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Triglyceride-Glucose Index in The Prediction of Adverse Cardiovascular Events in Patients with Coronary Artery Diseases

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Abstract

Cardiovascular disease remains a formidable threat to global health, with its prevalence steadily increasing over the past two decades, underscoring its pervasive and life-threatening impact on humanity.The triglyceride-glucose (TyG) index offers a novel perspective as an alternative indicator of increased long-term cardiovascular risk and insulin resistance. Elevated TyG index values have been correlated with an increased risk of cardiovascular events.

In this metanalysis, we searched for "triglyceride glucose index AND cardiovascular outcome" studies in PubMed, Cochrane, Web of sciences and Google scholar. We considered patients with coronary artery disease (CAD) who had a cardiovascular outcome at in-hospital or on follow-up, for a systemic review reported through hazard ratio (HR) analysis. Twenty studies were selected to examine the correlation between cardiovascular outcomes and TyG index in patients admitted for CAD. These twenty observational studies were comprised of1,52,846patients.

Included studies in our metanalysis revealed a significant association between the TyG index and Major Adverse Cardiovascular Events (MACE), with hazard ratios ranging from 1.06 to 12.92 after adjusting for confounders.In hospital-based MACE analysis involving 4839 participants, those in the highest quartile of TyG (≥9.37) exhibited a hazard ratio of 1.83 (95% CI: 1.27, 2.64), while a continuous increase in TyG index was associated with a hazard ratio of 1.23 (95% CI: 1.10, 1.38).Overall, the included studies consistently demonstrated a significant relationship between elevated TyG index levels and adverse cardiovascular outcomes.

Though further research is needed to solidify this associations, the TyG index holds promise as a simple and accessible tool for identifying individuals at risk of cardiovascular complications.

Keywords: Triglyceride Glucose Index, Cardiovascular Outcome, Major Adverse Cardiac Events.

Introduction:

Cardiovascular disease is the main cause of premature death and significantly adds to the worldwide burden of disease. The triglyceride glucose index (TyGindex)has been reported as a potential predictor

of adverse cardiovascular events in patients with coronary artery disease (CAD).[1-2]Similarly, the TyGindex calculated from fasting triglyceride and glucose levels, has been reported to reflect insulin resistance.[3]This increase in cardiovascular risk, highlights that TyG index has the potential to be used as a valuable tool for risk prediction in CAD patients. Cardiac risk factors, such as diabetes, hypertension, smoking, family history and dyslipidaemia are major cardiac risk factors for CVD. [4]

Insulin resistance, a key feature of metabolic syndrome, is not only linked to an elevated risk of cardiovascular disease but also shows a substantial correlation with an increased risk of major adverse cardiovascular events (MACE).[5]Persistent low-level inflammation resulting from obesity exacerbates insulin resistance, contributing to the onset and progression of diabetic complications. In addition,obesity is one of the established risk factors for diabetes mellitus.[6]Furthermore, higher glucose may cause myocardial damage in patient with diabetes, which affects the cardiac function. [7-8]The ischemic myocardium depends on glucose for anaerobic metabolism, thus requiring heightened glucose uptake and metabolism to sustain myocardial function. [9-11]The TyG index serves as an alternative measure to assess insulin resistance and in turn cardiovascular events, a condition which is primarily characterized by reduced insulin sensitivity, commonly observed in various metabolic disorders.

Further research and clinical studies are crucial to solidify its role in cardiovascular risk assessment. Limited data exists on the TyG index and its association with cardiovascular outcomes in the Indian population. While global studies suggest a potential link between elevated TyG index and cardiovascular risk, specific insights into the Indian context are sparse. Given the unique genetic, lifestyle, and dietary factors prevalent in India, dedicated research is essential to understand the applicability and predictive value of the TyG index in this population.Previously published studies have reported the relation of TyG index with coronary artery diseases and high major adverse cardiac events.

Our current systemic review metanalysis aimed to amalgamate published literature evidence, focusing on evaluating the association between TyG index, a marker derived from triglyceride and fasting glucose level and cardiovascular outcome, shedding light on its role as a predictive indicator for cardiac related events.

