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Original Research

Prognostic value of triglyceride-glucose index on predicting major adverse cardiovascular events in hypertensive patients: a systematic review and meta-analysis

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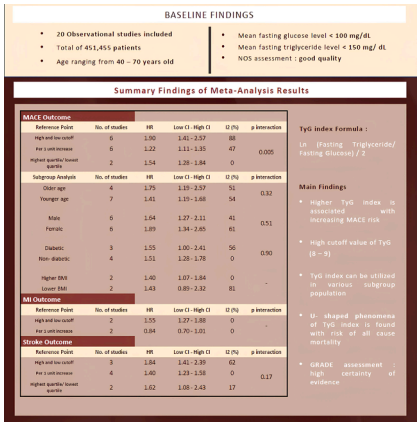
GRAPHICAL ABSTRACT

Summary findings of the association of TyG index with major adverse cardiovascular events



Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HIEC, hyperinsulinemic-euglycemic clamp; HOMA IR, homeostasis model assessment for insulin resistance; IR, insulin resistance; MACE, major adverse cardiovascular event; MI, myocardial infarction; RCT, randomized controlled trial; TyG, triglyceride-glucose.

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ABSTRACT

Background: Triglyceride- glucose (TyG) index, a marker of insulin resistance, has been shown to be associated with the incidence of cardiometabolic diseases including hypertension. However, the prognostic role of TyG index is unknown. Hence, we aim to determine the association of TyG index with major adverse cardiovascular events (MACE) in hypertensive patients.

Methods: Systematic searching was conducted on 3 databases up till November 2024. We included studies with hypertensive patients despite their comorbidities. Outcome measured is MACE and its individual components. Random effect model meta-analysis is done to pool the results with similar reference point.

Results: Twenty observational studies with a total of 451,455 patients of 40 – 70 years old are included. Meta-analysis result shows that higher TyG index is associated with a statistically significant increased risk of MACE (HR 1.90, CI: 1.41 – 2.57, I^2 88 %), myocardial infarction (HR 1.55, CI: 1.27 – 1.88, I^2 0 %), stroke (HR 1.84, CI: 1.41 – 2.39, I^2 62 %), all- cause mortality (HR 1.86, CI: 1.70 – 2.03, I^2 0 %) and cardiovascular mortality (HR 1.08, CI: 1.04 – 1.11, I^2 0 %). Subgroups of older and younger population, male and female gender, diabetic and non- diabetic population, and higher BMI patients retains the statistically significant risk of MACE ($p < 0.05$). U- shaped phenomena of TyG index is also demonstrated with the risk of all- cause mortality.

Conclusion: TyG index is a reliable prognostic marker of MACE in hypertensive patients and can be utilized in population despite their age, diabetic status, and gender.

1. Introduction

Hypertension impacts approximately one billion adults' population worldwide, and the global population of adults with hypertension is expected to increase to 1.56 billion by the year 2025[1,2]. Hypertension is a primary contributor to long-term major adverse cardiovascular events (MACEs)[3]. Identifying and managing cardiovascular disease (CVD) risk early in hypertensive patients is crucial for assisting clinicians and reducing the global burden of CVD.

Insulin resistance (IR) is a key factor in various metabolic disorders including CVD[3]. Previous research found an association between IR and major CVD risk factors including hypertension[4]. In recent years, numerous simplified mathematical models have been developed to assess insulin resistance[5]. Two them are the hyperinsulinemic-euglycemic clamp (HIEC) test, currently the most advanced method for measuring insulin resistance and is widely regarded as the "gold standard", and the homeostasis model assessment for IR (HOMA-IR)[6,7]. However, HIEC test is highly time consuming and expensive,[7]. while HOMA-IR relies on a serum insulin test, which is not readily available in all primary care hospitals,[8]. highlighting the need for a simpler and more accessible alternative.

One biomarker that has gathered considerable interest as an affordable diagnostic tool is the triglyceride glucose (TyG) index[9,10]. The TyG Index is notable for its simplicity of computation (TyG index = ln [fasting serum triglycerides (mg/dL) × fasting blood glucose (mg/dL)/2].)[9]. in addition to the widely available assay of triglyceride and glucose. One of the growing areas of interest is its potential to reflect underlying insulin resistance (IR)[11]. TyG index offers an inexpensive, accessible, and readily available biochemical marker to measure IR. Moreover, it is more practical since it does not rely on insulin measurements[11]. Previous meta-analysis has demonstrated an association between the TyG index and the incidence of hypertension[12]. However, the association between the TyG index and the risk of MACEs in hypertensive patients remains unclear. Additionally, to date, no comprehensive meta-analysis has specifically evaluated the prognostic value of the TyG index in hypertensive patients, particularly in predicting the risk of MACEs. This study aim to determine the association of TyG index with MACEs in hypertensive patients.

2. Methods

2.1. Search strategy

Searching on three databases (PubMed, Science direct, and CochraneLibrary) were conducted up until November 2024. Searching strategy includes different terminologies used to describe triglyceride- glucose index and hypertension. In the search strategy, we exceptionally entered keyword for the population (hypertensive patients) and the exposure (triglyceride- glucose index) together with their variations. A detailed search strategy is elaborated in **Supplementary 1**. This review article is officially registered in PROSPERO with ID CRD42025634989. We adhered to the PRISMA manuscript writing checklists and is elaborated in **Supplementary 2**.

2.2. Study selection

Systematic selection under prespecified inclusion and exclusion criteria was done by two reviewers independently (WH and MAW). Any discrepancies or disagreements of study selection results were further discussed with AN and ARK. We selectively include studies that fit with our research question as elaborated in our PICOTT framework (**Supplementary 3**). We included both observational studies (longitudinal or cross sectional) and post hoc randomized controlled trials.

The inclusion criteria are hypertensive patients of all ages, despite being primary or secondary hypertension that have been assessed for fasting triglyceride and glucose level. We included studies that studied the association of TyG index and major adverse cardiovascular events. We exclude studies reporting novel TyG parameter modifications such as TyG- body mass index, TyG- waist circumference, etc. We further excluded studies of review article, case report/ series, and animal studies. We also did not include studies that evaluate the incidence of hypertension in general population and exclude studies that do not have complete data.

2.3. Risk of bias assessment

All observational studies included in this review were assessed for risk of bias using the Newcastle-Ottawa Scale (NOS). Two reviewers (AN and MAW) independently conducted the risk of bias assessment, with any disagreements being resolved through consensus. Three domains were assessed, which are selection, comparability, and outcome. Furthermore, the selection domain comprises 4 items, namely representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and outcome not present at the start of the study. For the outcome domain, the items assessed were assessment of outcome, length of follow-up, and adequacy of follow-up.

