ORIGINAL ARTICLE

Evaluating the TyG Index's Role to Predict Cardiovascular Risk Score

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ABSTRACT

Introduction: The Triglycerides-Glucose Index (TyG), as a cost-effective and novel biomarker for insulin resistance, plays a pivotal role in the pathogenesis of heart disease. This study aims to assess the TyG's capacity to predict cardiovascular risk. To investigate the correlation between the TyG and the 10-year risk of heart disease determined by the Framingham Risk Score (FRS). **Materials and methods:** A comprehensive study of 3,832 Indonesian participants (aged 19-65, Male 3,415). TyG Index threshold determined by ROC curve analyses. Its relationship with cardiovascular risk was assessed using the chi-square test and bivariate correlation analysis. **Results:** 3,832 participants (1,647 with high TyG≥8.7795, mean age 38.86). There was a significant association between TyG Index and FRS (P=0.02, sensitivity 0.53 specificity 0.57 PR 1.537). TyG-BMI and FRS (P<0.001, sensitivity 0.63, specificity 0.55, PR 2.18). METS-IR (P<0.001, sensitivity 0.59, specificity 0.55, PR 1.862), treadmill exercise test and FRS (P<0.025, sensitivity 0.07, specificity 0.96, PR 2). Bivariate correlation analysis between FRS and TyG, TyG BMI, METS-IR, SBP, heart rate, weight, waist circumference, and fasting blood glucose (P<0.001). In subgroup analyses, there was no significant correlation between TyG Index and FRS in the diabetes and hypertension groups (P=0.360, P=0.344). **Conclusion:** This study shows a strong connection between the Triglycerides-Glucose Index and an elevated 10-year cardiovascular disease risk as determined by Framingham Risk Score. The effectiveness of The TyG Index in predicting cardiovascular risk is affected by hypertension and diabetes.
Malaysian Journal of Medicine and Health Sciences (2026) 22(SUPP1): 1-6. doi:10.47836/mjmhs.22.s1.1

Keywords: Metabolic syndrome, Insulin resistance, Cardiovascular diseases, Risk ssessment, Cardiovascular risk

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INTRODUCTION

Cardiovascular disease stands as a paramount concern for global public health, representing the leading cause of mortality. The impact of these diseases extends beyond individual health, contributing to a substantial burden on healthcare systems and necessitating early risk assessment and preventive strategies. In 2019, the prevalence of cardiovascular diseases rose to 523 million, resulting in 18.6 million deaths, an alarming increase from 271 million cases and 12.1 million deaths in a previous period (1). These epidemiological trends, particularly the 35% contribution of cardiovascular disease to all deaths in Asia in 2019, underscore the urgency of understanding and addressing this escalating health challenge (2).

The Framingham Risk Score serves as a pivotal instrument for estimating the 10-year risk of cardiovascular disease across diverse populations. The presence of metabolic syndrome and insulin resistance have been recognized as contributing variables that can increase the likelihood of cardiovascular risk, as evaluated by the utilization of Framingham Risk Score (3). Insulin resistance, characterized by reduced tissue sensitivity to insulin, results in impaired glucose uptake, leading to hyperglycemia. This condition triggers a cascade of metabolic changes impacting adipocyte function, promoting reactive oxygen species formation, and contributing to conditions such as obesity, inflammation, dyslipidemia, hypertension, endothelial dysfunction,

and atherosclerosis (4).

The TyG Index, recognized for its role as a novel biomarker of insulin resistance, exhibits correlations with an increased risk for developing type 2 diabetes mellitus, glucose metabolism impairment and insulin resistance (5). Recent studies highlight the TyG Index as a valuable tool for predicting cardiovascular incidents in individuals with type 2 diabetes mellitus (6). TyG Index also can predict CVD in individuals with normal glycemic status (7). This underscores its potential as an early predictive tool for cardiovascular disease, offering a valuable opportunity for risk stratification and intervention.

In addressing the global concern of cardiovascular disease, our study focuses on the nuanced relationship between the TyG Index and cardiovascular risk, specifically assessed through the Framingham Risk Score. Despite considerable progress in cardiovascular research, a critical gap persists regarding the intricate interplay of these metabolic markers. This investigation aims to fill this void by rigorously examining a substantial cohort, providing insights that may inform both clinical practices and broader public health strategies. Our study endeavors to contribute valuable information for early intervention and personalized risk stratification in the realm of cardiovascular health.

