Usefulness of Triglyceride-glucose index for detecting prevalent atrial fibrillation in a type 2 diabetic population

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ABSTRACT
Objectives: Atrial fibrillation (AF) is the most common arrhythmia, which significantly jeopardizes global cardiovascular health through the complicated heart failure and stroke. Published studies have demonstrated the impact of insulin resistance on the genesis of AF. Hence, monitoring insulin resistance may be a possible way to improve the detection of early-stage AF. Accordingly, our work aimed to investigate the association between TyG, a surrogate of insulin resistance, and the prevalent AF, and to evaluate the potential of TyG to refine the detection of prevalent AF in a diabetic population.

Methods: This cross-sectional study was derived from the National Metabolic Management Center Program and included 3244 diabetic patients between September 2017 and December 2020. TyG was calculated as ln(fasting TG (mg/dL)× FPG (mg/dL)/2). AF was diagnosed according to electrocardiography and subjects’ self-reports.

Results: The prevalence of AF was 6.57%. In the fully adjusted model, each SD elevation of TyG cast a 40.6% additional risk for prevalent AF. In the quartile analysis, the top quartile showed a 2.120 times risk of prevalent AF compared with the bottom quartile. Smooth curve fitting demonstrated that the association was linear in the full range of TyG, and subgroup analysis suggested that the association was robust in several common subpopulations of AF. Furthermore, ROC results displayed an improvement for the detection of prevalent AF when adding TyG into conventional cardiovascular risk factors (0.812 vs. 0.825, P = 0.019), and continuous net reclassification index (0.227, 95% CI: 0.088–0.365, P = 0.001) and integrated discrimination index (0.007, 95% CI: 0.001–0.012, P = 0.026) also showed the improvement achieved by TyG.

Conclusion: Our data supported a linear and robust correlation between TyG and the prevalent AF in a diabetic population. Moreover, our results implicated the potential usefulness of TyG to refine the detection of prevalent AF in a diabetic population.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia. In 2017, about 37.6 million individuals were suffering from AF worldwide [1]. By increasing the risk of heart failure and stroke, AF cast a significant burden on the global cardiovascular health [2]. As a major risk factor of AF, diabetes has been demonstrated to increase the risk of AF by 40%, and the prevalence of AF has reached around 5% in diabetic patients [3,4]. Therefore, improving the early detection of prevalent AF, especially in patients with major risk factors like diabetes, comes with great significance. However, due to the nature of AF during the early stage, the detection rate by a single electrocardiography (ECG) is limited. Accordingly, a method to improve the detection of early-stage AF is needed.

As the pathophysiological nature of type II diabetes, insulin resistance (IR) has been identified to associate with AF in both clinical and laboratory studies. Early studies have revealed the association between metabolic syndrome, characterized by high IR levels, and the prevalent AF [5,6]. A recent study demonstrated that a higher homeostasis model assessment of IR was independently associated with the development of AF [7]. Furthermore, a study displayed that IR level was associated with AF recurrence after catheter ablation [8]. Consistent with the findings from clinical studies, a laboratory study has shown that IR could lead to an increased vulnerability of atrial myocyte to AF through increasing sarcoplasmic reticulum calcium content, enhancing diastolic calcium sparks, prolonging calcium transient duration, reducing conduction velocity, and facilitating repetitive ectopic focal discharge [9]. The above studies suggest the potential of monitoring the IR level to improve the detection of early-stage AF. However, the current gold standard of IR, euglycemic insulin clamp, requires specific equipment which is always unavailable in the primary care settings [10]. Therefore,
an easy-acquired and cost-effective surrogate of IR is needed to improve the detection of early-stage AF.

Triglyceride-glucose index (TyG) is a newly proposed cost-effective surrogate of IR [11], and it has also been identified as a surrogate of IR among diabetic patients [12]. Previous studies have revealed its value in identifying or predicting multiple diseases associated with IR [13–16]. Nevertheless, the association between TyG and the prevalence of AF in patients with diabetes is still unknown. Accordingly, our current work aimed to evaluate the association between TyG and the prevalent AF, and to investigate the potential usefulness of TyG to refine the detection of prevalent AF in the diabetic population.

