Postprint: Association Between Triglyceride-Glucose Index and Atrial Fibrillation in Patients with Chronic Heart Failure

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Abstract

Background Insulin resistance (IR) is associated with atrial fibrillation (AF) and atrial remodeling, and studies on the correlation between the triglyceride-glucose (TyG) index, a novel, simple, and valuable indicator of IR, and the occurrence of AF in patients with chronic heart failure (CHF) are scarce. Objective To investigate the correlation between the TyG index and the risk of AF occurrence in CHF patients. Methods A total of 417 CHF patients hospitalized in the Department of Cardiology at The Second Affiliated Hospital of Zhengzhou University from January 2021 to January 2022 were retrospectively selected as study subjects. Patients were divided into two groups based on the occurrence of AF: an AF group (138 cases) and a non-AF group (279 cases). Based on quartiles, the TyG index was divided into four levels: Q1 (TyG index $ $8.20), Q2 (8.208.84). Baseline patient data were collected through the hospital electronic medical record system, including the TyG index, basic information, laboratory examination indicators, echocardiographic data, etc. The LASSO regression algorithm was used for variable screening, and multivariate Logistic regression analysis was employed to analyze the correlation between the TyG index and the risk of AF occurrence in CHF patients, and to construct a regression model. Simultaneously, receiver operating characteristic curve analysis was used to evaluate the predictive value of the TyG index for AF occurrence in CHF patients. A restricted cubic spline plot of the correlation between the TyG index and AF occurrence risk in CHF patients was constructed. Results Patients in the AF group had higher BMI, proportion of New York Heart Association (NYHA) functional class III-IV, hypertension prevalence, serum uric acid (SUA), triglycerides, blood urea nitrogen (BUN), fasting blood glucose, N-terminal pro-B-type natriuretic peptide, TyG index, left atrial diameter (LAD), and proportions of beta-blocker, calcium antagonist, and diuretic use than the non-AF group, while total cholesterol (TC),

endogenous creatinine clearance rate (Ccr), left ventricular ejection fraction, and proportion of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB) use were lower than those in the non-AF group (P<0.05). Multivariate Logistic regression analysis results showed that hypertension (OR=1.749, 95%CI=1.048~2.918, P=0.032), elevated BUN (OR=1.269, 95%CI=1.104~1.457, P=0.001), elevated SUA (OR=1.002, 95%CI=1.000~1.005, P=0.047), elevated TyG index (OR=2.360, 95%CI=1.397~3.987, P=0.001), elevated LAD (OR=1.065, 95%CI=1.034~1.097, P<0.001), and diuretic use (OR=4.019, 95%CI=2.140~7.548, P<0.001) were risk factors for AF occurrence in CHF patients; elevated Ccr (OR=0.985, 95%CI=0.975~0.996, P=0.006), elevated TC (OR=0.587, 95%CI=0.445~0.775, P<0.001), and ACEI/ARB use (OR=0.427, 95%CI=0.253~0.718, P=0.001) were protective factors for AF occurrence in CHF patients. After fully adjusting for confounding factors, compared with the Q1 level, the risk of AF occurrence in CHF patients at TyG index levels Q2, Q3, and Q4 was 1.902-fold, 2.060-fold, and 2.841-fold that of the Q1 level, respectively (P<0.05). Restricted cubic spline analysis showed that the TyG index was linearly and positively correlated with AF occurrence risk (P for nonlinearity=0.494). The areas under the curve for the TyG index and the LASSO-Logistic regression model in predicting AF occurrence in CHF patients were 0.66 (95%CI=0.608~0.724, P<0.001) and 0.843 (95%CI=0.803~0.882, P<0.001), respectively. Additionally, the correlation between the TyG index and AF was consistent across different subgroups. Conclusion In CHF patients, the TyG index is independently associated with AF occurrence and has certain clinical value in identifying AF development in this patient population.

