META-ANALYSIS

Triglyceride glucose index and the prognosis of patients with heart failure: A meta-analysis

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ABSTRACT

The triglyceride-glucose index (TyGI) is a novel indicator of insulin resistance, which has been associated with an increased risk of cardiovascular diseases. The aim of this meta-analysis was to determine the association between TyGI and the prognosis of patients with heart failure (HF). Cohort studies relevant to the aim of the meta-analysis were retrieved by searching electronic databases, including PubMed, Web of Science, and Embase. A random-effects model was used to combine the data, incorporating the influence of between-study heterogeneity. Twelve studies involving 20,639 patients with HF were included. Pooled results showed that compared to patients with the lowest category of TyGI at baseline, those with the highest TyGI index were associated with a higher risk of all-cause mortality during follow-up (relative risk [RR] 1.71, 95% confidence interval [CI] 1.46 - 2.00; $P < 0.001$; $I^2 = 55\%$). Sensitivity analyses limited to studies after adjustment for confounding factors showed similar results (RR 1.89, 95% CI 1.67 - 2.21; $P < 0.001$; $I^2 = 13\%$). Subsequent meta-analyses also showed that a high TyGI at baseline was related to the incidence of cardiovascular death (RR 1.87, 95% CI 1.42 - 2.47; $P < 0.001$; $I^2 = 57\%$), HF rehospitalization (RR 1.33, 95% CI 1.04 - 1.69; $P < 0.02$; $I^2 = 46\%$), and major adverse cardiovascular events (RR 1.69, 95% CI 1.39 - 2.06; $P < 0.001$; $I^2 = 17\%$) during follow-up. In conclusion, a high TyGI may be associated with a poor clinical prognosis for patients with HF.

Keywords: Heart failure; triglyceride-glucose index; prognosis; mortality; meta-analysis.

INTRODUCTION

Heart failure (HF) represents the severe phase and terminal stage of various cardiovascular diseases (CVD) [1-3]. From a pathophysiological standpoint, HF is characterized by an intrinsic deficiency in either the contraction or relaxation of the myocardium, leading to the activation of neurohormonal systems. This ultimately leads to a progressive deterioration in cardiac function and inadequate circulation to peripheral tissues [4]. With global aging and advancements in CVD treatment strategies, it is anticipated that the number of HF patients will continue to increase in future decades [5, 6]. Despite recent therapeutic developments for HF, the prognosis remains unfavorable for individuals with this condition [7]. Hence, there is a crucial need to identify new prognostic indicators for HF patients.

Insulin resistance (IR) has been linked to the onset and advancement of HF through the promotion of low-grade systemic inflammation, oxidative stress, and endothelial dysfunction [8]. Recent studies have proposed that the triglyceride-glucose index (TyGI), a metric derived from fasting plasma glucose (FPG) and triglyceride (TG) levels, can effectively indicate IR [9]. The TyGI has demonstrated a strong correlation with hyperinsulinemic-euglycemic clamp results, which are considered the gold standard for assessing IR [10-12]. Moreover, mounting evidence suggests that a high TyGI is associated with an elevated risk of CVD in the general population, including HF [13-15]. Nevertheless, prior research on the connection between TyGI and HF patient prognosis has yielded inconclusive findings [16-27]. To address this gap in knowledge, we conducted a meta-analysis to determine the association between TyGI and the prognosis of patients with HF.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (2020) [28, 29] was followed in this study. The Cochrane Handbook [30] for systematic review and meta-analysis was referenced throughout the study.

Literature analysis

Three main electronic databases including PubMed, Web of Science, and Embase were used for literature search with a predefined combined search term including (1) "TyG index" OR "triglyceride-glucose index" OR "triglyceride and glucose index" OR "triglyceride glucose index" OR "triacylglycerol glucose index" OR "TyGI"; combined with (2) "heart failure" OR "cardiac failure" OR "cardiac dysfunction". Only studies with human subjects and published in English were included. A second-round check-up for the references of the relevant articles was also conducted. The final database search was achieved on January 12, 2024.

Inclusion and exclusion criteria

The inclusion criteria were made according to the PICOS principle:

(1) P (patients): Patients with confirmed diagnosis of HF.

(2) I (intervention): The TyGI was measured at baseline according to the formula ln [TG (mg/dl) × FPG (mg/dl)]/2, and a high TyGI at baseline was considered as the exposure. The cutoff for the defining a high TyGI was consistent with the value which was used in the original studies. The baseline TyG index means TyG index measured at admission for patients with hospitalized HF patients (generally the acute HF) and TyG index measured at enrolment for stable HF patients (generally the chronic HF).

(3) C (comparison): Patients with a low level of TyGI at baseline was considered as the controls.

(4) O (outcome): The primary outcome of the meta-analysis was the incidence of all-cause mortality during follow-up compared between HF patients with the highest versus the lowest category of TyGI at baseline. The secondary outcomes were the incidence of cardiovascular (CV) death, HF-rehospitalization, and the composite outcome of major adverse cardiovascular events (MACE).

(5) S (study design): Cohort studies, including the prospective and retrospective cohort studies.

We excluded reviews, meta-analyses, studies with TyGI analyzed as continuous variables only, or studies without outcomes of interest that this current meta-analysis aimed to investigate, such as all-cause mortality, CV death, HF-rehospitalization, and MACE. In cases where there was potential overlap in patient population across multiple studies, only the study with the largest sample size was included in this analysis.

Data collection and quality assessment

Two separate authors conducted a thorough search of academic literature, performed data collection and analysis, and independently assessed the quality of the studies. Any discrepancies that arose were resolved by involving the corresponding author in the discussion for final decision-making. Data on study information, design, diagnosis of the patients, sample size, age, sex, and diabetic status of the patients, the cutoffs of TyGI, follow-up durations, outcomes reported, and variables adjusted in the regression model for studying the association between TyGI and clinical outcomes of patients with HF were gathered. The assessment of study quality was carried out using the Newcastle-Ottawa Scale (NOS) (31), which involved scoring based on criteria including participant selection process, comparability among groups, and validity of outcomes. This scale utilized a rating system ranging from 1 to 9 stars; higher stars indicated better study quality.

Ethical statement

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent to participate in the study was not required in accordance with local/national guidelines.