2. Methods

2.1 Study population

The National Metabolic Management Center (MMC) was founded in 2016 as a nationwide diabetes care system in China. Based on the Internet of Things technology and advanced medical equipment for diagnosing and managing diabetes and its complications, the MMC program was proposed to establish a nationwide, reproducible, and standardized platform [17]. Our study was derived from the cross-sectional data from one MMC center at Yuhuan Second People’s Hospital, Yuhuan city, Zhejiang province. Between September 2017 and December 2020, 4255 type 2 diabetic patients aged ≥18 years old were enrolled in the MMC program at Yuhuan Second People’s Hospital. In the current analysis, 770, 26, and 96 patients were excluded for lacking fasting plasma glucose (FPG), triglycerides (TG), and AF data, respectively. Furthermore, 119 subjects were also excluded because of incomplete covariates data. Finally, our current analysis included 3244 type 2 diabetic patients into the statistical analysis (Figure 1). The central ethics committee of Yuhuan Second People’s Hospital approved the study protocol of the MMC program (Approval number: 201732014), and the program was conducted on the base of the Declaration of Helsinki. All included subjects provided the informed consent.

2.2 Data collection

All included subjects were people with a confirmed diagnosis of diabetes according to the published guideline [18]. The whole data collection process was conducted by the trained medical staffs according to a standardized operation protocol for all MMC centers. At the first stage MMC visit, all baseline data (including questionnaires, clinical and laboratory examinations) were collected from every included diabetic patient through an MMC-specialized electronic medical record system [17].

Social demographic characteristics, lifestyle variates, and medical history data were recorded via questionnaire. Education level was categorized into two groups: below high school and higher school or above. Family annual income was classified into three levels: <30000 Yuan, 30000 to 100000

Figure 1. Flow-chart of subject’s selection.
Yuan, >100000 Yuan. Current smoking was defined as a subject answering 'Yes' to the question 'Are you a current smoker?'. Current drinking status was defined as a subject answering 'Yes' to the question 'Are you currently drinking?'.

Clinical examinations were also conducted at MMC during the first visit. Patients were asked to take off their shoes and only wear light-weight clothes before measuring height and weight. When holding in a standing position, the patient's standard height was recorded to the nearest 0.1 cm by a calibrated stadiometer, and the standard weight was recorded to the nearest 0.1 kg by a calibrated digital scale. A calibrated electronic blood pressure monitor was used for blood pressure measurement after the patients complete a five-minute resting. For every patient, one specified physician performed three consecutive measurements with a two-minute interval between every two measurements, and the mean value of these recordings was brought into statistical analysis. Standard twelve-leads ECG was conducted when the patient holding in a supine position. A specialized cardiologist was employed to read the ECG results and give the final report; the conclusion of the ECG report was then imputed into the MMC-specialized electronic medical record system manually.

Blood samples were collected for each patient in an 8-h fasting condition. Blood samples were collected from the antecubital vein via venipuncture and then collected in the EDTA vacutainer tubes. Then, the blood samples were transported immediately to the central lab of Yuhuan Second People's Hospital (certified by the MMC program) for centrifugation and the subsequent laboratory analysis, all blood samples were analyzed under standard conditions. After examination, the quantified values of serum creatinine (Scr), total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting plasma glucose (FPG) were attached to the MMC-specialized electronic medical record system automatically.

2.3 Definitions

Body mass index was defined as the weight (kg) divided by height squared (m²). Obesity was defined as BMI ≥ 28 kg/m² [19]. Anti-hypertensive therapy was defined as self-reported use of anti-hypertensive medicine in the past 1 month. Similarly, lipid-lowering therapy was determined for self-reported use of lipid-lowering medicine in the past 1 month. Hypertension was defined as mean systolic blood pressure (SBP) ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg; subjects with self-reported anti-hypertensive therapy were also classified as hypertensive patients [20]. CVD history included a clear history of coronary heart disease, stroke, or peripheral arterial disease. TyG was defined following the formula: ln[TG (mg/dL)/FPG (mg/dL)]/2 [11]. The definition of AF included: (1) the ECG report identified AF (defined as a standard 12-lead ECG recording of ≥30s showing heart rhythm with no discernible repeating P waves and irregular RR intervals was diagnosed of AF) [2]; (2) the subject's self-report of AF history with clear medical examination evidence [21].