Full Text

Preamble

Correlation between Triglyceride-Glucose Index and Atrial Fibrillation in Patients with Chronic Heart Failure

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Abstract

Background: Insulin resistance (IR) is associated with atrial fibrillation (AF) and atrial remodeling. However, the correlation between the triglyceride-glucose (TyG) index—a novel, simple, and valuable indicator of IR—and the development

of AF in patients with chronic heart failure (CHF) has been poorly studied. **Objective:** To investigate the correlation between TyG index and the risk of AF in CHF patients. **Methods:** We retrospectively selected 417 CHF patients hospitalized in the Department of Cardiovascular Medicine at The Second Affiliated Hospital of Zhengzhou University between January 2021 and January 2022. Patients were divided into two groups based on AF status: an AF group (138 cases) and a non-AF group (279 cases). The TyG index was categorized into four levels based on quartiles: Q1 (TyG index $\leq$ 8.20), Q2 (8.20 $<$ TyG index $\leq$ 8.44), Q3 (8.44 $<$ TyG index $\leq$ 8.84), and Q4 (TyG index $>$ 8.84). Baseline data were collected through the hospital' s electronic medical record system, including TyG index, basic demographics, laboratory parameters, and echocardiographic data. The LASSO regression algorithm was used for variable screening, and multivariate logistic regression was employed to analyze the correlation between TyG index and AF risk in CHF patients, with a regression model constructed. The predictive value of TyG index for AF occurrence was assessed using receiver operating characteristic curve analysis. Restricted cubic spline plots were generated to visualize the correlation between TyG index and AF risk. **Results:** The AF group exhibited higher BMI, higher proportion of NYHA functional class III-IV, higher prevalence of hypertension, and elevated levels of serum uric acid (SUA), triglycerides, blood urea nitrogen (BUN), fasting plasma glucose, N-terminal pro-B-type natriuretic peptide, TyG index, and left atrial diameter (LAD), as well as higher usage rates of β-blockers, calcium antagonists, and diuretics compared to the non-AF group. In contrast, the AF group had lower total cholesterol (TC), lower endogenous creatinine clearance (Ccr), lower left ventricular ejection fraction, and lower usage of ACEI/ARB medications ($P < 0.05$). Multivariate logistic regression analysis revealed that hypertension (OR = 1.749, 95%CI = 1.048-2.918, P = 0.032), elevated BUN (OR = 1.269, 95%CI = 1.104-1.457, P = 0.001), elevated SUA (OR = 1.002, 95%CI = 1.000-1.005, P = 0.047), elevated TyG index (OR = 2.360, 95%CI = 1.397-3.987, P = 0.001), elevated LAD (OR = 1.065, 95%CI = 1.034-1.097, P $<$ 0.001), and diuretic use (OR = 4.019, 95%CI = 2.140-7.548, P $<$ 0.001) were independent risk factors for AF in CHF patients. Conversely, elevated Ccr (OR = 0.985, 95%CI = 0.975-0.996, P = 0.006), elevated TC (OR = 0.587, 95%CI = 0.445-0.775, P $<$ 0.001), and ACEI/ARB use (OR = 0.427, 95%CI = 0.253-0.718, P = 0.001) were protective factors. After full adjustment for confounders, CHF patients in Q2, Q3, and Q4 had 1.902-fold, 2.060-fold, and 2.841-fold higher risks of AF, respectively, compared to Q1 ($P < 0.05$). Restricted cubic spline analysis demonstrated a linear positive correlation between TyG index and AF risk (P nonlinear = 0.494). The area under the curve (AUC) for TyG index and the LASSO-Logistic regression model in predicting AF occurrence were 0.661 (95%CI = 0.608-0.724, P $<$ 0.001) and 0.843 (95%CI = 0.803-0.882, P $<$ 0.001), respectively. The correlation between TyG index and AF remained consistent across subgroups. **Conclusion:** In CHF patients, TyG index is independently associated with AF occurrence and demonstrates significant clinical value in identifying patients at risk for AF.