MATERIALS AND METHODS

Study Design and Population

This observational cross-sectional study, conducted from March 2021 to March 2023, enrolled 3832 participants from the medical check-up unit in Balikpapan. Ethical approval (Approval No. 3221/E10000/2023-S0) was obtained from the Pertamina Balikpapan Hospital Ethics Committee. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, and all participants provided written informed consent.

Inclusion Criteria

This study included participants aged 19 to 65 years who underwent medical check up at Pertamina Hospital Balikpapan between March 2021 and March 2023. Participants had completed medical record data including Age, Gender, systolic blood pressure (SBP), antihypertensive medication status, BMI, smoking status, fasting blood glucose and triglycerides level.

Exclusion Criteria

Participants were excluded if they have incomplete medical record or invalid laboratory data, known history of cardiovascular disease.

Participant Criteria

Participants with a history of type 2 Diabetes Mellitus, fasting blood glucose exceeding 125 mg/dl, blood glucose >200 or use of antihyperglycemic drugs were classified as having Type 2 Diabetes Mellitus. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or a history of hypertension or medication use.

TyG Index Determination

The TyG Index threshold (8.7795) was established using Receiver Operating Characteristics (ROC) curve analysis. Participants were categorized into low and high TyG Index values based on maximum sensitivity and specificity determined by the ROC curve.

Framingham Risk Score (FRS) Calculation

Computed for each participant, FRS considered age, gender, SBP, hypertension medication, smoking status, and Body Mass Index. Risk categories included FRS <10% (low), 10-20% (moderate), and >20% (high).

Data Collection

Trained physicians conducted interviews to gather smoking status, physical activity, past medical history (hypertension, type 2 diabetes mellitus, cardiovascular disease), drug history, and family history. Anthropometric measurements, such as body height (BH), body weight (BW), waist circumference, and BMI, were calculated using established formulas. Blood pressure was monitored using an Automated Blood Pressure Monitor HEM 7120 after a 15-minute rest. Fasting blood specimens were collected for glucose, triglycerides, total cholesterol, LDL, and HDL assessments, TyG Index were assess by using formula TyG Index = ln[Fasting Blood Glucose * Fasting Triglyceride Serum]/2.

Statistical Analyses

Continuous variables were reported as mean values with standard deviations (SD), while categorical variables were presented as numbers and percentages. The Chi-square test compared categorical variables (FRS and TyG), and bivariate correlation analyses assessed FRS and TyG as numerical variables, with $P < 0.05$ considered statistically significant.

Ethical approval

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RESULTS

Baseline Characteristics

From the baseline data of 3832 participants, 1647 exhibited a higher TyG Index (TyG Index Value ≥ 8.7795), while 2185 showed a lower TyG Index (TyG Index value < 8.7795). The mean age of all respondents was 38.86 years. Notably, there was no statistically significant difference between the two groups, with

ages of 39.98 ± 8.98 in the higher TyG Index group and 38.21 ± 8.77 in the lower TyG Index group (P = 0.126). Observing gender distribution, men were more likely to have a high TyG index. Specifically, 89.2% of males fell into the higher TyG index category, compared to 10.7% of females. This discrepancy was statistically significant (P < 0.001*), as shown in Table I.

Respondents with a higher TyG index also exhibited a greater waist circumference (91.38 ± 19.30cm) compared to those with a lower index (85.97 ± 16.86cm), showing statistical significance (P < 0.001*). However, there was no significant difference in BMI between the two groups (P = 0.838). Smoking prevalence did not differ significantly between the lower TyG Index group (28%) and the higher TyG Index group (26%) (P = 0.535), as shown in Table I.

Univariate Analysis

In terms of comorbidities, a significant difference was observed in the prevalence of type 2 diabetes mellitus between the two groups. The high TyG Index group had a prevalence of 13.8%, while the low TyG Index group had a prevalence of 3% (P < 0.001*). Although hypertension showed a higher prevalence in the high TyG Index group (17%) than in the low TyG Index group (10.4%), this difference lacked statistical significance (P = 0.614). Other lipid profile markers, including LDL-C, HDL-C, TG, and TC, did not exhibit statistically significant differences between the two groups as shown in Table I.