2.4 Statistical analysis

According to their data distributions, continuous variables were summarized as mean values ± standard deviation (SD) or median (quartile 1 to quartile 3). Categorical variables were shown as frequency (percentage). Student's t-test or Mann-Whitney test were performed to compare continuous variables between groups according to the distributions of variables. Chi-square test was employed to detect the difference in categorical variables between groups. The rank-sum test was used to tell the difference between groups regarding ordinal categorical variables. Multivariate logistic regression was conducted to define the independent correlation between TyG and the prevalent AF. The results were summarized as odds ratios (ORs) and 95% confidence intervals (95% CI). A generalized additive model with a spline smoothing function and a logarithmic likelihood ratio test were employed to elucidate whether the correlation between TyG and prevalent AF was linear. For the second part of the analysis, receiver operating characteristic (ROC) analysis and reclassification analysis (including continuous net reclassification index, NRI, and integrated discrimination index, IDI) were used to assess the potential usefulness of TyG to improve the detection of prevalent AF. All the analysis was performed by statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA), and SPSS 25.0 software (IBM corp). Statistical significance was determined as a 2-tailed P value < 0.05.

3. Results

3.1 Characteristics of included subjects

The characteristics of the subjects were summarized in Table 1. Of the 3244 included subjects, 213 (6.57%) had a history of AF. Regarding the demographic data, age, and family annual income did not differ significantly between AF subjects and non-AF subjects; the AF group had higher percentages of the male gender, current smoking and drinking status, and a higher education level than the non-AF group. About the anthropometric data, height, weight, BMI, WC, and DBP were significantly higher in the AF group than in the non-AF group; and the SBP level showed a trend to be higher in the AF group. As for the laboratory data, Scr, TG, and HDL-c showed a significant difference between groups while FPG, TC, and LDL-c did not. For the medical history data, the rates of anti-hypertensive therapy and lipid-lowering therapy and the prevalence of hypertension were significantly higher in the AF group. CVD history did not display a significant difference between groups. Finally, the value of TyG was substantially higher in the AF group than in the non-AF group (9.51 ± 0.74 vs. 9.17 ± 0.67, P < 0.001). As displayed in Figure 2, TyG had a near-normal distribution (mean value: 9.19, SD: 0.68).
Table 1. Subjects’ characteristics.

| Variables                  | Total (n = 3244) | AF (n = 213) | non-AF (n = 3031) | P value |
|----------------------------|------------------|--------------|-------------------|---------|
| Age (years)                | 56.19 ± 10.86    | 55.97 ± 13.25| 56.21 ± 10.67     | 0.757   |
| Male (%)                   | 1780 (54.87)     | 154 (72.30)  | 1626 (53.65)      | <0.001  |
| Education level (%)        | 0.014            |              |                   |         |
| below high school          | 2903 (89.49)     | 180 (84.51)  | 2723 (89.84)      |         |
| high school or above       | 341 (10.51)      | 33 (15.49)   | 308 (10.16)       |         |
| Family annual income (CNY) |                  |              |                   | 0.660   |
| < 30000                    | 503 (15.51)      | 33 (15.49)   | 470 (15.51)       |         |
| 30000–10000                 | 1430 (44.08)     | 88 (41.31)   | 1342 (44.28)      |         |
| > 100000                   | 1311 (40.41)     | 92 (43.19)   | 1219 (40.22)      |         |
| Current smoking (%)        |                  |              |                   | 0.006   |
| Current drinking (%)       | 1098 (33.85)     | 88 (41.31)   | 1010 (33.32)      | 0.017   |
| Height (cm)                | 162.64 ± 8.38    |              | 162.51 ± 8.34     | <0.001  |
| Weight (kg)                | 67.26 ± 11.63    | 72.09 ± 12.91| 66.92 ± 11.47     | <0.001  |
| BMI (kg/m²)                | 25.35 ± 3.44     | 26.53 ± 3.40| 25.27 ± 3.34      | <0.001  |
| WC (cm)                    | 89.54 ± 9.53     | 94.23 ± 9.43| 89.21 ± 9.45      | <0.001  |
| SBP (mmHg)                 | 122.89 ± 19.12   | 135.24 ± 18.78| 121.66 ± 19.14   | 0.057   |
| DBP (mmHg)                 | 74.71 ± 11.28    | 76.42 ± 12.56| 74.59 ± 11.18     | 0.022   |
| Scr (µmol/L)               | 63.00 (51.00– 77.00) | 90.00 (77.00– 126.00) | 62.00 (50.00– 75.00) | <0.001  |
| FPG (mmol/L)               | 8.00 (7.00– 9.00) |              | 8.10 (7.00– 12.00)| 0.136   |
| HbA1c (%)                  | 7.70 (6.70– 8.70) |              | 7.50 (7.00– 8.50) | 0.157   |
| TC (mmol/L)                | 5.04 (4.27– 5.87) |              | 5.04 (4.28– 5.85) | 0.300   |
| TG (mmol/L)                | 1.36 (0.93– 2.00) |              | 1.32 (0.92– 1.95) | <0.001  |
| HDL-C (mmol/L)             | 1.17 (0.99– 1.39) |              | 1.18 (1.00– 1.40) | <0.001  |
| LDL-C (mmol/L)             | 2.96 ± 1.00       |              | 2.96 ± 0.99       | 0.452   |
| Antihypertensive therapy (%)|                  |              |                   |         |
| Lipid-lowering therapy (%) |                  |              |                   |         |
| Statins (%)                | 348 (10.73)      | 33 (15.49)   | 315 (10.39)       | 0.020   |
| Ezetimibe (%)              | 348 (100)        | 33 (100)    | 315 (100)         | -       |
| Fibrate (%)                | 7 (2.01)         | 1 (3.03)    | 6 (1.90)          | 0.241   |
| Anti-diabetic therapy (%)  |                  |              |                   |         |
| Insulin (%)                | 2394 (73.8)      | 161 (75.6)  | 2233 (73.7)       | 0.544   |
| Non-insulin (%)            | 693 (21.4)       | 55 (25.8)   | 638 (21.1)        | 0.101   |
| Hypertension (%)           |                  |              |                   |         |
| CVD history (%)            | 293 (9.03)       | 25 (11.74)  | 268 (8.84)        | 0.154   |
| TyG                       | 9.19 ± 0.68      | 9.51 ± 0.74 | 9.17 ± 0.67       | <0.001  |