Keywords: heart failure; atrial fibrillation; chronic heart failure; TyG index; insulin resistance; LASSO regression

Introduction

Chronic heart failure (CHF) represents the severe manifestation or advanced stage of various cardiovascular diseases and is associated with high mortality and rehospitalization rates. Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by rapid, disorganized atrial electrical activity and abnormal mechanical contraction, commonly observed in CHF patients. According to a national survey of hospitalized heart failure patients in China, approximately 24.4% of heart failure patients have coexisting AF, which significantly increases the risk of death and rehospitalization, severely impacts quality of life, and imposes a substantial economic burden.

Insulin resistance (IR), a state of reduced sensitivity and responsiveness to insulin, has been linked to AF through its effects on atrial electrical and structural remodeling. Early studies identified an association between metabolic syndrome, characterized by high IR levels, and AF, with mounting evidence demonstrating that IR and related conditions promote AF development. The homeostasis model assessment of insulin resistance (HOMA-IR) has traditionally served as the gold standard for evaluating IR; however, its clinical application is limited by its dependence on serum insulin level measurements and high cost. The triglyceride-glucose (TyG) index has emerged as a novel surrogate marker for IR, offering superior sensitivity and specificity compared to HOMA-IR. Clinical studies have demonstrated that the TyG index, as an indicator of IR, holds clinical value in identifying and predicting the occurrence and prognosis of atherosclerotic diseases, myocardial infarction, hypertension, stroke, and other cardiovascular conditions. Recent research has also identified a correlation between the TyG index and AF, though whether this relationship extends to CHF patients remains unclear. This study aims to explore the association between TyG index and AF in CHF patients, providing insights for early identification of high-risk patients, reduction of AF incidence, and improvement of adverse outcomes through individualized management.

Methods

Study Population

We retrospectively enrolled 417 CHF patients hospitalized in the Department of Cardiovascular Medicine at The Second Affiliated Hospital of Zhengzhou University between January 2021 and January 2022. Inclusion criteria were: (1) age $\geq$ 18 years; (2) diagnosis of CHF according to the "2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure." Exclusion criteria included: (1)

age > 80 years; (2) AF secondary to reversible causes such as acute thyrotoxicosis, pulmonary embolism, major surgery, or isolated atrial flutter without AF; (3) structural heart disease, severe valvular disease, acute myocardial infarction, other acute thromboembolic diseases, or rheumatic heart disease; (4) severe hepatic or renal disease, recent infection, active inflammation, or rheumatic diseases that might affect IR or TyG index; (5) pregnancy, miscarriage within six months, blood transfusion history, or surgical history; (6) incomplete clinical data. All patients provided informed consent, and the study protocol was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Zhengzhou University (approval number: 2023191).

Data Collection

Clinical data were extracted from the hospital' s electronic medical record system, encompassing inpatient, emergency, and outpatient records. Data collection included: (1) demographic information: sex, age, BMI, smoking history, alcohol consumption, blood pressure, pulse rate, comorbidities, medication use, heart failure type, and New York Heart Association (NYHA) functional class; (2) laboratory parameters: after an 8-10 hour fasting period, venous blood samples were collected to measure total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting plasma glucose (FPG), endogenous creatinine clearance (Ccr), serum creatinine (Scr), serum uric acid (SUA), blood urea nitrogen (BUN), glycated hemoglobin (HbA1c), and N-terminal pro-B-type natriuretic peptide (NT-proBNP); (3) echocardiographic parameters: left ventricular ejection fraction (LVEF), left atrial diameter (LAD), left ventricular end-diastolic diameter (LVED), interventricular septal thickness (IVSD), and left ventricular posterior wall thickness (IVPW).

Calculations: (1) BMI = weight (kg) / height^2 (m^2); (2) Ccr (male) = [(140 - age) × weight (kg) × 88.4] / [72 × Scr (mol/L)], Ccr (female) = [(140 -age) × weight (kg) × 88.4] / [85 × Scr (mol/L)]; (3) TyG index = ln[TG (mg/dL) × FPG (mg/dL) / 2].