Methods

Literature search:

We performed a rigorous literature search, including the use ofPubMed, Cochrane Library, and other search engines, looking for last 10 years data on our search strategy, “Triglyceride glucose index AND cardiovascular outcome”. Additional relevant studies were sought by exploring pertinent literature references.Duplicates were eliminated prior to initiating the screening process. Primary screening involved reviewing titles and abstracts, followed by acquiring and reading the full text of selected literature for a subsequent rescreening process. Studies with inappropriate study population, study design and events were removed (Figure 1).

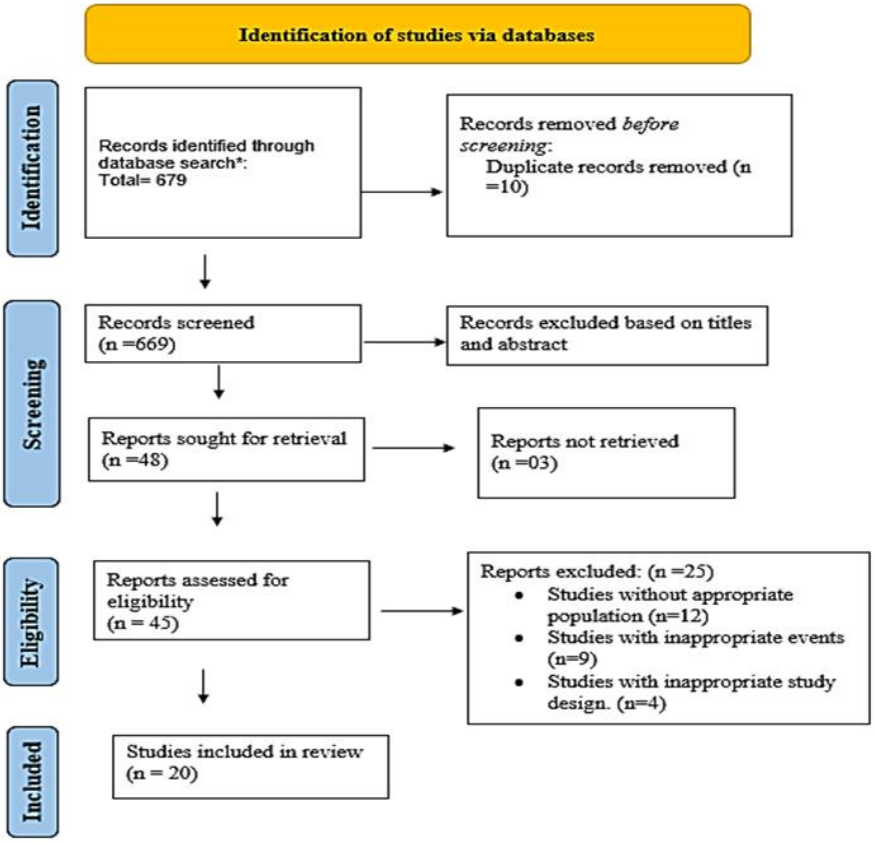

Figure 1: illustrates findings from the included study through the PRISMA flow chart.

Study selection:

Studies involving populations admitted for non-cardiovascular diseases, peripheral artery disease, those lacking presentation of cardiovascular events, focusing solely on the relation between calcification score and TyG-index, studies published in the last decade, and those involving only ICCU admitted patients were excluded. On the other hand,observational studies with patients admitted for coronary artery diseases, heart diseases and suspected stable CAD, chronic coronary syndrome, chronic total disease, chronic heart disease and acute ischemic stroke with cardiovascular outcome at hospitalization or follow up were included.We chose the articles with the higher information or the largest sample size when utilizing the same population across multiple studies.

Studies with the following criteria were considered: 1) full length articles 2) population with >18 years age 3) patients with TyG index measured at the time of admission 4) participants with any heart related disease (Studies with population admitted for coronary artery disease, acute coronary syndrome, and suspected stable CAD were considered). 5) Studies with cardiovascular outcome measured(the cardiovascular outcomes were defined as any cardiac events during hospitalization and at follow-up period, including cardiovascular death, cerebrovascular stroke, re-myocardial infarction, and re-vascularization). 6) Definitions: The TyG index calculated as [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. TyG index with continuous or categorized valueswere both considered.

Data extraction

We independently performed literature searches for data extraction and quality assessment of the included studies. The subsequent information was obtained through extraction of author's name, year of publication, country, mean age of population in their study, data extraction time period, type of population, sample size, follow-up time duration, the values of TyG index presented in their study, TyG index cut off, hazard ratio and adjustments.