Data were summarized as mean ± SD or frequency (percentage) according to their data type.

Abbreviations: AF: atrial fibrillation; CNY: Chinese Yuan; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; Scr: serum creatinine; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TyG: triglycerides-glucose index.

3.2 Association between TyG and the prevalent AF in the diabetic population

Multivariate logistic regression revealed a significant association between TyG and the prevalent AF; the results were shown in Table 2. Without any adjustment, each SD increase of TyG would increase the risk of prevalent AF by 61.0%. After adjusting for demographic characteristics (including age, gender, education level, current smoking, and drinking status), the risk for one SD increase of TyG augmented to 63.6%. By further adjusting BMI, WC, Scr, TC, HDL-c, SBP, anti-hypertensive therapy, lipid-lowering therapy, and CVD history, the risk for one SD increment of TyG attenuated to 40.6%. Regarding quartile analysis of the logistic regression, the top quartile showed a 2.120 times risk of prevalent AF than the bottom quartile after full adjustment, and there was a significant trend toward a higher risk of prevalent AF across the quartiles (P for trend < 0.001).

Our study further employed the smooth curve fitting analysis to validate the significant trend toward a higher risk of prevalent AF across the quartiles. The results were displayed in Figure 3. The risk of prevalent AF elevated linearly with the increment of TyG in the full range of TyG. Furthermore, the logarithmic likelihood test demonstrated a significant linearity (P for non-linearity = 0.233).

We further conducted a subgroup analysis to assess the robustness of the association between TyG and the prevalent AF in several common sub-populations of AF (Figure 4). The OR was used to indicate the risk change per SD increase of TyG, and the association was adjusted by all covariates in model 2 of Table 2 except for the variates used to define subgroups. As the figure demonstrated, age, gender, obesity, and hypertension did not have any significant interaction with the association between TyG and the prevalent AF (all P for interaction > 0.05), and the OR in each subgroup was consistent with the main results derived from the whole diabetic population.

3.3 Usefulness of TyG to improve the detection of prevalent AF in the diabetic population

ROC and reclassification analysis were performed to assess the usefulness of TyG in detecting the prevalent AF among our diabetic subjects (Table 3 and Figure S1). The AUC of TyG alone was 0.631 (95% CI: 0.614–0.648, P < 0.001). By introducing into common cardiovascular risk factors (including age, gender, education level, current smoking, current drinking, BMI, WC, Scr, TC, HDL, SBP, anti-hypertensive therapy, lipid-lowering therapy, and CVD history), TyG could improve the overall identifying ability for prevalent AF (0.812 vs. 0.825, P for comparison = 0.019). Consistent with the results of ROC analysis, both continuous NRI (0.227, 95% CI: 0.088–0.365, P = 0.001) and IDI (0.007, 95% CI: 0.001–0.012, P = 0.026) demonstrated a significant improvement from TyG to detect prevalent AF.