Statistical analysis

An association between TyGI and the clinical outcomes of patients with HF was presented using relative risk (RR) and corresponding 95% confidence interval (CI), compared between HF patients with the highest versus the lowest category of TyGI at baseline. Data of RRs and

standard errors were calculated based on the 95% CIs or p values, followed by a logarithmical transformation to ensure stabilized variance and normalized distribution [30]. The heterogeneity among studies was assessed using the Cochrane Q test and I^2 statistic [32, 33], with $I^2 > 50\%$ indicating significant statistical heterogeneity. A random-effects model was used for result aggregation considering the influence of clinical heterogeneity among the included studies [30], such as the variations of HF type (acute/chronic), different TyGI cutoff, and different follow-up duration etc.. For the primary outcome of all-cause mortality, the sensitivity analysis limited to studies with multivariate analyses after adjustment of potential confounding factors was performed. Additionally, multiple subgroup analyses were performed to evaluate the influences of study characteristics on the results, such as in acute or chronic HF, in HF with reduced or preserved ejection fraction (HFrEF or HFpEF), in diabetic or non-diabetic patients, as well as subgroup analyses according to the cutoffs of TyGI, follow-up duration, and NOS of the included studies. Medians of continuous variables were selected as the cutoff values for defining subgroups. For characteristics presented as the continuous variables, such as sample size, mean age, proportion of men, proportion of diabetic patients, and follow-up duration, a univariate meta-regression analysis was also performed [30]. Publication bias estimation involved constructing funnel plots initially evaluated through visual inspection for symmetricity before being analyzed using Egger's regression test [34], where $P < 0.05$ indicates statistical significance. These analyses were conducted using the RevMan Version 5.1 (Cochrane Collaboration, Oxford, UK) and Stata software version 12 (Stata Corporation, College Station, TX).

RESULTS

Study inclusion

The process of selecting relevant studies for inclusion in the meta-analysis is depicted in Figure 1. Initially, 342 potentially pertinent records were identified through thorough searches of three

databases. Among these, 85 were removed due to duplication. Subsequent screening based on the titles and abstracts resulted in the exclusion of an additional 236 studies that did not align with the aim of the meta-analysis. The full texts of the remaining 21 records underwent independent review by two authors, leading to the removal of a further nine studies for various reasons detailed in Figure 1. Ultimately, twelve cohort studies remained [16-27] and were considered suitable for subsequent quantitative analyses.

Overview of the studies' characteristics

Table 1 presents the summarized characteristics of the included studies. Overall, one prospective cohort [25] and 11 retrospective cohort studies [16-24, 26, 27] were included in the meta-analysis. These studies were published between 2021 and 2024, and performed in China, Portugal, Turkey, Japan, and the United States. All of the studies included adult populations with HF. The mean ages of the patients were 60.3 to 81.0 years. Methods for defining the cutoff of TyGI varied among the included studies, such as using the median [16, 27], tertiles [17-19, 22, 25, 26], and quartiles [20, 21, 23, 24] of the TyGI of patients included in each study. The cutoff value for a high TyGI varied from 8.65 to 13.2 among the included studies. The follow-up durations varied from within hospitalization to 60 months. The primary outcome of all-cause mortality was reported in 11 cohorts [17-27], while the secondary outcomes of CV death, HF rehospitalization, and MACE were reported in four [17, 19, 25, 26], three [17, 20, 25] and three studies [19, 21, 23], respectively. Univariate analyses were used in three studies when the association between TyGI and the clinical outcomes of patients with HF was reported [16, 21, 24], while multivariate analyses were used in the other nine studies [17-20, 22, 23, 25-27]. Variables such as age, sex, hemodynamic parameters, comorbidities, ejection fraction, and concurrent medications were adjusted to a varying extent among the included studies. The NOS of the included studies were six to nine stars, suggesting overall moderate to good study quality (Table 2).

Meta-analysis for the association between TyGI and all-cause mortality

Pooled results of 11 cohorts [17-27] with a random-effects model showed that compared to patients with the lowest category of TyGI at baseline, those with the highest TyGI index were associated with a higher risk of all-cause mortality during follow-up (RR: 1.71, 95% CI: 1.46 to 2.00, p < 0.001; Figure 2A) with moderate statistical heterogeneity ($I^2 = 55\%$). Further sensitivity analysis limited to studies with multivariate analyses after adjustment of confounding factors showed similar results (RR: 1.89, 95% CI: 1.67 to 2.21, p < 0.001; Figure 2B), while the extent of between-study heterogeneity was significantly lowered ($I^2 = 13\%$). Subsequent subgroup analyses did not suggest a significant difference between patients with AHF and CHF (p for subgroup difference = 0.33; Figure 3A), in patients with HFrEF and HFpEF (p for subgroup difference = 0.92; Figure 3B), in diabetic and non-diabetic patients (p for subgroup difference = 0.78; Figure 4A), in studies with different cutoffs of TyGI (p for subgroup difference = 0.78; Figure 4B), in studies with different follow-up duration (p for subgroup difference = 0.62; Figure 5A), or study quality scores (p for subgroup difference = 0.27; Figure 5B). Finally, the results of the univariate meta-regression analyses did not show that study characteristics such as sample size, mean age, proportion of men, proportion of diabetic patients, or follow-up duration could significantly modify the association between TyGI and all-cause mortality of patients with HF (p all > 0.05; Table 3).

Meta-analysis for the association between TyGI and other clinical outcomes

Pooled results of four [17, 19, 25, 26], three [17, 20, 25] and three studies [19, 21, 23] showed that a high TyGI at baseline was also related to the incidence of cardiovascular death (RR: 1.87, 95% CI: 1.42 to 2.47, p < 0.001; $I^2 = 57\%$; Figure 6A), HF-rehospitalization (RR: 1.33, 95% CI: 1.04 to 1.69, p < 0.02; $I^2 = 46\%$; Figure 6B), and MACE (RR: 1.69, 95% CI: 1.39 to 2.06, p < 0.001; $I^2 = 17\%$; Figure 6C) of HF patients during follow-up.

Publication bias

The funnel plots for the meta-analysis of the association between TyGI and all-cause mortality of HF are shown in Figure 6. The symmetrical nature of the funnel plots suggested the low likelihood of publication bias. The Result of the Egger's regression test also showed a low risk of publication bias ($p = 0.91$). The publication biases underling the meta-analyses for the three secondary outcomes could not be determined because only three or four studies were included.

DISCUSSION

This meta-analysis included 12 cohort studies and found that patients with HF and a high TyGI at the baseline had an elevated risk of all-cause mortality during the follow-up period. The sensitivity analysis indicated that this association remained significant even after adjusting for potential confounding factors in the studies. Subgroup and meta-regression analyses revealed no significant difference in the association between patients with AHF and CHF, HFrEF or HFpEF, or between those with and without diabetes. Study characteristics such as sample size, mean age, proportion of men, methods for determining the cutoff of TyGI, follow-up duration, or study quality scores did not significantly affect this association. Additional exploration suggested that a high baseline TyGI in HF patients was linked to increased risk of CV death, HF rehospitalization, and MACE during follow-up. In conclusion, this meta-analysis suggests a possible relationship between high TyGI levels and poor clinical outcomes for patients with HF.