2.4. Data extraction

Data from the included studies were retrieved by two reviewers (WH and AN) and two other reviewers (ARK, SR) evaluated all the collected data for inconsistency. Any discrepancy and dispute are discussed

thoroughly in a team meeting. Data extracted from each included study include author, study name/ center, period of study, inclusion and exclusion criteria, study design, sample size, age, gender, baseline glucose, triglyceride, and blood pressure level, use of insulin, reference point used for risk assessment, subgroups described in each study when available, types of regression used, duration of follow up, and clinical outcomes of interest.

2.5. Outcome measures

Main outcome being evaluated in this study is major adverse cardiovascular events (MACE). MACE is defined according to each study (**Supplementary 4**) but in general is a composite of myocardial infarction, stroke, acute heart failure, cardiovascular mortality, and additionally all-cause mortality. Additionally, each component of MACE is also evaluated as a single outcome of interest (myocardial infarction – fatal and non-fatal event; stroke – ischemic and hemorrhagic; all- cause mortality; cardiovascular mortality).

2.6. Statistical analysis

Statistical analysis is conducted with ReviewManager version 5.4. Clinical outcomes with binary data of MACE outcome and its individual components will be pooled using inverse variance random effect model to generate a pooled hazard ratio. Result from multivariate analysis will be selected for meta-analysis and the adjustment factors used in each studies are described in **Supplementary 4**. A separate statistical analysis will be done based on different reference value used in each study's regression analysis (per unit increase of TyG, specific TyG cutoff based on each study's criteria, highest to lowest quartile/ tertile level of TyG).

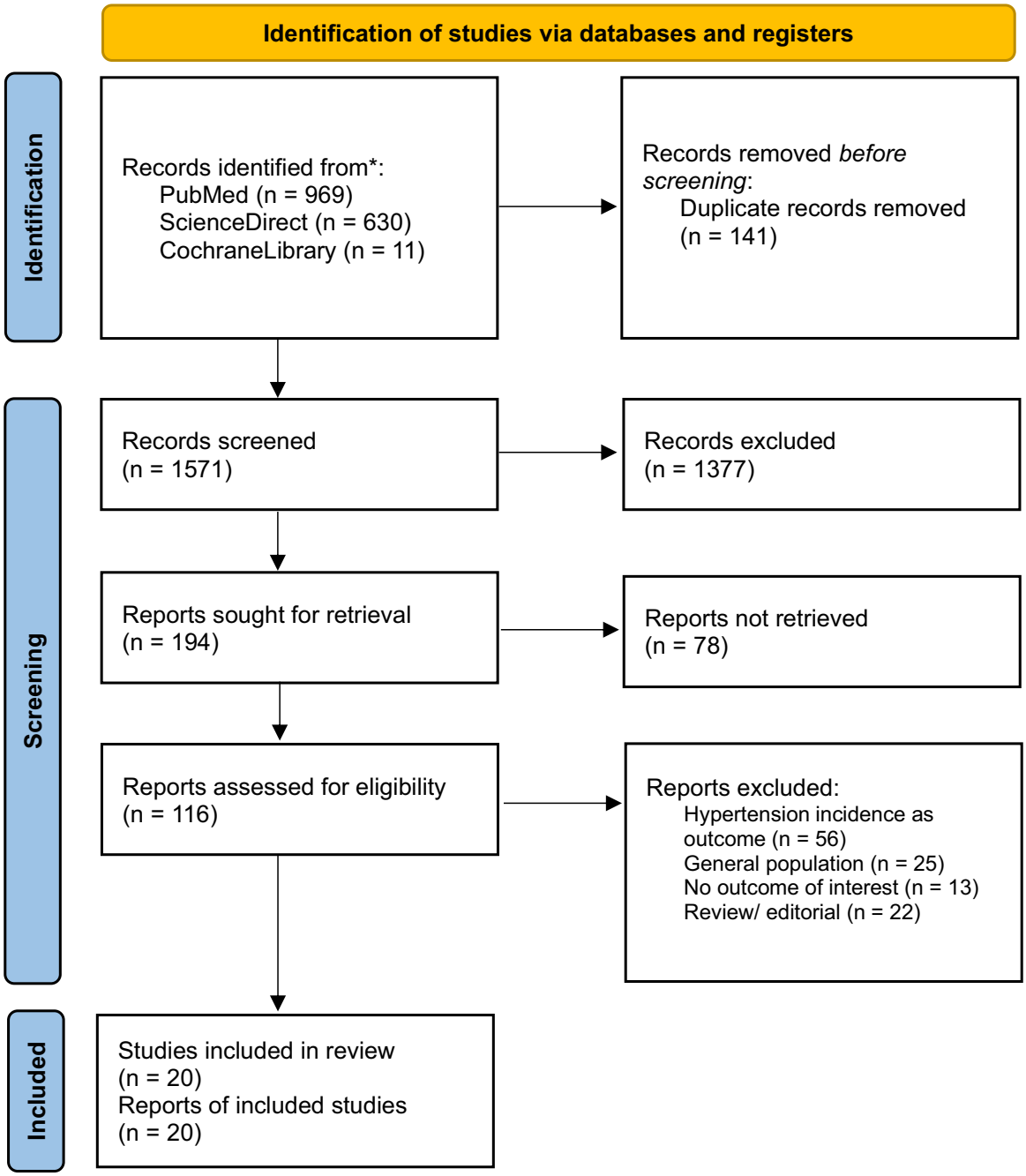


Fig. 1. PRISMA flow diagram.

Subgroup analysis will be done on elderly population and younger population, male and female population, diabetic and non- diabetic population, and higher and lower BMI population. Test for subgroup differences will be conducted with Z score test.

Due to the conflicting reported results from previous studies regarding the U- shaped phenomena between TyG index level and risk of MACE in hypertensive patients, we conducted a specific subgroup analysis comparing highest and lowest quartile level of TyG index with the middle quartile TyG index to determine the U shape phenomena. When both the highest and lowest quartile level is associated with a statistically significant increased risk of MACE when compared to the middle quartile, then the assumption of U- shaped phenomena is made.

Sensitivity analysis is conducted to assess the robustness of the data and evaluate the large effect size of a single study. Confidence interval of 95 % and p value < 0.05 were selected as statistical significance cutoff. Heterogeneity is being assessed by I^2 with an interpretation of $I^2 < 40$ % as not important heterogeneity, 30 – 60 % as moderate heterogeneity, 50 – 90 % as substantial heterogeneity, and 75 – 100 % as considerable heterogeneity. Publication bias is assessed with funnel plot for asymmetry. Finally, evidences generated from meta-analysis were evaluated with GRADE assessment for certainty.

