesis-generating, requiring prospective validation with comprehensive disease severity assessment.

The clinical value of this study lies in introducing the TyG index as a novel biomarker for assessing ischemic stroke risk in patients with both COPD and atrial fibrillation—a population at particularly high risk. Unlike previous studies that have largely focused on the general population, this research is the first to demonstrate a potential protective role of the TyG index in this specific patient group. Given its simplicity, low cost, and widespread availability, the TyG index holds potential value for clinical application as a supplementary tool, though its modest predictive performance (AUC=0.614) suggests it should not be used as a standalone predictor. Our findings suggest that higher TyG index values may indicate lower stroke risk among patients with COPD and AF, which could influence risk stratification strategies and encourage clinicians to consider the TyG index when individualizing anticoagulation therapy. We recommend that clinicians incorpo rate the TyG index as a supplementary tool to traditional risk scores when evaluating stroke risk, particularly for patients with intermediate CHA2DS2-VASc scores. However, as our findings differ from most prior literature, further large-scale, multicenter, prospective studies are necessary to confirm this protective effect and to elucidate the underlying patho-physiological mechanisms. Future research should also explore the impact of COPD severity, AF type, and comorbidities on the TyG index's predictive value, as well as assess the clinical and cost-effectiveness of integrating TyG into established risk models. Prospective studies with repeated TyG measurements are needed to assess whether TyG variability and trajectory patterns independently predict stroke risk and clarify causal pathways.

First, the small number of stroke events (n=32) limits the precision of effect size estimates, as evidenced by the wide confidence interval (0.10–0.57). Moreover, the low events-per-variable ratio in our multivariable models raises concerns about statistical power and model stability, potentially leading to overfitting. The large observed effect should be interpreted cautiously and requires validation in larger cohorts with adequate statistical power to detect more precise effect estimates. Second, this single-center study in a Chinese population limits generalizability to other ethnicities and settings, necessitating external validation. Third, as an observational study, our analysis establishes association rather than causality; although multiple confounders were adjusted, residual confounding from unmeasured variables—particularly COPD severity (FEV1%, GOLD stage), nutritional status (BMI, weight loss), and inflammatory markers (CRP, IL-6) cannot be excluded. Fourth, only a single TyG measurement at admission was used, precluding assessment of TyG variability over time. This limits interpretation because: (1) single measurements cannot distinguish chronic metabolic states from acute-phase responses to hospitalization; (2) TyG trajectory patterns (stable vs declining) may have different prognostic implications—gradual decline might reflect disease progression while stable levels reflect chronic phenotypes; and (3) longitudinal measurements would help distinguish true metabolic effects from reverse causality. Without repeated measurements, we cannot determine if associations reflect chronic states or dynamic changes with disease progression. Fifth, limited sample size precluded subgroup analyses to explore effect heterogeneity. With only 9 stroke events among 158 diabetic patients, diabetes-stratified analysis would yield unstable estimates. More critically, we lacked anticoagulation therapy data—the primary stroke prevention treatment in AF patients. If anticoagulation use differed between TyG groups (eg, clinicians avoiding anticoagulation in frail, low-TyG patients due to bleeding concerns), this could confound or fully explain the observed inverse association. Without data on anticoagulation type, dose, or adherence, we cannot disentangle metabolic effects from treatment effects. Future prospective studies must collect comprehensive anticoagulation data and include larger samples enabling adequately powered subgroup analyses. Most importantly, three interrelated limitations affect general-izability: (1) outcome assessment was restricted to the hospitalization period (median 9 days), excluding post-discharge events; (2) selection bias is inherent to hospital-based design, as severely ill COPD-AF patients are more likely hospitalized

than stable outpatients—our sample's high mean age (78 years) and prior stroke prevalence (15.2% vs 5–10% in community cohorts) suggest predominant capture of advanced-stage patients, and if such patients have lower TyG (nutritional depletion) and higher stroke risk (disease burden) while healthier outpatients are excluded, the observed inverse association may partly reflect selection bias rather than biological protection; (3) the inverse association may reflect acute-phase pathophysiology rather than chronic metabolic effects. Without data on non-hospitalized patients or disease severity markers, we cannot quantify these biases. Findings should be considered hypothesis-generating for hospitalized COPD-AF populations, requiring validation in population-based cohorts before broader generalization.

Conclusion

In summary, this study identified an unexpected linear inverse association between the TyG index and the risk of ischemic stroke in patients with both COPD and atrial fibrillation, which notably contrasts with the positive associations typically reported in the general population. This finding could represent either a true metabolic protective mechanism or reflect reverse causality whereby low TyG marks disease severity (malnutrition, poor metabolic reserve, chronic inflammation). Potential biological explanations for a protective effect include the "metabolic paradox" observed in AF populations and stroke subtype differences, as COPD-AF patients primarily experience cardioembolic rather than atherosclerotic strokes. Our lack of comprehensive COPD severity, nutritional, and inflammatory measures limits distinguishing between these explanations. While our results generate the hypothesis that higher TyG may indicate lower stroke risk in this population, definitive causal inference requires prospective validation with comprehensive disease severity assessment. This work provides preliminary evidence to reconsider metabolic marker interpretation, but conclusions remain tentative pending validation. As a simple and accessible biomarker, the TyG index shows potential value as a supplementary tool for stroke risk stratification in patients with COPD and AF, though its modest predictive performance necessitates validation in large-scale prospective studies before clinical implementation. However, given the single-center design, limited sample size precluding subgroup analyses, and particularly the absence of anticoagulation data, these findings require validation in large, multicenter prospective studies with comprehensive data collection.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (Xinyi Zhang) on reasonable request.

Ethics Approval and Informed Consent

This retrospective study was conducted at a single center and adhered to the principles of the Declaration of Helsinki. The trial received approval from the Ethics Committee of the Second Affiliated Hospital of Nanchang University (2023-KY-74)). Since this was a retrospective study, the written informed consent was waived by the Ethics Committee of the Second Affiliated Hospital of Nanchang University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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