This meta-analysis may be the first to comprehensively evaluate the link between TyGI at baseline and the clinical outcomes of HF patients. It is important to acknowledge the strengths in methodology before interpreting the findings. We conducted a thorough search of three widely used electronic databases and found twelve relevant cohort studies for this analysis. By including cohort studies only, the results of the meta-analysis were able to establish a longitudinal relationship between high TyGI and poor prognosis for these patients. Moreover,

focusing on studies with multivariate analyses when analyzing all-cause mortality showed consistent results and significantly reduced between-study differences (I^2 from 55% to 13%). These results support an independent association between high TyGI and increased risk of all-cause mortality in HF patients. Additionally, decreasing I^2 in the sensitivity analysis indicates that including studies with univariate analysis could be a major factor contributing to heterogeneity. Furthermore, additional subgroup and meta-regression analyses provided further support for the strength of the link between a high TyGI and an elevated risk of overall mortality in HF patients. Additionally, despite incorporating a limited number of studies, our meta-analyses also indicated that a high TyGI in HF patients at baseline was linked to an increased likelihood of CV death, rehospitalization due to HF, and MACE over the follow-up period. In summary, these results indicate that a high TyGI could serve as an indicator of unfavorable prognosis for individuals with HF.

Several studies indicate that TyGI has various advantages as a new indicator of IR. The hyperinsulinemic-euglycemic clamp test is considered the most accurate method for assessing IR but it is complex and expensive for routine clinical use [35]. In clinical settings, alternative indices of IR include the homeostatic model assessment of insulin resistance (HOMA-IR) and TyGI. While HOMA-IR is commonly used in clinical contexts [36], TyGI has been proposed as a reliable surrogate marker for IR [37]. Although there is no consensus on the optimal index for indicating IR, a previous study suggested that TyGI shows a stronger correlation with the results of the hyperglycemic clamp test compared to HOMA-IR [38]. The TyGI is a proposed surrogate index for IR that can be easily calculated using routine biochemical analysis of TG and FPG levels upon admission, without the need for insulin assays [9]. Compared to the gold-standard hyperinsulinemic-euglycemic clamp test, the TyGI provides a cost-effective and efficient way of measuring IR. Previous studies have validated its ability to accurately reflect IR severity. An early study demonstrated the efficacy of the TyG index in identifying

individuals with IR across diverse populations including healthy volunteers, obese individuals, and patients with diabetes [10]. The TyGI showed high sensitivity (96.5%) and specificity (85.0%) compared to the hyperinsulinemic-euglycemic clamp test [10]. Additionally, another study in patients with acute ischemic stroke suggested that TyGI may perform better than HOMA-IR [38], supporting its practical utility as a prognostic indicator in these patients

The link between a high TyGI and unfavorable prognosis for HF patients may indicate the significant role of IR in the progression of HF. In myocardium, IR and the resulting decrease in cardiac insulin metabolic signaling are increasingly recognized as key contributors to HF development [39, 40]. Multiple factors have been associated with IR in HF patients, including oxidative stress, high blood glucose levels, elevated lipid levels, disrupted release of adipokines/cytokines, inappropriate activation of the renin-angiotensin II-aldosterone system and sympathetic nervous system – all contributing to worsening cardiac function [39, 40]. Furthermore, recent research suggests that cardiac IR can directly lead to mitochondrial dysfunction in cardiomyocytes leading to further impairment of cardiac metabolic flexibility in cases of HF [8, 41]. In addition, IR-induced endothelial dysfunction and lipotoxicity may impair the systolic and diastolic function of the cardiomyocytes [42], which is also likely to play a key role underlying the association between IR and poor prognosis of HF patients.

Consistently, there is growing evidence indicating that metformin, a widely recognized antidiabetic drug that targets IR, may provide advantages for patients with HF. A previous comprehensive analysis revealed that individuals with diabetes and HF who used metformin experienced a slight decrease in overall hospitalizations [43]. In addition, a recent meta-analysis indicated that metformin could potentially reduce the risk of all-cause mortality in patients with HFpEF [44]. These findings further support the role of IR as a prognostic factor and a potential treatment target for patients with HF.

The study is limited by several factors. Eleven of the studies analyzed were conducted retrospectively, potentially introducing biases in selection and recall that may have affected the results. Besides, the protocol of the meta-analysis was not prospectively registered in PROSPERO. Moreover, there was inconsistency in the cutoff values for TyGI among the included studies, contributing to heterogeneity. Further research is needed to determine an optimal cutoff for TyGI in predicting poor prognosis for patients with HF. Although sensitivity analysis focused on studies with multivariate analyses showed similar outcomes, unadjusted confounding factors could still influence the association. For example, none of the included studies reported the methods for measuring FPG and TG, which may affect the association between TyGI and clinical outcome of patients with HF. Moreover, obesity status indicated by the body mass index (BMI) may affect the association between TyGI at baseline and the prognosis of patients with HF. However, only six of the included studies reported the mean BMI at baseline [17, 19, 20, 23, 25, 26]. Accordingly, we could not determine the influence of BMI on the association between TyGI at baseline and the prognosis of patients with HF, which should be addressed in large-scale prospective studies in the future. In addition, the potential use of antidiabetic and lipids lowering medications may affect the association between TyG index at baseline and the prognosis of patients with HF. However, we are unable to determine the influences of these treatments because none of the included studies reported the stratified data according to the use of the antidiabetic and lipids lowering medications. Lastly, our reliance solely on observational research means that a definitive causal link between high TyGI and poor prognosis for patients with HF could not be firmly established.

CONCLUSION

The findings of the meta-analysis indicate that patients with HF who have a high TyGI at the baseline may face a greater likelihood of negative clinical outcomes during their follow-up, in comparison to those with a low TyGI. Further confirmation through extensive prospective

studies and exploration of the underlying mechanisms is needed. Given the convenience and cost-effectiveness of this parameter, these results support the possible use of TyGI as a prognostic marker for HF patients.

Data availability

All the data generated during the study are included within the manuscript.

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TABLES AND FIGURES WITH LEGENDS

TABLE 1. Characteristics of the included studies

Study	Country	Study design	Diagnosis	No. of patients	Mean age (years)	Men (%)	DM (%)	Methods to determine TyGI cutoff	Mean BMI (kg/m^2)	Cutoff value for high TyGI	Follow-up duration (months)	Outcomes reported	Variables adjusted or matched
Guo et al. 2021 (17)	China	RC	CHF	546	65.2	66.3	100	T3:T1	21.1	9.06	27.6	CV death; HF rehospitalization	Age, sex, BMI, SBP, DBP, HR, CRP, eGFR, NT-proBNP, HbA1c, LVEF, AF, NYHA class, and concurrent medications
Cunha et al. 2021 (16)	Portugal	RC	CHF	275	69	70.5	NR	Median	NR	8.65	60	All-cause mortality	None