Definitions

AF diagnosis was based on the "2020 European Guidelines for the Diagnosis and Management of Atrial Fibrillation," defined as AF rhythm on a standard 12-lead ECG recording or a single-lead ECG tracing ≥ 30 seconds showing no discernible P waves with irregular RR intervals.

NYHA functional classification was categorized into four classes according to standard criteria: Class I: no symptoms during ordinary physical activity; Class II: slight limitation during ordinary activity, with symptoms such as shortness of breath or palpitations during moderate exertion; Class III: marked limitation during less-than-ordinary activity, with symptoms occurring during

mild exertion; Class IV: inability to perform any physical activity without discomfort.

Heart failure type was classified according to the "2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure"based on LVEF: heart failure with reduced ejection fraction (HFrEF, LVEF $< 40\%$), heart failure with preserved ejection fraction (HFpEF, LVEF $\geq 50\%$), and heart failure with mid-range ejection fraction (HFmrEF, LVEF 40–49%).

Comorbidities: (1) Coronary artery disease was defined as $\geq 50\%$ stenosis in at least one major coronary artery on prior or admission coronary CT/angiography; (2) Hypertension was defined as documented history or three separate measurements of right upper arm blood pressure $\geq 140/90$ mmHg (1 mmHg = 0.133 kPa) under resting conditions; (3) Diabetes mellitus was diagnosed according to the "2020 Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes," including typical symptoms with random glucose ≥ 11.1 mmol/L, FPG ≥ 7.0 mmol/L, 2-hour oral glucose tolerance test ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$.

Smoking history was defined as daily consumption of at least one cigarette for over six months; **alcohol consumption** was defined as drinking more than 50 g per occasion, at least three times per week.

Grouping

Patients were divided into two groups based on AF status: the AF group (138 cases) and the non-AF group (279 cases). The TyG index was further categorized into four quartile levels: Q1 (TyG index ≤ 8.20), Q2 ($8.20 <$ TyG index ≤ 8.44), Q3 ($8.44 <$ TyG index ≤ 8.84), and Q4 (TyG index > 8.84).

Statistical Analysis

Data analysis was performed using SPSS 26.0 and R 4.3.2 software. Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean $\pm$ standard deviation and compared using independent samples t-tests; non-normally distributed variables are expressed as median (P25, P75) and compared using non-parametric rank-sum tests. Categorical data are presented as frequencies and percentages, compared using ^{2} tests. LASSO regression was employed for variable screening, followed by binary multivariate logistic regression analysis to examine the association between TyG index and AF risk, with regression models constructed and receiver operating characteristic (ROC) curves plotted to evaluate predictive value. Restricted cubic spline (RCS) analysis was used to assess and visualize the relationship between TyG index and AF risk. Subgroup analyses were conducted by sex (male/female), smoking status (yes/no), alcohol consumption (yes/no), age ($<$ 60/$\geq$ 60 years), diabetes (yes/no), hypertension (yes/no), BMI ($<$ 24/$\geq$ 24 kg/m^2), and LAD ($\leq$ 35/$>$ 35 mm) to test the robustness of the association.

All reported P-values are two-tailed, with $P < 0.05$ considered statistically significant.

Results

Baseline Characteristics

Among the 417 CHF patients, 219 (52.5%) were male and 198 (47.5%) female, with a mean age of (67.3 ± 10.2) years. No significant differences were observed between groups in age, sex, smoking status, alcohol consumption, blood pressure, pulse rate, coronary artery disease, diabetes, LDL-C, HDL-C, Scr, HbA1c, LVED, IVSD, or use of lipid-lowering agents, aldosterone antagonists, oral hypoglycemic agents, or insulin ($P > 0.05$). However, the AF group demonstrated significantly higher BMI, greater proportion of NYHA class III–IV, higher hypertension prevalence, and elevated levels of SUA, TG, BUN, FPG, NT-proBNP, TyG index, and LAD, along with higher usage rates of β-blockers, calcium antagonists, and diuretics. Conversely, the AF group had lower TC, Ccr, LVEF, and ACEI/ARB usage compared to the non-AF group ($P < 0.05$) .