Table I: Baseline characteristic of the study participants categorized by dichotomous TyG-index

Variables	Triglycerides-Glucose Index		P-value	Total (n=3832)
	Low TyG Index (<8.7795) (n=2185)	High TyG Indeks (≥8.7795) (n=1647)		
Age	38.21±8.77	38±8.98	0.126	38 ±8.86
Gender				
Male	1950 (89.2)	1465 (88.9)	< 0.001*	3415 (0.89)
Female	235 (10.7)	182 (11.1)		417 (10.88)
WC (cm)	85.87±16.86	91.38±19.30	< 0.001*	88±14.33
BMI (kg/m2)	25.46±4.27	27.42±7.93	0.838	26±6.1
Smoking	609 (28)	403 (26)	0.535	1012 (26.4)
T2DM	66 (3)	227 (13.8)	< 0.001*	293 (7.6)
Hypertension	227 (10.4)	280 (17)	0.614	507 (13)
HDL-C	44.84±10.40	37.60±7.61	0.849	41.73 ± 9.97
LDL-C	132.57(36.52)	135.26 ±47.77	0.912	133.72 ± 38.88
TC	196 (38)	217 ±60	0.919	205.25 ± 50.73
TG	93 (27)	218 ±104	< 0.001*	146.91 ± 94.72
FBG	91 (10)	107 ±41	< 0.001*	98.85 ± 29
SBP	114 (10.44)	118 ±10.88	0.307	116 ± 10.78
Medication HT	88 (4)	75 (4,6)	0.445	163 (4.2)
Medication DM	42 (1.9)	28 (1.7)	0.793	70 (1.8)

Data is displayed in the form of mean ± standard deviation (SD) or as a percentage frequency
Triglyceride and Glucose Index(TyG), Low-Density Lipoprotein Cholesterol (LDL-C), Fasting Blood Glucose (FBG), Body Mass Index (BMI), Type 2 Diabetes Mellitus (T2DM), High Density Lipoprotein Cholesterol (HDL-C), Waist Circumference (WC), Total Cholesterol (TC), Systolic Blood Pressure (SBP) and Triglyceride Serum (TG).

Bivariate Analysis

Evaluating the relationship between the Triglycerides Glucose Index and Framingham Risk Score (FRS) using chi-square analyses revealed a significant association (P = 0.02). The TyG Index emerged as a useful tool for categorizing individuals with low and high cardiovascular disease risk, demonstrating sensitivity of 0.53, specificity of 0.57, and a prevalence ratio (PR) of 1.537. The TyG-BMI Index displayed an even stronger relationship with FRS (P < 0.001), exhibiting sensitivity of 0.63, specificity of 0.55, and PR of 2.18. METS-IR with FRS also demonstrated a significant relationship (P < 0.001) with sensitivity of 0.59, specificity of 0.55, and PR of 1.862 as shown in Table II.

Table II: Framingham Risk Score association with other variables.

Variables	P-value	Sensitivity	Specificity	Prevalence Ratio
TyG	0.02	0.53	0.57	1.537
TyG BMI	0.000*	0.63	0.55	2.18
METS-IR	0.000*	0.59	0.55	1.86
PLR	0.513	0.50	0.46	0.911
MLR	0.065	0.46	0.47	0.77
TC HDL Rasio	0.060	0.46	0.59	1.3
LDL HDL Rasio	0.326	0.45	0.58	1.15
TG HDL Rasio	0.842	0.48	0.51	1.02
TET	0.025	0.07	0.96	2

The TyG Triglycerides glucose index, TyG BMI Triglycerides glucose-body mass index, METS-IR the metabolic score for insulin resistance, PLR platelet lymphocyte ratio, MLR monocyte lymphocyte ratio, TC HDL Total cholesterol – high density lipoprotein ratio. LDL HDL low density lipoprotein- high density lipoprotein ratio, TG HDL triglycerides – high density lipoprotein ratio. TET treadmill exercise test.

The Treadmill exercise test exhibited a statistically significant association with FRS (P=0.025). While the test's sensitivity was 0.07, indicating a low ability to identify individuals with high FRS, its specificity was 0.96, suggesting a high ability to identify individuals with low FRS (Prevalence Ratio = 2).

In exploring the correlation of FRS with other biomarkers, some variables, including TC-HDL, LDL/HDL ratio, TG-HDL, and Monocyte-lymphocyte ratio, did not show statistically significant relationships with FRS ($P > 0.05$). Further exploration is needed to understand their potential correlations with other biomarkers Table II.

Subgroup Analysis

Subgroup analysis revealed that the TyG Index's predictive value was most pronounced in the TET Positive ($P < 0.001$), TET Negative ($P = 0.002$), Non-Hypertension ($P < 0.001$), and Non-DM ($P < 0.001$) groups. However, the TyG Index exhibited insignificance in relation to FRS in the DM and hypertension groups ($P = 0.360$ and $P = 0.344$, respectively), indicating limitations in its predictive capability for specific comorbidities.

This comprehensive analysis underscores the potential of the TyG Index as a valuable tool in cardiovascular risk assessment, emphasizing its strengths and limitations across diverse populations and health conditions.