3. Results

3.1. Study selection and characteristics

Systematic searching from three databases resulted in a total of 1610 articles after which 141 duplicates are removed and further title and abstract screening resulted in 116 articles to be assessed for eligibility through full text evaluation. Eventually, 20 articles[13–22]. are included in the review and all of them are included in the meta-analysis. (Fig. 1) Among the 20 studies, three of them are prospective cohort studies, one is post hoc RCT study, and the remaining are retrospective cohort studies. A total of 451,455 hypertensive patients are included in which 10 studies specifically included patients with cardiovascular diseases. One study included elderly population and one study included only younger population. Overall, the average fasting glucose level from the included studies are below 100 mg/dL (< 5.51 mmol/L) and the average fasting triglyceride are below 150 mg/dL (< 1.7 mmol/L). The follow up time in the included studies range from 1 – 13 years. (Table 1)

3.2. Risk of bias assessment

Using the NOS, all the studies were rated as good quality. Most studies scoring eight on the NOS. All 20 studies received the maximum number of stars for the following items: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, outcome not present at the start of the study, and adequacy of follow-up. (**Supplementary 5**)

3.3. Data synthesis

3.3.1. TyG index and MACE outcome

Six studies evaluated the association of higher TyG index cutoff compared to lower TyG index cutoff with the outcome of MACE. Cutoff criteria from each study varied from 7.8 – 9.3 which may contribute to the heterogeneity observed. Higher TyG index cutoff is associated with a statistically significant increased risk of MACE (HR 1.90, CI: 1.41 – 2.57) however the result is found to be heterogenous (I^2 88 %) (Fig. 2) (Table 2). Sensitivity analysis by leave one out analysis did not find any important change in heterogeneity level (removal of study by Zhang Y et al. resulted in the most reduction of I^2 into 79 %). Removal of studies with acute coronary syndrome population (Huang J et al. and Qiu et al.) also did not result in changes in heterogeneity level.

Six studies evaluated the association of per 1 unit increase of TyG index and MACE outcome. Every 1 unit increase of TyG index is associated with a statistically significant risk of MACE (HR 1.22, CI: 1.11 – 1.35, I^2 47 %). (Fig. 2) Sensitivity analysis by leave one out analysis found that removal of study by Li C et al. resulted in a reduction of heterogeneity level to 37 % and the risk remains statistically significant ($p < 0.0001$).

Two studies evaluated the association of different tertile/ quartile comparison with MACE outcome. Tao S et al. reported the comparison the 4th quartile and the 1st quartile of TyG index in their population while Yang K et al. reported the comparison of the 3rd and 1st tertile of TyG index in their population. We finally decided to pool the result and found that higher tertile/ quartile is associated with a statistically significant risk of MACE. (Fig. 2)

Furthermore, to evaluate the U-shaped phenomena of TyG index and risk of MACE, additional analysis comparing highest tertile level (T3) versus the middle tertile level (T2) of TyG index and the lowest tertile level (T1) with T2 were done. No statistically significant result were found. (**Supplementary 6**)

3.3.1.1. Age subgroups. Four and seven studies evaluated the association of TyG index with MACE outcome in older and younger age population, respectively. Cutoffs of older and younger age varied between 65 and 75 years old. Li C et al. study specifically recruited only patients < 40 years old. Older age and younger age are both associated with a statistically significant increasing risk of MACE (HR 1.75 and 1.41, respectively). However, the hazard risk difference of the two subgroups is not statistically significant (p 0.32). (**Supplementary 7**) Additional analysis of only including studies with similar reference point (Huang J et al. and Zhang et al. with higher and lower TyG index cutoffs) also did not result in a statistically significant hazard risk difference between the two subgroups (p 0.095).

3.3.1.2. Gender subgroups. Six studies evaluated the association of TyG index with MACE outcome in male and female population. Male and female population are both associated with a statistically significant increased risk of MACE (HR 1.64 and 1.89, respectively) and the difference of hazard risk between both groups are not statistically significant (p 0.51). (**Supplementary 8**) Additional analysis of only including studies with similar reference point (Huang et al., Li et al., Zhang et a. with higher and lower TyG index cutoffs) also did not result in a statistically significant hazard risk difference (p 0.37).

3.3.1.3. Diabetic subgroups. Three and four studies evaluated the association of TyG index with MACE outcome in diabetic and non- diabetic population, respectively. Both groups are associated with a statistically significant increased risk of MACE (HR 1.55, and 1.51, respectively) and the hazard risk difference between the two subgroups are not statistically significant (p 0.90). (**Supplementary 9**)

3.3.1.4. BMI subgroups. Two studies evaluated the association of TyG index with MACE outcome in higher and lower BMI population. Cutoffs of higher and lower BMI in the two studies are 25 and 28 kg/m^2. Higher BMI is associated with a statistically significant increased risk of MACE (HR 1.40, CI: 1.07 – 1.84) while lower BMI does not show similar significance (HR 1.43, CI: 0.89 – 2.32). (**Supplementary 10**)

3.3.2. TyG index and MI outcome

Four studies evaluated the risk of MI outcome with per unit increase of TyG index and with higher TyG index cutoff. Higher TyG cutoffs used in the included studies are 8.43 and 8.57. Higher TyG index cutoff is associated with a statistically significant increased risk of MI outcome (HR 1.55, CI: 1.27 – 1.88) while per unit increase of TyG index is not (HR 0.84, CI: 0.70 – 1.01). (**Supplementary 11**)

3.3.3. TyG index and stroke outcome

Four studies evaluated the risk of stroke outcome based on higher

Table 1
Characteristics of included studies.