Heart Failure Types by Group

No significant difference was observed in HFrEF proportions between the two groups ($P > 0.05$). The AF group had a higher proportion of HFmrEF and a lower proportion of HFpEF compared to the non-AF group ($P < 0.05$). While TyG index levels did not differ significantly between AF and non-AF patients with HFrEF ($P > 0.05$), AF patients with HFmrEF and HFpEF exhibited significantly higher TyG index levels than their non-AF counterparts ($P < 0.05$) .

LASSO Regression Variable Selection

All variables were included in LASSO regression for screening [Figure 1: see original paper]. Through cross-validation at $\lambda = 0.043$ (lambda.1se), ten variables with non-zero coefficients were identified: hypertension, Ccr, BUN, SUA, TC, TyG index, LAD, ACEI/ARB use, calcium antagonist use, and diuretic use.

Multivariate Logistic Regression Model for AF in CHF

Using AF occurrence as the dependent variable (no = 0, yes = 1) and LASSO-selected variables as independent variables (see assignment table), multivariate logistic regression revealed that hypertension (OR = 1.749, 95%CI = 1.048–2.918, P = 0.032), elevated BUN (OR = 1.269, 95%CI = 1.104–1.457, P = 0.001), elevated SUA (OR = 1.002, 95%CI = 1.000–1.005, P = 0.047), elevated TyG index (OR = 2.360, 95%CI = 1.397–3.987, P = 0.001), elevated LAD (OR = 1.065, 95%CI = 1.034–1.097, P < 0.001), and diuretic use (OR = 4.019, 95%CI

= 2.140–7.548, P < 0.001) were independent risk factors for AF. Elevated Ccr (OR = 0.985, 95%CI = 0.975–0.996, P = 0.006), elevated TC (OR = 0.587, 95%CI = 0.445–0.775, P < 0.001), and ACEI/ARB use (OR = 0.427, 95%CI = 0.253–0.718, P = 0.001) were protective factors . The logistic regression equation was constructed as: Logit(P) = 0.552 × hypertension + 0.224 × BUN -0.015 × Ccr + 0.002 × SUA -0.538 × TC + 0.902 × TyG index + 0.018 × LAD -0.318 × ACEI/ARB use -0.287 × diuretic use -10.879.

Association Between TyG Index Levels and AF Risk

Using AF occurrence as the dependent variable (no = 0, yes = 1) and TyG index quartiles as the independent variable (Q1 = 0, Q2 = 1, Q3 = 2, Q4 = 3) with Q1 as reference, logistic regression showed that in Model 1 (unadjusted), Q2, Q3, and Q4 were associated with 1.914-fold, 2.097-fold, and 2.878-fold higher AF risks, respectively (P < 0.05). Model 2 (adjusted for age, sex, BMI, smoking, alcohol consumption, NYHA class, and hypertension) yielded adjusted risks of 1.818, 2.056, and 2.635 for Q2, Q3, and Q4 (P < 0.05). Model 3 (further adjusted for Ccr, BUN, SUA, TC, LAD, and medication use) demonstrated that Q2, Q3, and Q4 had 1.902-fold, 2.060-fold, and 2.841-fold higher AF risks compared to Q1 (P < 0.05) . RCS analysis confirmed a linear increase in AF risk with rising TyG index (P nonlinear = 0.494) [Figure 2: see original paper].

Predictive Value of TyG Index and LASSO-Logistic Model

The TyG index alone predicted AF occurrence with an AUC of 0.661 (95%CI = 0.608–0.724, P < 0.001), optimal cutoff value of 8.38, sensitivity of 86.2%, and specificity of 55.7%. The LASSO-Logistic regression model achieved an AUC of 0.843 (95%CI = 0.803–0.882, P < 0.001), sensitivity of 81.0%, and specificity of 68.9% [Figure 3: see original paper].

Subgroup Analysis

To assess the robustness of the TyG index-AF association, subgroup analyses were performed across sex, age, BMI, hypertension, diabetes, smoking, alcohol consumption, and LAD strata. The TyG index remained significantly associated with AF risk in all subgroups (P < 0.05), with no significant interactions detected (P interaction > 0.05) .