DISCUSSION

TyG Index and Cardiovascular Risk

Our investigation delves into the relationship between the Triglycerides-Glucose Index (TyG) and cardiovascular risk, aiming to enhance risk assessment strategies. Initially identified as an insulin resistance marker (8), the TyG Index reveals compelling associations with traditional cardiovascular risk factors (6,7). Its links with obesity, metabolic syndrome, and recognized risk elements spotlight its potential to identify at-risk individuals (4). A standout finding is the robust association between TyG Index and 10-year cardiovascular risk (9–13), , suggesting its utility as a cost-effective biomarker. The significant p-value (0.02) and sensitivity/specificity around 50-60% position TyG as a complementary risk factor in clinical practice. A prevalence ratio of 1.537 underscores TyG's effectiveness in predicting cardiovascular risk, making it 1.537 times more likely for high TyG individuals to exhibit a greater Framingham Risk Score.

Insulin Resistance and Cardiovascular Pathogenesis

Understanding TyG's role as an insulin resistance indicator becomes crucial in unraveling cardiovascular disease mechanisms. Insulin resistance is recognized as a contributor to metabolic dysfunction and cardiovascular disease (14). Insulin resistance contributes to metabolic dysfunction (14), endothelial damage (5), and the formation of atherosclerotic plaque (15). Our results align with previous research, showing consistent correlations between TyG Index and Framingham Risk Score. These associations remain robust across categorical and numerical analyses, corroborating findings from Barzegar et al. (2020) and Yueqiao Si et al. (2021) (7,16). While the TyG Index alone showed the correlation with pathogenesis and risk for cardiovascular disease, the combination with BMI significantly enhances the power of TyG Index in assessing cardiovascular risk (17). TyG-BMI and METS-IR emerge as key players in predicting cardiovascular risk and also proven to be a reliable surrogate marker for insulin resistance and risk of cardiovascular disease (17,18). Their combined impact, especially TyG-BMI's reinforced significance with a p-value < 0.001 and a Prevalence Ratio of 2.18, highlights their potential in identifying individuals at varying cardiovascular risk levels. METS-IR introduces a novel approach as a non-insulin biomarker, displaying a robust correlation with Framingham Risk Score. Sensitivity of 0.59 and specificity of 0.55 accentuate its accuracy in identifying high-risk individuals. While not as significant as other variables, the Treadmill Exercise Test proves valuable in cardiovascular risk assessment, displaying a sensitivity of 0.07 and a high specificity of 0.96. Its role lies in efficiently categorizing individuals with low-risk Framingham Risk Scores.

Holistic Cardiovascular Risk Assessment

Our study emphasizes the need for a comprehensive approach to cardiovascular risk assessment. Integrating

TyG Index, TyG-BMI, METS-IR, and the Treadmill Exercise Test with traditional risk factors provides a more accurate understanding of cardiovascular risk. Recognizing the TyG Index as a prognostic tool in clinical practice is underscored by its potential to predict cardiovascular events and its correlation with insulin resistance (5). TyG Index cost-effectiveness and ease of use make it a valuable addition to risk management strategies (5,9).

Towards Public Health Impact

An in-depth understanding of TyG, insulin resistance, and their role in cardiovascular disease development is pivotal for reducing the burden of cardiovascular disease on public health (11,19). In summary, our study contributes nuanced insights into the TyG Index's potential as a practical and informative biomarker in cardiovascular risk assessment, offering a balance between simplicity, cost-effectiveness, and prognostic accuracy.

Limitations

Cross sectional design prevents us from observing the causal relationship between variables. The data comes from a single centre, which reduces the external validity of this study, also the randomization is not performed, which may introduce selection bias.

CONCLUSION

The TyG Index, a cost-effective surrogate biomarker for insulin resistance, demonstrates significant predictive abilities for 10-year cardiovascular risk assessed by the Framingham Risk Score. Alongside risk scores like TyG-BMI Index, METS-IR, and clinical assessment, it supports crucial clinical decisions. Further investigations are needed, especially in populations with co-morbidities like type 2 diabetes mellitus and hypertension. The Treadmill Exercise Test aids in identifying low-risk patients. Collaborative efforts between patients and healthcare providers are key to maximizing the TyG Index's utility in battling cardiovascular disease. As research evolves, the TyG Index remains a pivotal player in this ongoing fight.

ACKNOWLEDGEMENT

This study was presented in abstract form at the ACSA-2023 and published as a part of the symposium supplementary materials. The full manuscript has not been previously published or submitted elsewhere. No external funding was received for this study.

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