Huang et al. 2022 (19)	China	RC	ADHF	932	61.8	62.1	32.8	T3:T1	24.2	9.32	15.7	All-cause mortality; CV death; MACE	Age, sex, BMI, SBP, DBP, HR, CRP, eGFR, BNP, HbA1c, SUA, LVEF, DM, HTN, VHD, AF, and concurrent medications
Han et al. 2022 (18)	China	RC	ADHF	4441	70.6	48.4	32.1	T3:T1	NR	8.78	During hospitalization	All-cause mortality	Age, sex, NYHA class, HR, SBP, albumin, TBIL, LDL-C, BUN, SCr, SUA, HGB, serum sodium, cTnI, NT-proBNP, LVEF, and the history of CAD, HTN, AF, DM, smoking, and concurrent medications

Study	Country	Design	Population	N				Comparison				Outcomes	Adjustment variables
Shi et al. 2022 (20)	China	RC	HF	901	NR	44.5	25.8	Q4:Q1	20.9	NR	6	All-cause mortality; HF rehospitalization	Age, sex, BMI, NYHA class, CHF, hypertension, DM, CKD, LVEF, eGFR, hsCRP, BNP, albumin, cholesterol, and LDL-C, and concurrent medications
Ozcan et al. 2023 (22)	Turkey	RC	HFrEF after ICD	773	61.5	81.9	35.6	T3:T1	NR	13.2	38	All-cause mortality	Age, sex, HTN, DM, NYHA Class, BUN, and LVEF
Zhou et al. 2023 (25)	China	PC	AHF, HFpEF	823	73	48.1	42	T3:T1	25.5	8.98	37.9	All-cause mortality; CV death; HF rehospitalization	Age, sex, BMI, SBP, HbA1c, HDL-C, SCr, Hb, cTnT, NT-proBNP, DM, hyperlipidemia, AF, LVEF, LAD, and concurrent medications

Zhou et al. 2023 (26)	China	RC	CHF	6697	64	68.4	44.6	T3:T1	25.2	8.93	46.8	All-cause mortality; CV death	Age, sex, BMI, smoking, drinking status, HbA1c, TBil, albumin, eGFR, TC, LDL-C, cTnT, sodium, NT-proBNP, LVEF and NYHA classification, HTN, DM, AF, previous MI, stroke, and concurrent medications
Yang et al. 2023 (24)	USA	RC	ADHF	1393	71	59	37.6	Q4:Q1	NR	NR	During hospitalization	All-cause mortality	None
Iwakura et al. 2023 (21)	Japan	RC	AHF, HFpEF	917	81	44.7	39.3	Q4:Q1	NR	NR	12.7	All-cause mortality; MACE	None

Sun et al. 2023 (23)	China	RC	Ischemic HF after PCI	2055	60.3	82.2	38.5	Q4:Q1	25.9	9.41	36	All-cause mortality; MACE	Age, sex, HR, BMI, NYHA class, prior PCI, platelet, albumin, TC, LDL-C, potassium, SUA, LVEF, coronary lesion severity, and concurrent medications
Cheng et al. 2024 (27)	China	RC	ADFH	886	71	55.5	0	Median	NR	9.44	During hospitalization	All-cause mortality	Age, sex, cardiogenic shock, NT-proBNP, albumin, TC, LDL-C, TBIL, comorbidities of HTN, CHD, AF, and concurrent medications

DM, diabetes mellitus; TyGI, triglyceride glucose index; RC, retrospective cohort; PC, prospective cohort; CHF, chronic heart failure; AHF, acute heart failure; ADHF, acute decompensated heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; NR, not reported; T, tertile; Q, quartile; CV, cardiovascular; HF, heart failure;

MACE, major adverse cardiovascular events; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CRP, C-reactive protein; eGFR, estimated glomerular filtrating rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; SUA, serum uric acids; HGB, hemoglobin; DM, diabetes mellitus; HTN, hypertension; VHD, valvular heart disease; TBIL, total bilirubin; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; MI, myocardial infarction; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; cTnI, cardiac troponin I; cTnT, cardiac troponin T.

TABLE 2. Study quality evaluation via the Newcastle-Ottawa scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Guo et al. 2021 (17)	0	1	1	1	1	1	1	1	1	8
Cunha et al. 2021 (16)	0	1	1	1	0	0	1	1	1	6
Huang et al. 2022 (19)	0	1	1	1	1	1	1	1	1	8
Han et al. 2022 (18)	1	1	1	1	1	1	1	0	1	8
Shi et al. 2022 (20)	0	1	1	1	1	1	1	0	1	7
Ozcan et al. 2023 (22)	0	1	1	1	1	1	1	1	1	8
Zhou et al. 2023 (25)	1	1	1	1	1	1	1	1	1	9

Zhou et al. 2023 (26)	1	1	1	1	1	1	1	1	9
Yang et al. 2023 (24)	1	1	1	1	0	0	1	0	1	6
Iwakura et al. 2023 (21)	0	1	1	1	0	0	1	1	1	6
Sun et al. 2023 (23)	0	1	1	1	1	1	1	1	1	8
Cheng et al. 2024 (27)	0	1	1	1	1	1	1	0	1	7

TABLE 3. Univariate meta-regression analysis for the outcome of all-cause mortality

Variables	RR for the association between TyGI and all-cause mortality of HF patients		
	Coefficient	95% CI	P values
Sample size	0.000035	-0.000054 to 0.000123	0.40
Mean age (years)	-0.017	-0.043 to 0.009	0.16
Men (%)	0.0055	-0.0107 to 0.0218	0.46
Diabetes (%)	-0.0081	-0.0213 to 0.0051	0.20
Follow-up duration (months)	-0.0048	-0.0140 to 0.0044	0.27