Results:

The twenty observational cohort studies[12-31]with the total population of1,52,846 (Range: 386-141243)were enrolled between the year 2002 to 2020 with mean age of 59.4 years, published from 2018-2023. A study byZhai*et al.*[19]reported in-hospital mortality while other nineteen studies had only reported major cardiac adverse eventsat 1 year to 13.2years median time follow-up. To evaluate the independent effect of TyG index for cardiovascular outcome, studies presented in tertials and quartiles[13,14,16-21,23,24,26,29-31]showed the value of TyG index ranging from 7.08 to 9.62 and studies with continuous value[12,15,22,25,27,28] had a mean value of 9.60±0.42 for TyG index as an independent predictor of MACE.

Major adverse cardiac events or cardiovascular events:

A total of seventeen studies with major adverse cardiac events at follow up were reported, including 140213 patients with different diagnosis like ACS, premature ACS, acute myocardial infarction, coronary heart disease, acute ischemic stroke, or transient ischemic attack (TIA), MINOCA participants, and chronic coronary syndrome. The hazard ratio for highest TyG index value in the studiesranged from 1.15to 12.92. These data indicatehigher TyG index is significantly associated with higher incidences of MACE,both during in-hospitalization and throughout the follow-up period.

Furthermore,three studies reported cardiac death;one of which was in-hospitaland two reported death at follow-up[19].The study with in-hospital cardiac death reported a HR=1.83 (1.27, 2.64) for TyG ≥9.37 quartiles and HR = 1.23 (1.10, 1.38) for TyG index value (continuous) in 4839 participants. Similarly, studies by Neglia*et al.*[14]and Zhou*et al.*[29]showed HR =2.41 (1.55–3.75) and HR=1.94 (1.63-2.30), respectively, at 5 years with a median of 3.9 years of follow-up.

Discussion

There is a significant amount of literature that points towards a possible relationship between TyG index and many metabolic diseases. The clinical evidence indicates a positive association between an elevated TyG index and adverse outcomes in individuals with coronary artery diseases. In this systemic review we found that a higher TyG index was indeed associated with all-cause mortality, non-fatal myocardial infarction (MI), recurrent myocardial infarction, unstable angina, congestive heart failure, stroke and post-discharge revascularization [percutaneous coronary intervention (PCI)] andcoronary artery bypass grafting (CABG).These results indicate that elevated TyG index levels could be linked to an increased risk of coronary artery disease, thusserving as an independent risk factor for cardiovascular disease incidence in the general populationbeyond the traditional clinical information. The TyG index is a marker calculated using the formula [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. This index has been proposed as a simple and cost effective tool to assess insulin resistance. Higher TyG values are associated with increased insulin resistance, indicating a potential risk factor for conditions like Type 2 Diabetes Mellitus (T2DM) and cardiovascular diseases. Monitoring the TyG index can provide insights into metabolic health and aid in early identification of insulin resistance.

The hyperinsulinemic-euglycemic clamp is considered the gold standard for assessing insulin resistance (IR), but it has its drawbacks, such as being costly, time consuming and invasive. Homeostasis model assessment of IR (HOMA_IR) is widely used, but relies on insulin concentration examination, which is not routinely measured clinically. Our systemic review of available literature demonstrates that the TyG index is a cost effective and valid surrogate marker of insulin resistance, offering a reproducible and reliable alternate. [32-34]

Animal studies suggest that insulin resistance plays a key role in both the initial and advanced phases of atherosclerosis, while hyperglycaemia primarily influences the early stages of this condition. Furthermore, it appears that insulin resistance alters the impact of insulin on the vascular wall, exhibiting an anti-atherogenic effect in insulin-sensitive states and a pro-atherogenic effect in insulin resistance stage.[35-36]Similarly, research indicates that individuals with type 1 diabetes who exhibit elevated levels of insulin resistance tend to have an increased risk of coronary disease.[37-38] Insulin resistance extends beyond reduced glucose uptake; it constitutes a multifaceted syndrome significantly elevating cardiovascular disease risk. The intricate connections between insulin resistance and accompanying dyslipidaemia, hypertension, hypercoagulability and atherosclerosis result from various likely causes and the interaction of genes influencing insulin resistance with those independently affecting lipid metabolism, blood pressure regulation, coagulation and arterial wall biology.[39-40]