Author	Study Name/ Sites	Year	Study Design	Population	Sample size	Age	Gender	Glucose level	Triglyceride level	Blood Pressure (mmHg)	Follow up
Cui H et al.	Kailuan study	2024	Retrospective cohort	Stage 1 and stage 2 hypertension (18 - 98 years)	88,384	51.07±12.39	Male 79.36 % (70,142/ 88,384)	5.47±1.65 mmol/ L	1.67±1.37 mmol/ L	129.88±20.76	mean 13.66 years
Ding W et al.	NHANES study	2024	Retrospective cohort	Patients with cardiovascular disease above 18 years	2185	66.86±0.36	Male 57.08 % (1247/ 2185)	(-)	(-)	(-)	mean 89.5 months
Hu L et al.	CHRS study	2022	Retrospective cohort	Hypertensive patients age > 60 years	8487	68,77	Male 52.76 %	6.01±1.31 mmol/ L	1.64±1.06 mmol/ L	149.79±18.23	median 1.72 years
Huang J et al.	Tianjin Medical University General Hospital	2024	Retrospective cohort	STEMI patients with hypertension	699	66.0 (58.0–73.0)	Male 74.1 % (518/699)	6.4 (5.4–8.5) mmol/ L	145.0 (111.0–201.0) mg/ dl	145.0 (128.0- 159.0)	(-)
Huang Z et al.	Kailuan study	2022	Prospective cohort	Hypertensive patients age > 18 years	19.924	56.78±11.13	Male 82.02 % (16,342/ 19,924)	(-)	(-)	141.43±19.05	median 9.97 years
Kazibwe et al.	SPRINT study	2024	Retrospective cohort	Hypertension patients without diabetes	9323	67.9 ± 9.38	Male 64.53 % (6016/ 9323)	98.8 ± 13.52 mg/ dl	119.08±59.03 mg/ dl	139.67±15.57	mean 3.8 years
Lee et al.	NHIS NSC 2.2 Database	2024	Retrospective cohort	Age > 19 years old patients	233.546	47.9 ± 13.3	Male 53.6 %	97.21±22.53 mg/ dl	118.46±70.20 mg/ dl	122.38±14.76	median 8.13 years
Li C et al.	Fuwai hospital	2024	Prospective cohort	Young hypertensive patients aged 18 - 40 years old	2.834	31.9 ± 5.8	Male 71.2 %	5.03±1.17 mmol/ L	1.82±1.31 mmol/ L	154.57±21.0	median 2.6 years
Liu H et al.	MIMIC- IV database	2024	Retrospective cohort	Patients with acute myocardial infarction	5208	64.0 years	Male 65.4 %	134.46±47.71 mg/ dl	124.65±65.38 mg/dl		
Liu Y et al.	Fuwai Central China Cardiovascular Hospital	2023	Retrospective cohort	Coronary heart disease and hypertensive patients (18 - 75 years)	1467	60.5 ± 9.4	Male 69.6 % (1021/1467)	5.40 (4.70–6.46) mmol/ L	1.36 (1.02–1.84) mmol/ L	134.1 ± 15.2	1 year
Pang et al.	NHCS USA	2023	Retrospective cohort	Hypertensive patients middle aged and elderly	3614	62.5 (no SD data)	Male 50.4 % (1821/3614)	(-)	(-)	(-)	mean 7.87 years
Qiu et al.	Fujian provincial hospital	2024	Retrospective cohort	Patients with type 1 MI	320	69.00 (62.00–74.50)	Women 100 % (320/320)	110.70 (93.96–142.65) mg/dL	133.30 (98.76–178.48) mg/ dl	SBP: 131.00 (114.50–147.00); DBP: 74.00 (66.00–83.00)	median 34.37 months
Tao S et al.	Hospital Information System Database in China - Japan Friendship Hospital	2023	Retrospective cohort	Coronary heart disease and hypertensive patients aged 18 - 80 years	810	66 (57–74)	Male 70.49 % (571/810)	5.91 (5.13–6.9) mmol/L	1.44 (1.06–1.94) mmol/L	SBP: 136 (123, 149); DBP: 79 (70, 86)	1 year
Wan Y et al.	SSACB study	2023	Prospective cohort	Adults with previous CVD history (20 - 74 years)	42,651	55.7 ± 11.1	Female 59.7 % (25,447/ 42,651)	4.9 (4.4, 5.5) mmol/ L	1.4 (1.0, 2.0) mmol/ L	SBP: 132.8 ± 19.3; DBP: 79.6 ± 10.6	median 4.7 years
Yang K et al.	SPRINT study	2021	Post hoc RCT	Hypertension patients without diabetes aged 50 - 75 years	9323	(-)	(-)	(-)	(-)	(-)	median 3.26 years
Zhang et al.	China Patient- Centered Evaluative Assessment of Cardiac Events study	2023	Retrospective cohort	High cardiovascular risk hypertensive patients aged 35 - 75 years old	2250	(-)	(-)	(-)	(-)	(-)	3.5 years
Zhang N et al.	CSPPT study	2023	Prospective cohort	Hypertensive patients age 45 - 75 years	7569	59.4 ± 7.6	Male 39.5 % (2991/7569)	(-)	(-)	SBP: 168.5 ± 21.1; DBP: 95.3 ± 12.1	median 4.5 years
Zhang Y et al.	Cardiovascular center of Beijing Friendship Hospital Database (CBD) bank	2020	Retrospective cohort	Patients diagnosed with ACS	3181	(-)	(-)	(-)	(-)	(-)	median 33.3-month (IQR 13.8, 49.8)
Zheng H et al.	NHANES study	2024	Retrospective cohort	Patients with CHD and hypertension	1126	(-)	(-)	(-)	(-)	(-)	median 76 months
Zhou et al.	NHANES study	2022	Retrospective cohort	Hypertensive patients > 18 years	8554	60.12 ± 16.07	Male 49.29 % (4216/ 8554)	115.87 ± 42.86 mg/dL	150.58 ± 117.66 mg/dL	SBP: 135.62 ± 21.35; DBP: 71.00 ± 16.07	median 82 months

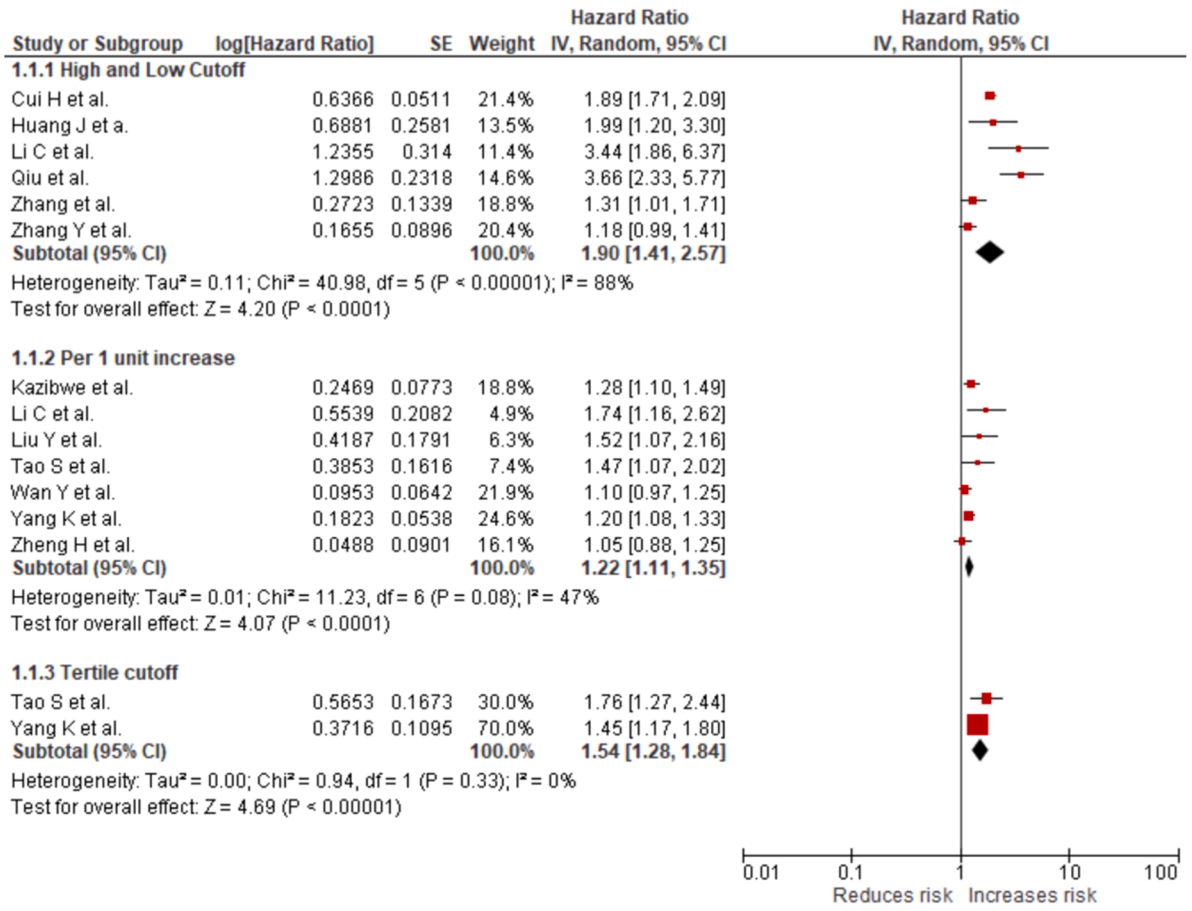


Fig. 2. Association of TyG index with risk of MACE outcome based on different reference points used.