TyGI: Triglyceride glucose index; RR: Risk ratio; CI: Confidence interval; HF: Heart failure;
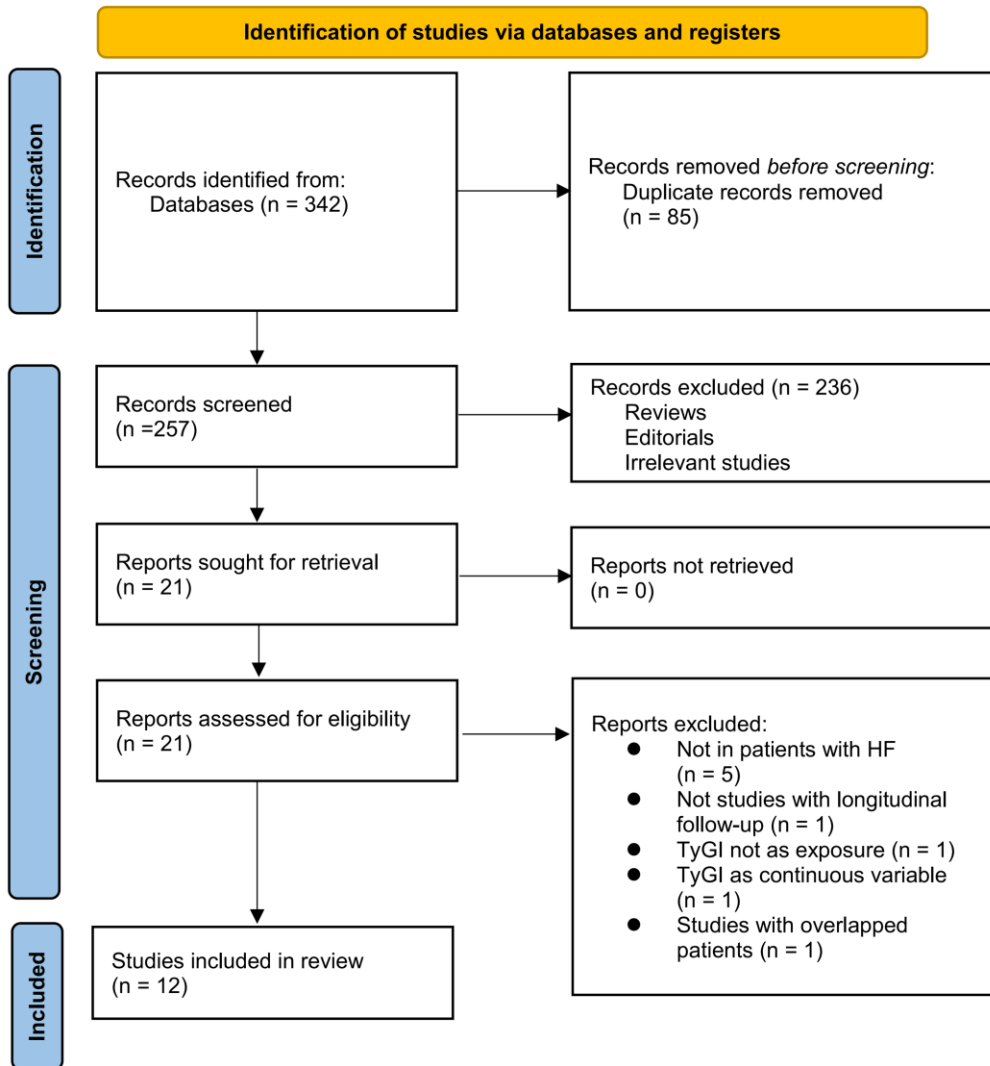
FIGURE 1. Process of conducting literature search and identifying studies.

A

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Cunha 2021	0.07696104	0.17348855	10.6%	1.08 [0.77, 1.52]
Huang 2022	0.73716407	0.27039118	6.2%	2.09 [1.23, 3.55]
Han 2022	0.73236789	0.24543374	7.1%	2.08 [1.29, 3.36]
Shi 2022	0.51282363	0.50620739	2.2%	1.67 [0.62, 4.50]
Ozcan 2023	1.35583515	0.67005552	1.3%	3.88 [1.04, 14.43]
Zhou 2023a	0.37156356	0.12939995	13.5%	1.45 [1.13, 1.87]
Zhou 2023b	0.60976557	0.06778142	18.1%	1.84 [1.61, 2.10]
Yang 2023	0.28517894	0.39001465	3.5%	1.33 [0.62, 2.86]
Iwakura 2023	0.3220835	0.11551307	14.6%	1.38 [1.10, 1.73]
Sun 2023	0.77932488	0.19168778	9.5%	2.18 [1.50, 3.17]
Cheng 2024	0.80647587	0.13178299	13.3%	2.24 [1.73, 2.90]
Total (95% CI)			**100.0%**	**1.71 [1.46, 2.00]**

Heterogeneity: Tau² = 0.03; Chi² = 22.14, df = 10 (P = 0.01); I² = 55%
Test for overall effect: Z = 6.66 (P < 0.00001)

B

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Huang 2022	0.73716407	0.27039118	4.8%	2.09 [1.23, 3.55]
Han 2022	0.73236789	0.24543374	5.7%	2.08 [1.29, 3.36]
Shi 2022	0.51282363	0.50620739	1.4%	1.67 [0.62, 4.50]
Ozcan 2023	1.35583515	0.67005552	0.8%	3.88 [1.04, 14.43]
Zhou 2023a	0.37156356	0.12939995	17.8%	1.45 [1.13, 1.87]
Zhou 2023b	0.60976557	0.06778142	43.1%	1.84 [1.61, 2.10]
Sun 2023	0.77932488	0.19168778	9.1%	2.18 [1.50, 3.17]
Cheng 2024	0.80647587	0.13178299	17.3%	2.24 [1.73, 2.90]
Total (95% CI)			**100.0%**	**1.89 [1.67, 2.12]**

Heterogeneity: Tau² = 0.00; Chi² = 8.03, df = 7 (P = 0.33); I² = 13%
Test for overall effect: Z = 10.44 (P < 0.00001)

FIGURE 2. Forest plots for the meta-analysis of the association between TyGI and all-cause mortality of patients with HF. (A) Forest plots for the overall meta-analysis; (B) Forest plots for the sensitivity analysis limited to studies after adjustment of confounding factors.

FIGURE 3. Forest plots for the subgroup analyses of the association between TyGI and all-cause mortality of patients with HF. (A) Forest plots for the subgroup analysis in acute and chronic HF; (B) Forest plots for the subgroup analysis in HFrEF and HFpEF.

A

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 DM				
Huang 2022	0.45742485	0.39396717	2.3%	1.58 [0.73, 3.42]
Han 2022	0.49469624	0.20764889	7.3%	1.64 [1.09, 2.46]
Zhou 2023a	0.42526774	0.17565038	9.5%	1.53 [1.08, 2.16]
Zhou 2023b	0.66782937	0.08054291	24.0%	1.95 [1.67, 2.28]
Subtotal (95% CI)			43.1%	1.83 [1.61, 2.10]
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 3 (P = 0.56); I² = 0%				
Test for overall effect: Z = 8.92 (P < 0.00001)				
1.5.2 Non-DM				
Huang 2022	0.70309751	0.30137716	3.8%	2.02 [1.12, 3.65]
Han 2022	0.74668795	0.209288	7.2%	2.11 [1.40, 3.18]
Zhou 2023a	0.3074847	0.15439676	11.5%	1.36 [1.00, 1.84]
Zhou 2023b	0.43178242	0.09733663	20.2%	1.54 [1.27, 1.86]
Cheng 2024	0.80647587	0.13178299	14.3%	2.24 [1.73, 2.90]
Subtotal (95% CI)			56.9%	1.77 [1.44, 2.18]
Heterogeneity: Tau² = 0.03; Chi² = 8.86, df = 4 (P = 0.06); I² = 55%				
Test for overall effect: Z = 5.38 (P < 0.00001)				
Total (95% CI)			100.0%	1.76 [1.56, 1.99]
Heterogeneity: Tau² = 0.01; Chi² = 11.40, df = 8 (P = 0.18); I² = 30%				
Test for overall effect: Z = 9.15 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%				