4. Discussion

In the present analysis, our results demonstrated a significant association between TyG level and the prevalent AF in a diabetic population. Furthermore, the association was positively linear in the whole range of TyG, suggesting the risk of prevalent AF increased proportionally with the elevation of TyG. Moreover, our data revealed that the significant association was robust in several common subpopulations of AF, implicating the robustness of the association toward these common risk factors of AF. Additionally, our findings demonstrated significant improvements in the ROC and reclassification analysis when adding TyG into conventional.
Abbreviations: association, employed.

4.1 The linear association between TyG and the risk of prevalent AF

The results from the current analysis supported our hypothesis about the association between TyG and the prevalent AF and the potential usefulness of TyG for detecting prevalent AF in a diabetic population. The first part of our statistical analysis focused on the association between TyG and the prevalent AF in the diabetic patients. In the multivariate logistic regression analysis, our data displayed a significant association between TyG and the prevalent AF in the diabetic population after adjusting for demographic, laboratory, anthropometric, and medical history covariables, suggesting the association was significant and independent of the conventional cardiovascular risk factors. The logistic regression was conducted under the assumption that the association was linear in the full range of TyG. To confirm this assumption, a smooth curve fitting analysis together with a logarithmic likelihood test were employed. The smooth curve fitting analysis showed that the association between TyG and prevalent AF was positively linear in the whole range of TyG, and the logarithmic likelihood test demonstrated that the association was insignificant for non-linearity. These results implicated the risk of prevalent AF increased proportionally with the elevation of the TyG level, without any threshold or saturation effect, in the full range of TyG. The above 2 steps demonstrated the association between TyG and prevalent AF in the diabetic population, but whether this conclusion is applicable to common subpopulations of AF patients (defined by age, gender, obesity, hypertension) remained unknown. Subgroup analysis was designed to address this question. The results displayed that the main findings in the whole diabetic population were consistent in these subpopulations. Therefore, our main results are applicable to people elder or younger, male or female, obesity or not, with or without hypertension.

4.2 Value of TyG to detect prevalent AF

In the second part of our statistical analysis, the focus was shifted to the potential usefulness of TyG to improve the detection of prevalent AF in the diabetic population, and both ROC and reclassification analysis were employed to assess the effectiveness of TyG at a different angle. For TyG itself, the AUC for identifying prevalent AF was limited.

Table 2. Multivariate logistic regression assessing the association between TyG and the prevalent AF.

| Variables                  | Odds Ratio (95% CI) | Crude | P value | Model 1 | P value | Model 2 | P value |
|----------------------------|---------------------|-------|---------|---------|---------|---------|---------|
| TyG (Per 1 SD increase)    |                     |       |         |         |         |         |         |
| Quartiles of TyG           |                     |       |         |         |         |         |         |
| Quartile 1                 | Reference           |       |         | Reference|         |         |         |
|                           |                     |       | <0.001  | 1.636 (1.422, 1.882) | <0.001  | 1.406 (1.197, 1.650) | <0.001  |
| Quartile 2                 | 1.305 (0.808, 2.108) | 0.276 |         | 1.384 (0.854, 2.244) | 0.187   | 1.166 (0.694, 1.957) | 0.562   |
| Quartile 3                 | 1.724 (1.093, 2.719) | 0.019 |         | 1.807 (1.139, 2.865) | 0.012   | 1.286 (0.774, 2.136) | 0.332   |
| Quartile 4                 | 3.141 (2.063, 4.783) | <0.001 |         | 3.279 (2.130, 5.048) | <0.001  | 2.120 (1.303, 3.348) | 0.002   |
| P for trend                |                     | <0.001 |         | <0.001  |         | <0.001  |         |

Crude: no adjustment; Model 1: adjusted for age, gender, education level, current smoking, and drinking status; Model 2: further adjusted for BMI, WC, Scr, TC, HDL, SBP, anti-hypertensive therapy, lipid-lowering therapy, anti-diabetic therapy, and CVD history.