Discussion

AF and CHF frequently coexist, each condition exacerbating the other. In CHF patients, increased ventricular filling leads to elevated cardiac pressure and volume load, causing atrial mechanical dilation that shortens atrial refractory period, prolongs conduction time, accelerates automaticity, and promotes

heterogeneous depolarization/repolarization, thereby facilitating atrial electrical and structural remodeling that promotes AF. Conversely, AF' s irregular electrical activity exacerbates left atrial fibrosis, impairs left ventricular function, and creates hemodynamic disturbances that worsen heart failure. Patients with both conditions face higher all-cause mortality and longer hospitalizations compared to those with either condition alone, underscoring the need for early identification of high-risk individuals and preventive interventions.

The TyG index is a simple, easily calculated metric that demonstrates high sensitivity (96.5%) and specificity (85.0%) compared to the euglycemic-hyperinsulinemic clamp. Growing evidence links TyG index to AF across diverse populations. LIU et al. found a U-shaped association in the general population without cardiovascular disease, while SHI et al. demonstrated a linear relationship in type 2 diabetes patients. WEI et al. reported significant associations in patients undergoing septal myectomy for hypertrophic obstructive cardiomyopathy, and ZHANG et al. identified correlations in non-alcoholic fatty liver disease patients. Our study extends these findings to CHF patients, demonstrating a significant, linear dose-response relationship between TyG index and AF risk across the entire range.

Hypertension represents a well-established independent AF risk factor, accounting for approximately 26.6% of AF cases. The Framingham Heart Study demonstrated a doubling of AF risk in hypertensive patients, while Chinese studies show each standard deviation increase in diastolic pressure associates with 37% higher AF prevalence. Our findings align with these observations. Additionally, we found that renal dysfunction (elevated BUN, reduced Ccr) and hyperuricemia independently increased AF risk, consistent with prior research. Left atrial enlargement also emerged as a significant risk factor, with each 5 mm increase in LAD associated with 1.4-fold higher AF incidence in Framingham data.

Interestingly, we found an inverse association between TC and AF risk, mirroring a meta-analysis showing lower TC impairs calcium handling, adrenergic signaling, and myofilament structure, compromising cardiomyocyte contractility and promoting AF. Regarding medications, diuretic use increased AF risk, with prior Chinese cohort studies identifying thiazide >40 mg/day and furosemide $ $40 mg/day as significant risk factors. In contrast, ACEI/ARB use demonstrated protective effects, reducing AF incidence by 88% and 90% respectively compared to β-blockers and diuretics through beneficial myocardial and vascular remodeling.

While age, sex, BMI, blood pressure, and hyperglycemia are established AF risk factors, the applicability of TyG index to diabetic populations remains debated. CHEN et al. reported associations only in non-diabetic patients, whereas SHI et al. found strong correlations in diabetic cohorts. Our subgroup analyses demonstrate that the TyG index-AF association in CHF patients is robust across all subgroups, including diabetes status, without significant interactions.

Our study has limitations. First, as a single-center cross-sectional study with

limited sample size, we cannot establish causality between TyG index and AF incidence. Second, we did not distinguish between paroxysmal and persistent AF, which may have different relationships with TyG index. Third, while the TyG index alone showed modest discriminative ability (AUC = 0.661), its integration into comprehensive risk models substantially improved predictive performance (AUC = 0.843). Future multi-center prospective studies with larger samples are needed to validate TyG index for AF risk stratification and prognosis assessment.

In conclusion, hypertension, elevated BUN, elevated SUA, increased TyG index, enlarged LAD, and diuretic use are independent risk factors for AF in CHF patients, while elevated Ccr, elevated TC, and ACEI/ARB use are protective. The TyG index is independently and linearly associated with AF risk in CHF patients and holds clinical value for early identification of high-risk individuals. Routine monitoring of TyG index in CHF management may facilitate individualized risk assessment and reduce AF incidence.

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