0.1 0.2 0.5 1 2 5 10

B

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 Median				
Cunha 2021	0.07696104	0.17348855	10.6%	1.08 [0.77, 1.52]
Cheng 2024	0.80647587	0.13178299	13.3%	2.24 [1.73, 2.90]
Subtotal (95% CI)			23.9%	1.57 [0.77, 3.21]
Heterogeneity: Tau² = 0.24; Chi² = 11.21, df = 1 (P = 0.0008); I² = 91%				
Test for overall effect: Z = 1.24 (P = 0.22)				
1.6.2 T3:T1				
Huang 2022	0.73716407	0.27039118	6.2%	2.09 [1.23, 3.55]
Han 2022	0.73236789	0.24543374	7.1%	2.08 [1.29, 3.36]
Ozcan 2023	1.35583515	0.67005552	1.3%	3.88 [1.04, 14.43]
Zhou 2023a	0.37156356	0.12939995	13.5%	1.45 [1.13, 1.87]
Zhou 2023b	0.60976557	0.06778142	18.1%	1.84 [1.61, 2.10]
Subtotal (95% CI)			46.3%	1.78 [1.53, 2.07]
Heterogeneity: Tau² = 0.01; Chi² = 4.85, df = 4 (P = 0.30); I² = 18%				
Test for overall effect: Z = 7.52 (P < 0.00001)				
1.6.3 Q4:Q1				
Shi 2022	0.51282363	0.50620739	2.2%	1.67 [0.62, 4.50]
Yang 2023	0.28517894	0.39001465	3.5%	1.33 [0.62, 2.86]
Iwakura 2023	0.3220835	0.11551307	14.6%	1.38 [1.10, 1.73]
Sun 2023	0.77932488	0.19168778	9.5%	2.18 [1.50, 3.17]
Subtotal (95% CI)			29.8%	1.61 [1.23, 2.11]
Heterogeneity: Tau² = 0.02; Chi² = 4.35, df = 3 (P = 0.23); I² = 31%				
Test for overall effect: Z = 3.43 (P = 0.0006)				
Total (95% CI)			100.0%	1.71 [1.46, 2.00]
Heterogeneity: Tau² = 0.03; Chi² = 22.14, df = 10 (P = 0.01); I² = 55%				
Test for overall effect: Z = 6.66 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.50, df = 2 (P = 0.78), I² = 0%				

0.1 0.2 0.5 1 2 5 10

FIGURE 4. Forest plots for the subgroup analyses of the association between TyGI and all-cause mortality of patients with HF. (A) Forest plots for the subgroup analysis according to the diabetic status of the patients; (B) Forest plots for the subgroup analysis according to the methods for determining the cutoffs of TyGI.

A

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 < 24 months				
Huang 2022	0.73716407	0.27039118	6.2%	2.09 [1.23, 3.55]
Han 2022	0.73236789	0.24543374	7.1%	2.08 [1.29, 3.36]
Shi 2022	0.51282363	0.50620739	2.2%	1.67 [0.62, 4.50]
Yang 2023	0.28517894	0.39001465	3.5%	1.33 [0.62, 2.86]
Iwakura 2023	0.3220835	0.11551307	14.6%	1.38 [1.10, 1.73]
Cheng 2024	0.80647587	0.13178299	13.3%	2.24 [1.73, 2.90]
Subtotal (95% CI)			46.9%	1.79 [1.41, 2.27]

Heterogeneity: Tau² = 0.04; Chi² = 9.17, df = 5 (P = 0.10); I² = 45%
Test for overall effect: Z = 4.82 (P < 0.00001)

1.7.2 24 months or longer				
Cunha 2021	0.07696104	0.17348855	10.6%	1.08 [0.77, 1.52]
Ozcan 2023	1.35583515	0.67005552	1.3%	3.88 [1.04, 14.43]
Zhou 2023a	0.37156356	0.12939995	13.5%	1.45 [1.13, 1.87]
Zhou 2023b	0.60976557	0.06778142	18.1%	1.84 [1.61, 2.10]
Sun 2023	0.77932488	0.19168778	9.5%	2.18 [1.50, 3.17]
Subtotal (95% CI)			53.1%	1.64 [1.28, 2.11]

Heterogeneity: Tau² = 0.05; Chi² = 12.91, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 3.86 (P = 0.0001)

Total (95% CI)			100.0%	1.71 [1.46, 2.00]

Heterogeneity: Tau² = 0.03; Chi² = 22.14, df = 10 (P = 0.01); I² = 55%
Test for overall effect: Z = 6.66 (P < 0.00001)
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%

B

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 NOS = 6~7				
Cunha 2021	0.07696104	0.17348855	10.6%	1.08 [0.77, 1.52]
Shi 2022	0.51282363	0.50620739	2.2%	1.67 [0.62, 4.50]
Yang 2023	0.28517894	0.39001465	3.5%	1.33 [0.62, 2.86]
Iwakura 2023	0.3220835	0.11551307	14.6%	1.38 [1.10, 1.73]
Cheng 2024	0.80647587	0.13178299	13.3%	2.24 [1.73, 2.90]
Subtotal (95% CI)			44.2%	1.50 [1.09, 2.07]

Heterogeneity: Tau² = 0.08; Chi² = 13.33, df = 4 (P = 0.010); I² = 70%
Test for overall effect: Z = 2.50 (P = 0.01)

1.8.2 NOS = 8~9				
Huang 2022	0.73716407	0.27039118	6.2%	2.09 [1.23, 3.55]
Han 2022	0.73236789	0.24543374	7.1%	2.08 [1.29, 3.36]
Ozcan 2023	1.35583515	0.67005552	1.3%	3.88 [1.04, 14.43]
Zhou 2023a	0.37156356	0.12939995	13.5%	1.45 [1.13, 1.87]
Zhou 2023b	0.60976557	0.06778142	18.1%	1.84 [1.61, 2.10]
Sun 2023	0.77932488	0.19168778	9.5%	2.18 [1.50, 3.17]
Subtotal (95% CI)			55.8%	1.82 [1.59, 2.09]

Heterogeneity: Tau² = 0.00; Chi² = 5.83, df = 5 (P = 0.32); I² = 14%
Test for overall effect: Z = 8.73 (P < 0.00001)

Total (95% CI)			100.0%	1.71 [1.46, 2.00]