Abbreviations: TyG: triglycerides-glucose index; AF: atrial fibrillation; CI confidence interval; SD: standard deviation; BMI: body mass index; WC: waist circumference; Scr: serum creatinine; TC: total cholesterol; HDL-c: high density lipoprotein cholesterol; SBP: systolic blood pressure; CVD: cardiovascular disease.

Figure 2. Distribution of TyG values. The TyG values followed a near-normal distribution.
However, when introducing TyG into conventional risk factors of cardiovascular diseases, we observed a significant improvement of the model for the prevalent AF identifying ability. These results implicated the potential usefulness of TyG to refine the detection of prevalent AF in the diabetic population. However, we noticed that ROC analysis focused on the integral ability of the combined model to identify prevalent diseases. In other words, ROC analysis actually investigated the power of the whole model (cardiovascular risk factors + TyG) to detect the prevalent AF rather than evaluating the ability of TyG itself to refine the detection of prevalent AF. Therefore, ROC analysis may underestimate or overestimate the value of

Figure 3. Smooth curve fitting by GAM to evaluate the linearity of the correlation between TyG and the prevalent AF. The model was adjusted for age, gender, education level, current smoking and drinking status, BMI, WC, Scr, TC, HDL, SBP, anti-hypertensive therapy, lipid-lowering therapy, anti-diabetic therapy, and CVD history (The same as Model 2 in Table 2). The solid line in the plot referred to the estimated risk of prevalent AF, and the dotted lines indicated the pointwise 95% CI. As we can see in the plot, the association followed a linear pattern in the whole range of TyG, with a P for non-linearity = 0.234.

Figure 4. Subgroup analysis for the association between TyG and prevalent AF.
TyG itself [22], and we may not acquire accurate information regarding whether adding TyG into conventional cardiovascular risk factors would refine the accuracy of the identification of prevalent AF [23]. To address this question, statisticians have proposed reclassification analysis (including NRI and IDI) to evaluate the potential value of a novel marker to refine the identification of prevalent diseases from an angle different from ROC analysis [24–26]. In the current study, by introducing TyG into cardiovascular risk factors, both continuous NRI and IDI demonstrated a significant improvement in detecting prevalent AF. Based on the ROC and reclassification analysis, we have more evidence to conclude that applying TyG to the diabetic population may help to refine the detection of prevalent AF.

### 4.3 Comparison with previous data

Our findings were consistent with the results of two previous studies which reported the association between TyG and postoperative AF in patients with other baseline cardiovascular diseases [27,28]. In 2021, Wei et al. revealed a significant association between TyG level and the risk of postoperative AF in 409 patients with hypertrophic obstructive cardiomyopathy who underwent septal myectomy [27]. The OR for TyG reached 4.218 in their report, which is much larger than the results in our work, suggesting the potential powerful association between TyG and AF in this population. However, even with a high OR, the TyG index did not improve the prediction of postoperative AF when adding it into conventional risk factors. We hypothesize that the controversy between logistic regression and ROC results in their work was because they did not verify whether the association between TyG and AF was linear. There could be a saturation or threshold effect in the association between TyG and AF in their work, and the significant association could only exist in a part range of the TyG index. Under this condition, it is no surprise that merely adding TyG into conventional risk factors could not significantly improve postoperative AF prediction. In our analysis, although the OR for the association between TyG and prevalent AF was not as high as reported in Wei et al.’s study, we verified that the association was linear in the whole range of TyG, suggesting the value of TyG as a linear indicator of prevalent AF in the diabetic population. And both ROC and reclassification analysis suggested the significant value of TyG to improve the detection of prevalent AF. In another study, Ling et al. revealed that the TyG index was associated with new-onset AF in 549 patients who underwent percutaneous coronary intervention for myocardial infarction [28]. In their study, the OR for AF reached a high value of 8.884, but they did not verify whether the association between TyG and AF was linear in the full range of TyG, and they also did not evaluate whether adding TyG into conventional risk factors would improve the prediction of AF onset. Based on the 2 previous articles and our findings, we can conclude that the TyG index may associate closely with AF in patients with baseline cardiometabolic diseases. Additionally, findings from Tang Q et al.’s study were also similar with our findings [29]. In their work, they revealed an elevated pre-ablation TyG index was associated with an increased risk of late AF recurrence after radiofrequency catheter ablation in non-diabetic patients. Both of our analysis and their work highlighted the impact of TyG on the management of AF. However, their results suggest the value of TyG in predicting AF recurrence in non-diabetic patients while our findings implicate the usefulness of TyG to detect AF in diabetic patients.