and lower TyG index cutoff. The cutoffs used in the four studies ranged from 8.43 – 9.15. There is a statistically significant increased risk of stroke in the higher TyG index group (HR 1.84, CI: 1.41 – 2.39, I^2 62 %) compared to the lower TyG index group. Sensitivity analysis by leave one out analysis to address the heterogeneity level shows that removal of Zhang et al. study reduces the heterogeneity level to 0 % while still maintaining statistical significance of outcome. (Fig. 3)

Four studies evaluated the risk of stroke outcome based on per unit increase of TyG index and the result showed that per unit increase of TyG index is associated with 1.40 times increased risk of outcome with a statistically significant result ($p < 0.0001$). (Fig. 3)

Two studies evaluated the risk of stroke outcome in the highest quartile TyG index (Q4) compared to the lowest quartile group (Q1). Highest quartile group is associated with a statistically significant increased risk of stroke (HR 1.62) compared to the lowest quartile group. (Fig. 3)

Evaluation of the U-shaped phenomena based on quartile group level showed that when the highest and lowest TyG quartile group is compared to the middle quartile group (Q2 or Q3), no statistically significant increased risk of stroke outcome is found in the lowest quartile group. Only comparison between Q4 and Q2 group is associated with a statistically significant risk of outcome. (**Supplementary 12**)

3.3.3. TyG index and All- cause mortality outcome

Three and two studies evaluated the risk of all- cause mortality and TyG index based on higher and lower cutoff and highest and lowest quartiles group, respectively. Higher and lower cutoffs used in the included studies ranged from 8.43 – 9.45. Both reference points showed a statistically significant result of increasing risk of all- cause mortality (HR 1.86 and 1.32, respectively). We did not include study by Ding et al. due to different reference point used (tertile groupings). (Fig. 4**A**)

Evaluation of the U-shaped phenomena showed that the highest quartile group (Q4) and lowest quartile group (Q1) are associated with a statistically significant increased risk of all- cause mortality when compared to the middle quartile group (Q2) but not with Q3 group. There is an increased 1.55 and 1.13 risk of all- cause mortality in Q4 and Q1 group, respectively, when compared to Q2 group ($p < 0.0001$). (**Supplementary 13**)

3.3.3. TyG index cardiovascular mortality outcome

Two studies evaluated the risk of cardiovascular mortality in the highest TyG quartile group and the lowest quartile group. There is a statistically significant increased risk of cardiovascular mortality in the highest quartile group compared to the lowest quartile group (HR 1.08, CI: 1.04 – 1.11). (Fig. 4**B**)

Evaluation of the U- shaped phenomena did not show any statistically significant increased risk in comparison of the highest quartile group (Q4) and lowest quartile group (Q1) with the middle quartile group except for the statistically significant increased risk of outcome when comparing Q4 TyG group and Q2 group (HR 1.72, CI: 1.05 – 2.82). (**Supplementary 14**)

3.4. GRADE assessment

GRADE assessment of MACE, MI, stroke, all-cause mortality, and cardiovascular mortality revealed a high certainty of evidence. (**Supplementary 15**)

Table 2
Summary findings of meta- analysis.

MACE Outcome Reference Point	No. of studies	HR	Low CI - High CI	I2 (%)	p interaction
High and low cutoff	6	1.90	1.41 - 2.57	88	0.005
Per 1 unit increase	6	1.22	1.11 - 1.35	47	
Highest quartile/ lowest quartile	2	1.54	1.28 - 1.84	0	
Subgroup Analysis	**No. of studies**	**HR**	**Low CI - High CI**	**I2 (%)**	**p interaction**
Older age	4	1.75	1.19 - 2.57	51	0.32
Younger age	7	1.41	1.19 - 1.68	54	
Male	6	1.64	1.27 - 2.11	41	0.51
Female	6	1.89	1.34 - 2.65	61	
Diabetic	3	1.55	1.00 - 2.41	56	0.90
Non- diabetic	4	1.51	1.28 - 1.78	0	
Higher BMI	2	1.40	1.07 - 1.84	0	–
Lower BMI	2	1.43	0.89 - 2.32	81	
MI Outcome					
Reference Point	**No. of studies**	**HR**	**Low CI - High CI**	**I2 (%)**	**p interaction**
High and low cutoff	2	1.55	1.27 - 1.88	0	–
Per 1 unit increase	2	0.84	0.70 - 1.01	0	
Stroke Outcome					
Reference Point	**No. of studies**	**HR**	**Low CI - High CI**	**I2 (%)**	**p interaction**
High and low cutoff	3	1.84	1.41 - 2.39	62	0.17
Per 1 unit increase	4	1.40	1.23 - 1.58	0	
Highest quartile/ lowest quartile	2	1.62	1.08 - 2.43	17	
All Cause Mortality Outcome					
Reference Point	**No. of studies**	**HR**	**Low CI - High CI**	**I2 (%)**	**p interaction**
High and low cutoff	2	1.86	1.70 - 2.03	0	0.002
Highest quartile/ lowest quartile	3	1.32	1.08 - 1.60	51	
Cardiovascular Mortality Outcome					
Reference Point	**No. of studies**	**HR**	**Low CI - High CI**	**I2 (%)**	**p interaction**
Highest quartile/ lowest quartile	3	1.08	1.04 - 1.11	0	–

4. Discussions

The main findings from this study are as follows: (1) TyG index is associated with an increased risk of MACE, MI, stroke, all- cause mortality, and cardiovascular mortality outcomes (2) Subgroup analysis revealed that the statistically significant increasing risk of MACE outcome is seen in both older and younger population, male and female population, diabetic and non- diabetic population, and only in population with higher BMI (3) There are no statistically significant hazard risk difference between the subgroups being studied (4) U- shaped phenomena of TyG index and outcome risk is only seen in all- cause mortality outcome.