Insulin resistance contributes to cardiovascular disease through dual pathways: the formation of atherosclerotic plaques and the development of ventricular hypertrophy and diastolic abnormalities, both culminating in heart failure.[41] Numerous extensive population-based studies indicate that hyperinsulinemia, which serves as a surrogate marker for insulin resistance, anticipates the occurrence of coronary heart disease. [42-44] The TyG index demonstrates links to adverse outcomes across various cardiovascular diseases. This includes patients with stable coronary artery disease (CAD) who exhibit less developed collateral networks in the coronary vessels and those with chronic total occlusion. [13,45] In a recent study, the TyG index was found to predict long-term outcomes. Notably, a TyG value of >9.68 showed 65% sensitivity and 63% specificity, yielding an area under the curve (AUC) of 0.7 (95% CI, 0.65–0.77).[46]The National Health and Nutrition Examination Survey (NHANES) data from 2001 to 2020 reported the TyG index value of>8.96 was significantly correlated with Congestive Heart Failure (CHF) (AUC: 54.75%, 95% CI:0.542-0.614), stroke (AUC:52.32%,95%CI:0.529)-0.584), heart attack (HA) (AUC:55.67%, 95%CI:0.595-0.646), and coronary heart disease (CHD) (AUC: 50.31%,95%CI:0.592-0.646).[47]Similarly,ahigh-risk population of CVD Cohort Study, whichincluded 102,061 subjects reporteda high risk of CVD in those with a TyG value of 9.04 (specificity 0.575, sensitivity 0.754). The area under the ROC curve was 0.780 (confidence interval [CI]: 0.777, 0.783, $p < 0.01$). [48]A TyG index exceeding 10 showed a notable correlation with coronary stenosis above 70%, demonstrating a sensitivity of 57% and specificity of 75%.[49]Yang*et al*.reported thatan AUC of 0.677 (95% CI 0.597–0.754) for predictive TyG index value and reported TyG is more effective than triglyceride or blood glucose level alone. [22]Similarly,a moderate predictive value ofthe TyG index was reported for MACE (AUC 0.66, 95% CI: 0.61e0.71, $p < 0.001$) in MINOCA patients.[24] An observational study with Receiver Operating Characteristic(ROC) curve analysis for the TyG indexshowed that the AUC was 0.670 (95% CI: 0.633– 0.707, $P < 0.001$) in T2 Diabetes ACS patients. In addition, this study reported that theTyG index and the GRACE risk score had a combinedAUC value of 0.751 (95% CI: 0.718–0.784, $P < 0.001$) for cardiovascular events.[27]This study therefore demonstrates the predictive value of higher TyG index on ROC.

The event-free survival analysis according to the quartile of TyG index, as reported by Jin*et al.*,shows that the patients within the highest quartile of TyG index (>9.17) presented with significant lower event-free survival at 36 month follow-up.[13] Another similar study with TyG index usingtertilesrevealed that the cumulative incidence of MACE increased with higher tertilesvalue (mean value 9.841)of the TyG index with log-rank test, P = 0.005 at 3 years follow-up. [15]In addition, Yue *et al.*, reported a significant log rank value for MACCEssurvival curves plot using TyG index value in tertiles.[16]In a similar study Zhang *et al.*demonstrated that the incidence of MACE with a high TyG index was significantly higher ($p<0.001$) among T2DM patientsat five years.[20]The findings across these studies consistently suggest that there is a direct correlation between elevated TyG index value and cardiovascular complications.

The TyG index serves as an indicator of insulin resistance in both fasting blood glucose (reflecting liver insulin resistance) and fasting triglycerides (reflecting insulin resistance from adipose cells).[50] Hence, the TyG index offers a more comprehensive assessment of insulin resistance. Furthermore, the metabolic consequences of insulin resistance, such as elevated blood glucose and dyslipidaemia, synergistically contribute to increased blood pressure. This synergy can result in damage to both the vascular and kidney systems, posing a significant risk to cardiovascular and renal health. [51]

The hyperglycaemia end products and free radicals inactivates nitric oxide (NO) and causes damage to endothelium, leading to vasodilation which in turn impairs myocardial energy metabolism. Another mechanism includes upregulation of the renin angiotensin system and increased reactive oxygen species, which impairs cardiac calcium processing capacity and leads to mitochondrial defects. [11] In addition, insulin resistance and inadequate insulin signalling can inappropriately activate the renin angiotensin-aldosterone system, leading to oxidative stress, inflammation and impaired immune modulation. These factors collectively pose a significant threat to cardiac function.[52-53]