### 4.4 Laboratory evidence supporting the association between IR and AF

Previous basic studies have provided laboratory evidence for the association between IR and AF. Early animal studies have demonstrated that the diabetic rat atrium had increased interstitial fibrosis, reduced expression of connexin 40, and decreased conduction velocity, leading to prolongation and dispersion of action potential duration [30,31]. A recent study by Chan et al. demonstrated that IR could lead to increased vulnerability of atrial myocyte to AF through increasing sarcoplasmic reticulum calcium content, enhancing diastolic calcium spikes, prolonging calcium transient duration, reducing conduction velocity, and facilitating repetitive ectopic focal discharge; and these changes were mediated through increased expression of TGF-beta1 (one of the major profibrotic mediators in the atria) and collagen, increased superoxide production, and abnormal upregulation of calcium-homeostasis-related proteins [9]. Consistent with Chan et al.’s findings, a previous study has demonstrated that pioglitazone, an insulin sensitizer, could attenuate atrial fibrosis in a rat model of AF via suppressing TGF-beta1 [32]. Oxidative stress caused by increased superoxide production could induce arrhythmogenic hyperphosphorylation of calcium-handling proteins through the activation of CaMKII, and CaMKII hyperactivity has been revealed to associate with AF [33]. Inhibition of reactive oxygen species or ox-CaMKII has been demonstrated to protect against proarrhythmic intracellular calcium handling in IR atria [34].

### Table 3. ROC and reclassification analysis for TyG to improve the detection of prevalent AF.

| Model                      | AUC (95% CI) | P value | P for comparison | NRI (continuous) | P value | IDI | P value |
|----------------------------|--------------|---------|------------------|------------------|---------|-----|---------|
| TyG                        | 0.631 (0.614, 0.648) | <0.001  | -                | -                | -       | -   | -       |
| Clinical risk factors*     | 0.812 (0.798, 0.825) | <0.001  | -                | -                | -       | -   | -       |
| Clinical risk factors + TyG| 0.825 (0.811, 0.838) | <0.001  | 0.019            | 0.227 (0.088, 0.365) | 0.001   | 0.007 (0.001-0.012) | 0.026 |

Clinical risk factors: age, gender, education level, current smoking, current drinking, BMI, WC, Scr, TC, HDL, mSBP, anti-hypertensive therapy, lipid-lowering therapy, anti-diabetic therapy, and CVD history.

Abbreviations: ROC: receiver-operating curve; TyG: triglycerides-glucose index; AF: atrial fibrillation; AUC: area under the curve; NRI: net reclassification index; IDI: integrated discrimination index; BMI: body mass index; WC: waist circumference; Scr: serum creatinine; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; SBP: systolic blood pressure; CVD: cardiovascular disease.
4.5 Limitations

It is necessary to list the limitations of our study when interpreting our results. Firstly, the cross-sectional nature of our research determined that our results could only provide a clue for the association between TyG and the prevalent AF and the potential usefulness of TyG to improve the detection of prevalent AF in the diabetic population. Secondly, our definition of AF relied on one-time electrocardiography and self-reports from patients. Therefore, the accuracy of the AF prevalence in our population could be compromised. Thirdly, our study was based on a diabetic population in southeastern China; whether our findings are applicable to patients with a different race and various socioeconomic and geographic conditions as well as different stages of AF is still unknown. Fourthly, our current study could not distinguish the subtype of AF (paroxysmal or persistent) based on current diagnostic criteria. Whether the association between TyG and the prevalent AF different between AF subtypes still need further studies to evaluate. Fifthly, the prevalence of AF among our population was relatively low when compared with the prevalence in other diabetic populations. Furthermore, the disproportion in the sample size of the studied subgroups could also cast an impact on the results of our analysis. Lastly, as in any observational epidemiologic study, residual confounding caused by some unincluded covariables could lead to bias in our results. For example, our database did not include information about electrolyte disturbances and agents that increased the risk of AF, and the duration of diabetes and the exact type of non-insulin anti-diabetic medications were also missed in a majority of our patients. Based on the above points, longitudinal studies with a larger sample size, a more reliable AF definition and differentiation and more detailed information about covariables are warranted in the future.

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