TyG index is a comprehensive statistical tool used to evaluate insulin resistance and had been shown to be highly correlated with HOMA-IR, [13,23]. one of the go to markers for identifying insulin resistance. However, due to the limitations of HOMA-IR, TyG index appears to be an alternative solution due to its practical use and not being influenced by insulin treatment and non- functioning beta cells of the pancreas[24]. Extending the results from previous studies that have associated TyG index and incidence of numerous metabolic disorders,[25]. our results further revealed the clinical significance of TyG index pertaining to adverse clinical outcomes specifically in hypertensive population. Specifically, study by Hariyoglu et al. also found that patients with high cardiovascular risk were associated with a higher risk of MACE[26,27]. Association of TyG index and hypertension occurs in part to the increased adrenergic sympathetic system, over-activation of the renin angiotensin aldosterone system, and enhanced sodium reabsorption which also eventually lead to increased cardiac workload with vascular damage that eventually results in increased risk of cardiovascular diseases[28,29]. In our study, we showed exactly the association of higher TyG index and the increased risk of MACE, MI, stroke, and mortality. Although how TyG index may enhance the prognostic value of individual parameters of fasting blood glucose and triglyceride levels remain unknown, several pathomechanism have been proposed. TyG index, reflecting insulin resistance, may impose metabolic imbalance with increasing inflammation and oxidative stress. This imbalances limit glucose bioavailability and allows fatty acid metabolism to take place which eventually lead to increased myocardial oxygen consumption[30,31]. Insulin resistance may also affect both macro and microcirculation through production of increased glycosylated products which will impair endothelial function[32]. Insulin resistance also contribute to platelet overactivation and induce thrombosis[33]. Insulin resistance inducing hyperglycemia and dyslipidemia may also promote the initiation and/ or progression of atherosclerosis[34]. Additionally, since cardiovascular disorders occur due to the interaction of multiple risk factors[35]., it is possible that the use of integrated parameters, such as to TyG index, may have an additional prognostic value.

As TyG index relies on fasting triglyceride and glucose level, its level can be theoretically influenced by patients' dyslipidemia and diabetic status. Proper management of such comorbidities may also be beneficial in adding the prognostic value of TyG index[25]. In the subgroup analysis of our study, we however showed that both diabetic and non-diabetic status are associated with an increasing risk of MACE. This finding revealed the prognostic role of TyG index is independent of diabetic status. However, it is important to emphasize that the included patients in our study had a well-controlled fasting blood glucose level. Additionally, although insulin resistance is proposed to be more prevalent in menopausal women due to the reduced protective effects of estrogen[36]., our study showed that both gender (male and female) are associated with a similar increasing risk of MACE with an increasing TyG index. Although the specific menopausal status in the female population is unknown, the average age in the included studies suggest an older population.

In this study, we also showed that TyG index can be useful in both the older group and younger group despite a higher prognostic value in the older group but there is a non- statistically significant difference between the groups. Younger age group is of particular concern due to the tendency to overlook the adverse clinical outcomes associated with cardiovascular risk factors, moreover, we found that only subgroup population with higher BMI is associated with a statistically significant result but not with the population with a lower BMI.

Interestingly, we found a statistically significant U shape phenomena of TyG index with all-cause mortality but not with other clinical outcomes. HOMA-IR, regarded as one of the more common insulin resistance markers, has also demonstrated similar finding[13]. Low TyG index may indicate either low fasting triglyceride and/ or glucose level or improved insulin resistance. The associated increased risk of outcome may occur possibly due to the earlier cause where low levels of both parameters have been proven to be a risk factor for increasing adverse outcome[37,38].

Despite most of the significant findings, there are several limitations and recommendations to be acknowledged before implementing the evidence derived from this study. The moderate to high heterogeneity presented in some of the meta-analysis result may occur due to the different in reference point used (especially specific dichotomous outcome) in which the cutoff used in each study is usually defined based on each study's population. Hence, we addressed this by calculating the pooled effect with a random effect model to account for this heterogenous population. Secondly, we are not able to conduct subgroup analysis in our pooled population based on the severity (grade) of hypertension and based on the status of dyslipidemia as a comorbid. We hypothesize that severity of hypertension can impact the prognostic value of TyG index, however, future studies with more data are recommended to prove this hypothesis. Thirdly, we are unable to demonstrate the