Lipids non-enzymatic glycosylation, in conjunction with hypertriglyceridemia and hyperglycaemia, are contributing factors in the development of atherosclerosis. Hypertriglyceridemia, specifically, can lead to the production of LDL, fostering atherosclerosis and diminishing the protective impact of high-density lipoprotein.[54]The degree of coronary artery disease (CAD) correlates significantly with factors such as the arterial stenosis and calcification, the presence of coronary plaque, the occurrence of multi-vessel disease and the development of in-stent restenosis post angioplasty. In comparison with HOMA-IR, the TyG index can be more independently linked with the presence of calcified coronary artery plaques under cardiac computed tomography. [55]The GRACE score which predicts the in-hospital and 6-month mortality, whencombined with TyG index, can provide better predictive value in ACS patients. [28]Shen *et al.*reported that incorporating the TyG index into the prediction model, along with the Gensini score (quantifying angiographic atherosclerosis)and left ventricular ejection fraction (LVEF) can estimate the risk of all-cause mortality.[56]Similarly, the inclusion of syntax score and TyGindex in a baseline risk model demonstrated an incremental impact on predicting major adverse cardiovascular Events (MACE). [57]

Furthermore, arterial stiffness represents an early form of functional damage in the vascular aging process, characterized by a reduction in arterial elasticity and an increase in pulse pressure. A growing number of studieshave strongly indicated that arterial stiffness serves as a robust predictor for the future risk of acute coronary syndrome, heart failure and stroke. [58-61]Previous studies have shown the predictive value of TyG index in identifying arterial stiffness in healthy elderly population.[62-63] These findings consolidate the relationship between the TyG index and cardiovascular events, elucidating the contributing factors and associated parameters influencing these outcomes(Figure 2).

A recent study on sex-specificcomparison between TyGindex and modified triglyceride glucose indices in theprediction ofnew-onset hypertension in middle-aged and older adults reported that TyG is significantly associated with new-onset hypertension only in female gender while TyG waist circumference and TyG waist to height ratio are significantly associated with new-onset hypertension in both genders.[64]The reasons behind the different relationship between TyG index and new onset hypertension in men and women are still not clear. TyG value of >9.53 is a strong risk factor for cardiac events in females compared to males. [65]Likewise, the disparity in insulin resistance related fat distribution between genders may elucidate the relatively higher increase in coronary calcification in women compared to men with type 1 diabetes.[37]The relationship of cardiovascular diseases, including atherosclerosis, hypertension, the acute coronary syndrome and retinopathy have been thoroughly investigated with TyG index.[66]

Exploring the TyG index in Indian context could unveil valuable insights into the early detection of cardiovascular events and contribute to more targeted preventive strategies. Further research and collaboration are warranted to bridge this gap in knowledge and establish a comprehensive understanding of the TyG index's role in assessing cardiovascular risk among the diverse population in India. Such endeavours will not only enhance our understanding of metabolic health but also inform more tailored and effective public health interventions.

Conclusion

The TyG index emerges as a valuable tool in predicting major cardiovascular events.Its simplicity and cost-effectiveness make it a compelling alternative to the homeostatic model assessment of Insulin Resistance (HOMA-IR). The TyG index, derived from routine lipid and glucose measurements, serves as an effective indicator of insulin resistance, thus offering clinicians a practical means of assessing cardiovascular risk. As a predictor of adverse outcomes, its ease of calculation and widespread availability puts it favourably in clinical settings, contributing to more accessible and efficient risk assessment when compared to traditional methods. Nonetheless, further research and integration of TyG index into routine practice could enhance our ability to identify individuals at higher risk of cardiovascular events, enabling targeted interventions and improved patient outcomes.

It is imperative to acknowledge that our systematic review is not devoid of limitations, which warrant critical consideration and scrutiny. Even with the meticulous control of various confounding variables in the studies, certain factors,such asdietary habits and lifestyle remain unavoidable and cannot be eliminated. Moreover, variations in the definition of major adverse cardiovascular events (MACE) and study design may impact the interpretation of the results. The majority of analysed data in our metanalysis originated from East Asian populations, which underscores the necessity for further research to assess the applicability of the TyG index in diverse races and ethnicities.

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