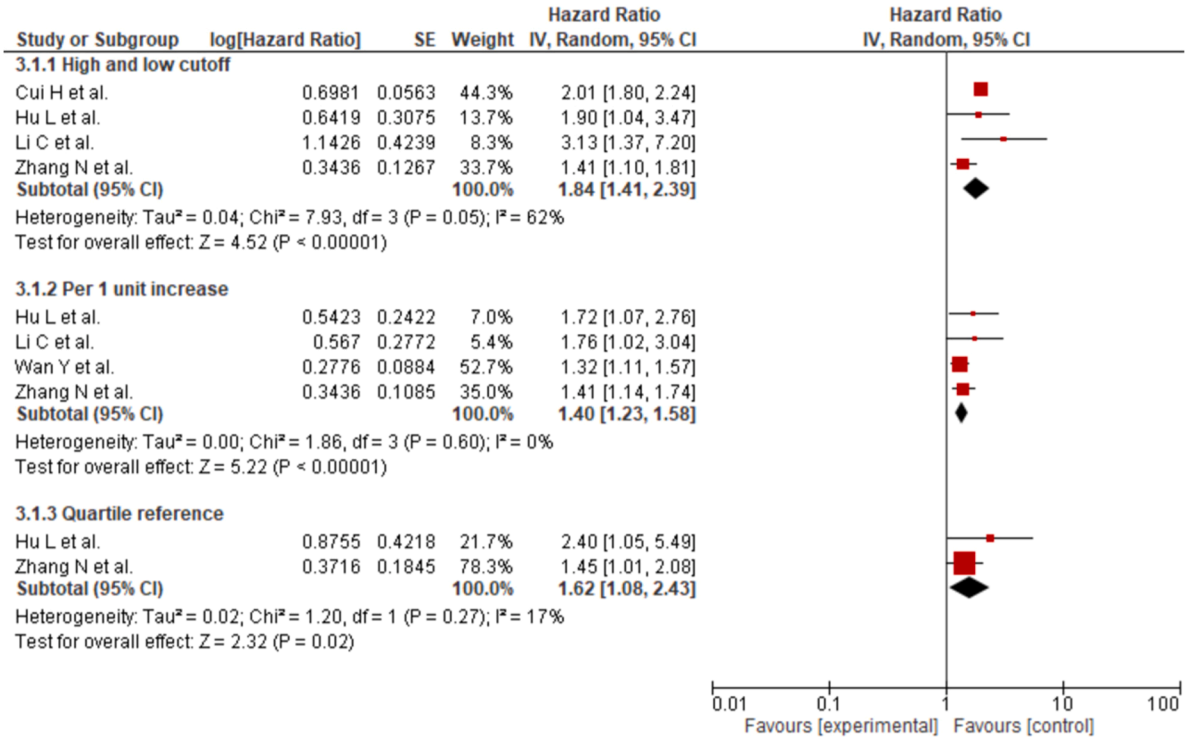
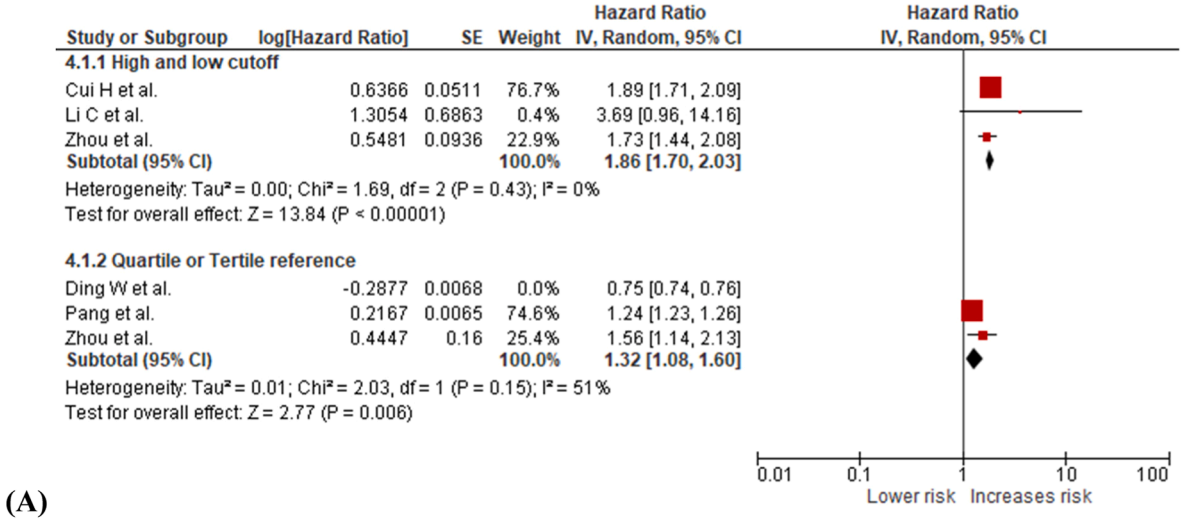
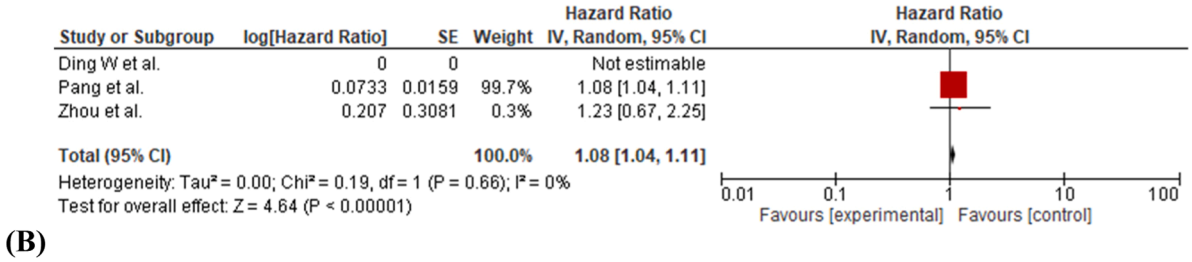


Fig. 3. Association of TyG index with risk of stroke outcome based on different reference points used.



(A)



(B)

Fig. 4. Association of TyG index with risk of (A) all cause mortality and (B) cardiovascular mortality outcome based on different reference points used.

prognostic value of monitoring the trends TyG index as a prognostic tool. Several studies have shown that TyG index is fluctuating over time and a more robust measurement of this changes may have an additional value. We also recommend to study the improved TyG index that incorporates BMI, waist circumference, glucose tolerance, and other parameters that have been researched previously. Additionally, due to the

advancing of artificial intelligence in healthcare, the role of machine learning in identifying high risk patients is also worth exploring. Several studies have shown the potential of machine learning in detecting high risk patients and hence, are promising for the development of better healthcare. Machine learning can also aid in determining high risk covariates in a statistical analysis that could help identify confounders that might alter the conclusion of a study[39–41].

5. Conclusion

TyG index is a reliable prognostic marker of adverse clinical outcomes in hypertensive patients and it can be utilized in population despite their age, diabetic status, and gender.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.100996.

References

[1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet [Internet]. 2005;365(9455):217–23. Available from: https://www.sciencedirect.com/science/article/pii/S0140673605177411.

[2] Forrester SJ, Dolmatova EV, Griendling KK. An acceleration in hypertension-related mortality for middle-aged and older Americans, 1999-2016: an observational study. PLoS One 2020;15(1):e0225207.

[3] Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest 2000;106(4):453–8. Aug.

[4] Wang F, Han L, Hu D. Fasting insulin, insulin resistance and risk of hypertension in the general population: a meta-analysis. Clin Chim Acta 2017;464:57–63. Jan.

[5] Van Minh H, Tien HA, Sinh CT, Thang DC, Chen CH, Tay JC, et al. Assessment of preferred methods to measure insulin resistance in Asian patients with hypertension. J Clin Hypertens (Greenwich) 2021;23(3):529–37. Mar.

[6] Janchevska A, Gucev Z, Tasic V, Polenakovic M. Homeostasis model assessment - insulin resistance and sensitivity (HOMA-IR and IS) index in overweight children born small for gestational age (SGA). Pril (Makedonska Akad na Nauk i Umet Oddelenie za Med Nauk 2018;39(1):83–9. Jul.

[7] Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metab 2015;19(1):160–4.

[8] Xu J, Xu W, Chen G, Hu Q, Jiang J. Association of TyG index with prehypertension or hypertension: a retrospective study in Japanese normoglycemia subjects. Front Endocrinol (Lausanne) 2023;14:1288693.

[9] Ramdas Nayak VK, Satheesh P, Shenoy MT, Kalra S. Triglyceride Glucose (TyG) Index: a surrogate biomarker of insulin resistance. J Pak Med Assoc 2022;72(5):986–8.

[10] Cho YK, do Han K, Kim HS, Jung CH, Park JY, Lee WJ. Triglyceride-glucose index is a useful marker for predicting future cardiovascular disease and mortality in young Korean adults: a nationwide population-based cohort study. J lipid Atheroscler 2022;11(2):178–86.

[11] Wang S, Wang Q, Yan X. Association between triglyceride-glucose index and hypertension: a cohort study based on the China health and nutrition survey (2009-2015). BMC Cardiovasc Disord 2024;24(1):168. Mar.

[12] Lukito AA, Kamarullah W, Huang I, Pranata R. Association between triglyceride-glucose index and hypertension: a systematic review and meta-analysis. Narra J 2024;4(2):e951. Aug.

[13] Hou XZ, Lv YF, Li YS, Wu Q, Lv QY, Yang YT, et al. Association between different insulin resistance surrogates and all-cause mortality in patients with coronary heart disease and hypertension: NHANES longitudinal cohort study. Cardiovasc Diabetol 2024;23(1):86.

[14] Zhang Y, Ding X, Hua B, Liu Q, Gao H, Chen H, et al. High triglyceride-glucose index is associated with adverse cardiovascular outcomes in patients with acute myocardial infarction. Nutr Metab Cardiovasc Dis [Internet]. 2020;30(12):2351–62. https://doi.org/10.1016/j.numecd.2020.07.041. Available from:.

[15] Liu H, Wang L, Zhou X, Wang H, Hao X, Du Z, et al. Triglyceride-glucose index correlates with the occurrence and prognosis of acute myocardial infarction complicated by cardiogenic shock: data from two large cohorts. Cardiovasc Diabetol 2024;23(1):337. Sep.

[16] Li C, Zhang Y, Wu X, Liu K, Wang W, Qin Y, et al. Prognostic value of the triglyceride-glucose index for adverse cardiovascular outcomes in young adult hypertension. Clin Hypertens 2024;30(1):25. Sep.

[17] Lee JH, Jeon S, Lee HS, Lee JW. Trajectories of triglyceride-glucose index changes and their association with all-cause and cardiovascular mortality: a competing risk analysis. Cardiovasc Diabetol 2024;23(1):364.

[18] Kazibwe R. Triglyceride-glucose index and cardiovascular events in non-diabetic hypertension: secondary analysis of sprint. Am J Prev Cardiol [Internet]. 2024;19:100740. Available from, https://www.sciencedirect.com/science/article/pii/S2666667724001089.

[19] Huang J, Zhang J, Li L, Chen M, Li Y, Yu X, et al. Triglyceride-glucose index and hsCRP-to-albumin ratio as predictors of major adverse cardiovascular events in STEMI patients with hypertension. Sci Rep 2024;14(1):28112. Nov.

[20] Huang Z, Ding X, Yue Q, Wang X, Chen Z, Cai Z, et al. Triglyceride-glucose index trajectory and stroke incidence in patients with hypertension: a prospective cohort study. Cardiovasc Diabetol 2022;21(1):141.

[21] Hu L, Bao H, Huang X, Zhou W, Wang T, Zhu L, et al. Relationship between the triglyceride glucose index and the risk of first stroke in elderly hypertensive patients. Int J Gen Med 2022;15:1271–9.

[22] Ding W, Fang C, Wang L, Fang C. Triglyceride-glucose index and risk of all-cause and cardiovascular mortality in patients with cardiovascular disease: analysis from 1999 to 2018 NHANES data. Medicine 2024;103(46):e40534.

[23] Sun Y, Ji H, Sun W, An X, Lian F. Triglyceride glucose (TyG) index: a promising biomarker for diagnosis and treatment of different diseases. Eur J Intern Med [Internet]. 2025;131:3–14. Available from: https://www.sciencedirect.com/science/article/pii/S0953620524003753.

[24] Chang AM, Smith MJ, Bloem CJ, Galecki AT, Halter JB, Supiano MA. Limitation of the homeostasis model assessment to predict insulin resistance and β-Cell dysfunction in older people. J Clin Endocrinol Metab [Internet]. 2006;91(2):629–34. https://doi.org/10.1210/jc.2005-1803. Feb 1Available from:.

[25] Tao LC, ni Xu J, ting Wang T, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol [Internet]. 2022;21(1):1–17. https://doi.org/10.1186/s12933-022-01511-x. Available from.

[26] Hayıroğlu Mİ, Çınar T, Çiçek V, Palice A, Ayhan G, Tekkeşin Aİ. The triglyceride-glucose index can predict long-term major adverse cardiovascular events in turkish patients with high cardiovascular risk. J lipid Atheroscler 2022;11(3):280–7. Sep.

[27] Özcan KS, Hayıroğlu MI, Çınar T. Admission triglyceride-glucose index is predictor of long-term mortality and appropriate implantable cardiac defibrillator therapy in patients with heart failure. Biomark Med 2023;17(10):487–96. May.

[28] da Silva AA, do Carmo JM, Li X, Wang Z, Mouton AJ, Hall JE. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited. Can J Cardiol [Internet]. 2020;36(5):671–82. Available from: https://www.sciencedirect.com/science/article/pii/S0828282X20301690.

[29] Gao S, Ma W, Huang S, Lin X, Yu M. Impact of triglyceride-glucose index on long-term cardiovascular outcomes in patients with myocardial infarction with nonobstructive coronary arteries. Nutr Metab Cardiovasc Dis [Internet]. 2021;31(11):3184–92. Available from: https://www.sciencedirect.com/science/article/pii/S0939475321003483.
[30] Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2012;17(5):330–41. Oct.
[31] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116(7):1793–801. Jul.
[32] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes [Internet]. 2005;54(6):1615–25. https://doi.org/10.2337/diabetes.54.6.1615. Jun 1Available from:.
[33] Galassetti P, Davis SN. Effects of insulin per se on neuroendocrine and metabolic counter-regulatory responses to hypoglycaemia. Clin Sci (Lond) 2000;99(5):351–62.
[34] Alexopoulos AS, Qamar A, Hutchins K, Crowley MJ, Batch BC, Guyton JR. Triglycerides: emerging targets in diabetes care? Review of moderate hypertriglyceridemia in diabetes. Curr Diab Rep. 2019;19(4):13. Feb.
[35] Roth GA, Mensah GA, CO Johnson, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update From the GBD 2019 study. J Am Coll Cardiol 2020;76(25):2982–3021.
[36] Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 2008;32(6):949–58. Jun.
[37] Liao HW, Saver J, Yeh HC, Chen CHS, Wu YL, Lee M, et al. Low fasting glucose and future risks of major adverse outcomes in people without baseline diabetes or cardiovascular disease: a systematic review and meta-analysis. BMJ Open 2019;9(7):e026010.
[38] Jain M, Jain A, Yerragondu N, Brown RD, Rabinstein A, Jahromi BS, et al. The triglyceride paradox in stroke survivors: a prospective study. Neurosci J 2013;2013:870608.
[39] Yilmaz A, Hayıroğlu Mİ, Salturk S, Pay L, Demircali AA, Coşkun C, et al. Machine learning approach on high risk treadmill exercise test to predict obstructive coronary artery disease by using P, QRS, and T waves' Features. Curr Probl Cardiol [Internet]. 2023;48(2):101482. Available from: https://www.sciencedirect.com/science/article/pii/S0146280622003796.
[40] El-Bouri WK, Sanders A, Lip GYH. Predicting acute and long-term mortality in a cohort of pulmonary embolism patients using machine learning. Eur J Intern Med [Internet]. 2023;118:42–8. Available from: https://www.sciencedirect.com/science/article/pii/S0953620523002364.
[41] Cicek V, Orhan AL, Saylik F, Sharma V, Tur Y, Erdem A, et al. Predicting short-term mortality in patients with acute pulmonary embolism with deep learning. Circ J 2024. Nov.