Heterogeneity: Tau² = 0.03; Chi² = 22.14, df = 10 (P = 0.01); I² = 55%
Test for overall effect: Z = 6.66 (P < 0.00001)
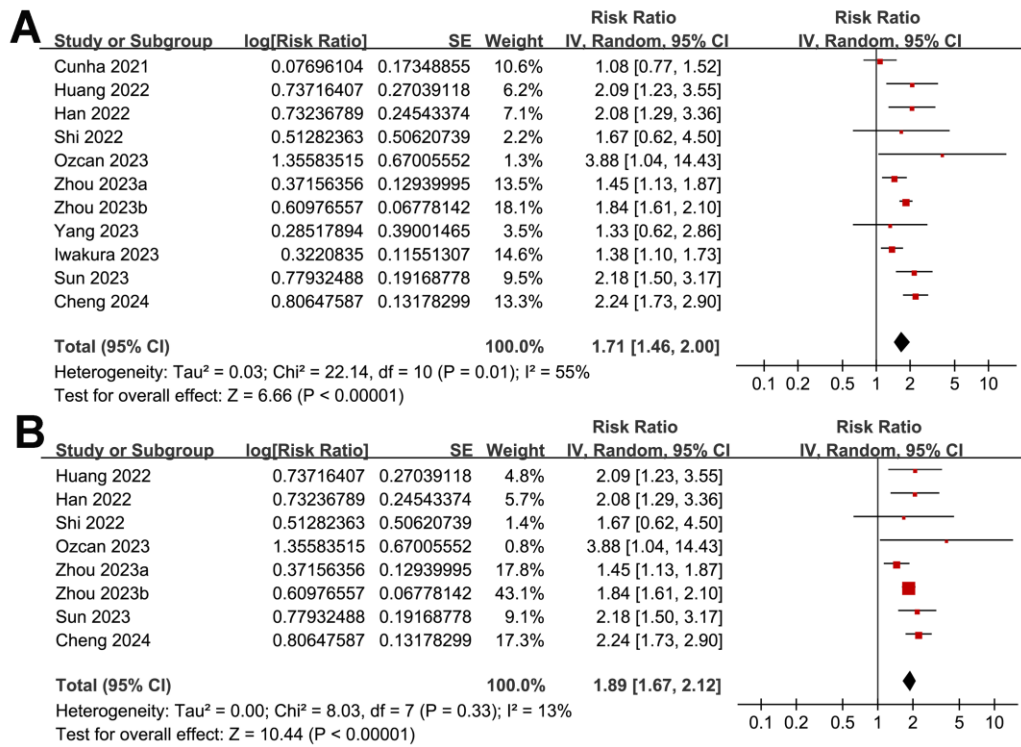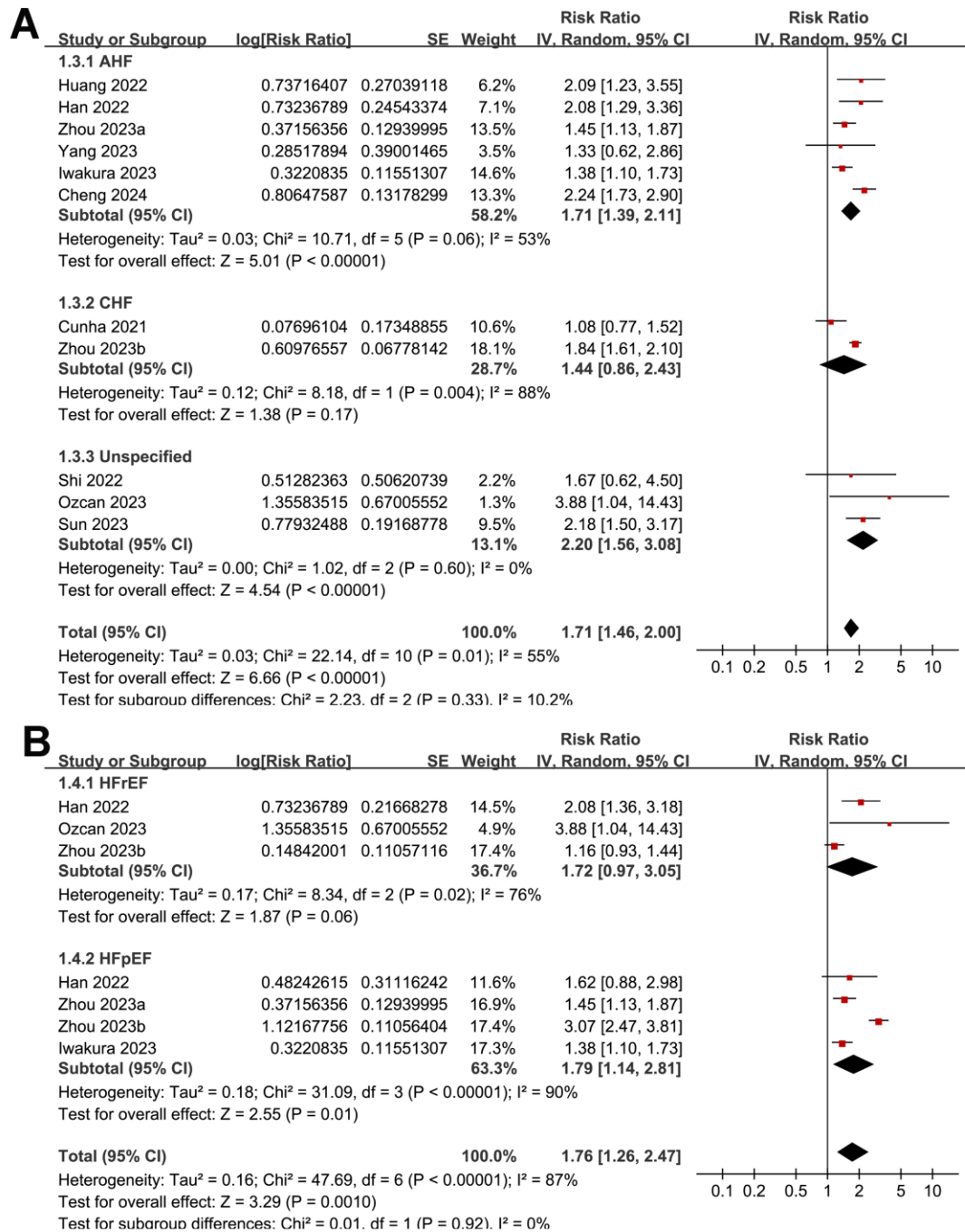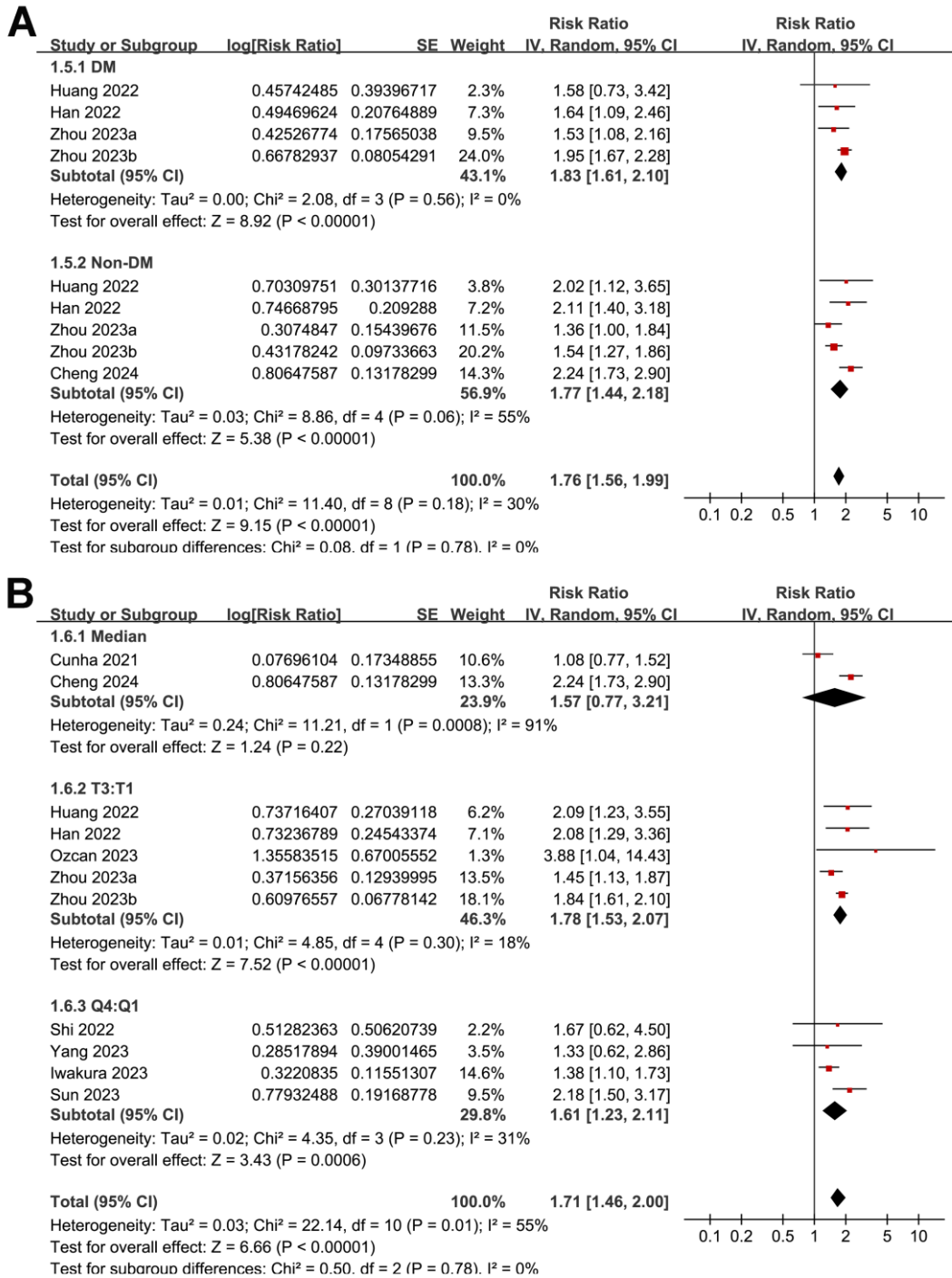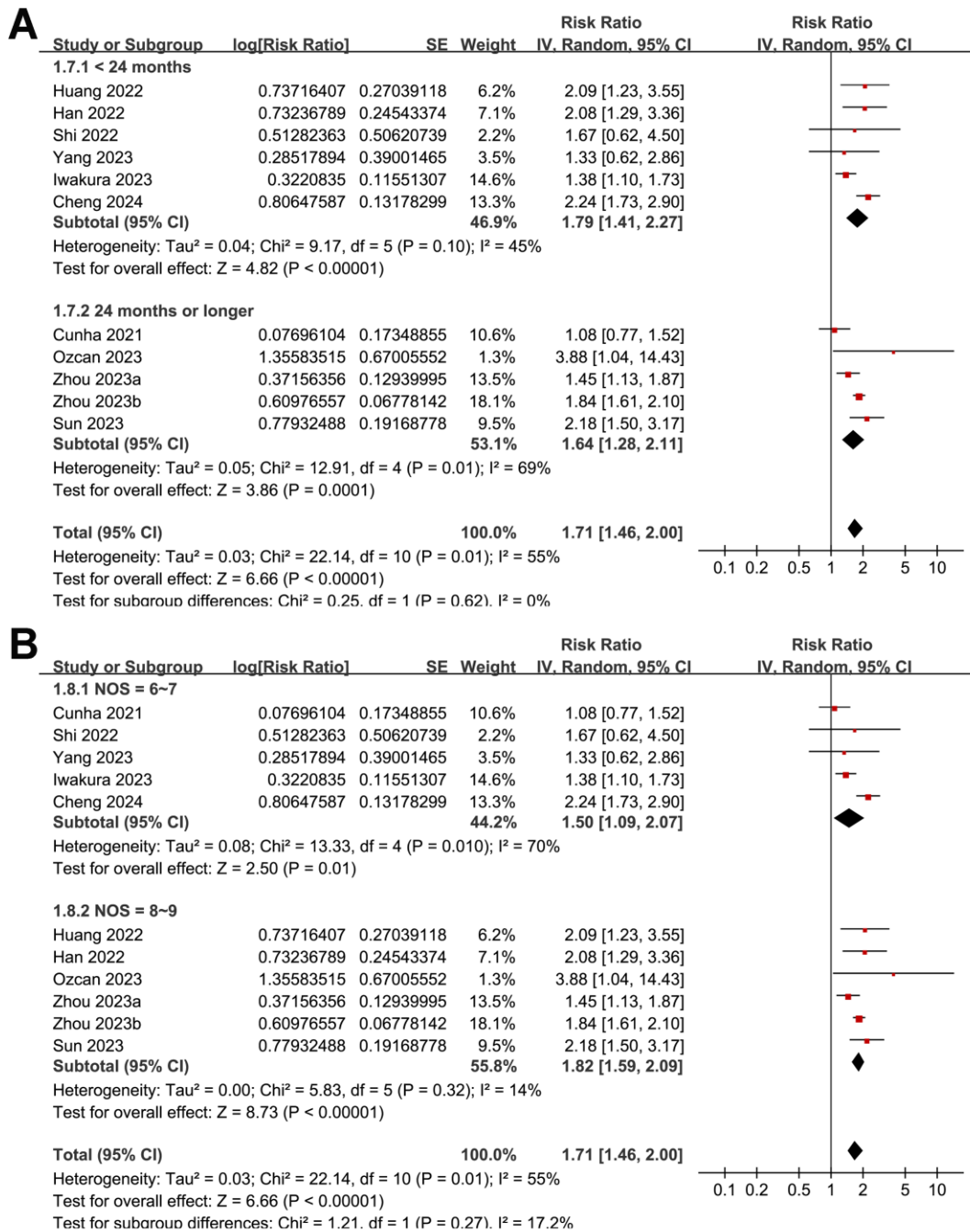Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.2%

FIGURE 5. Forest plots for the subgroup analyses of the association between TyGI and all-cause mortality of patients with HF. (A) Forest plots for the subgroup analysis according to the follow-up duration; (B) Forest plots for the subgroup analysis according to the study quality scores.
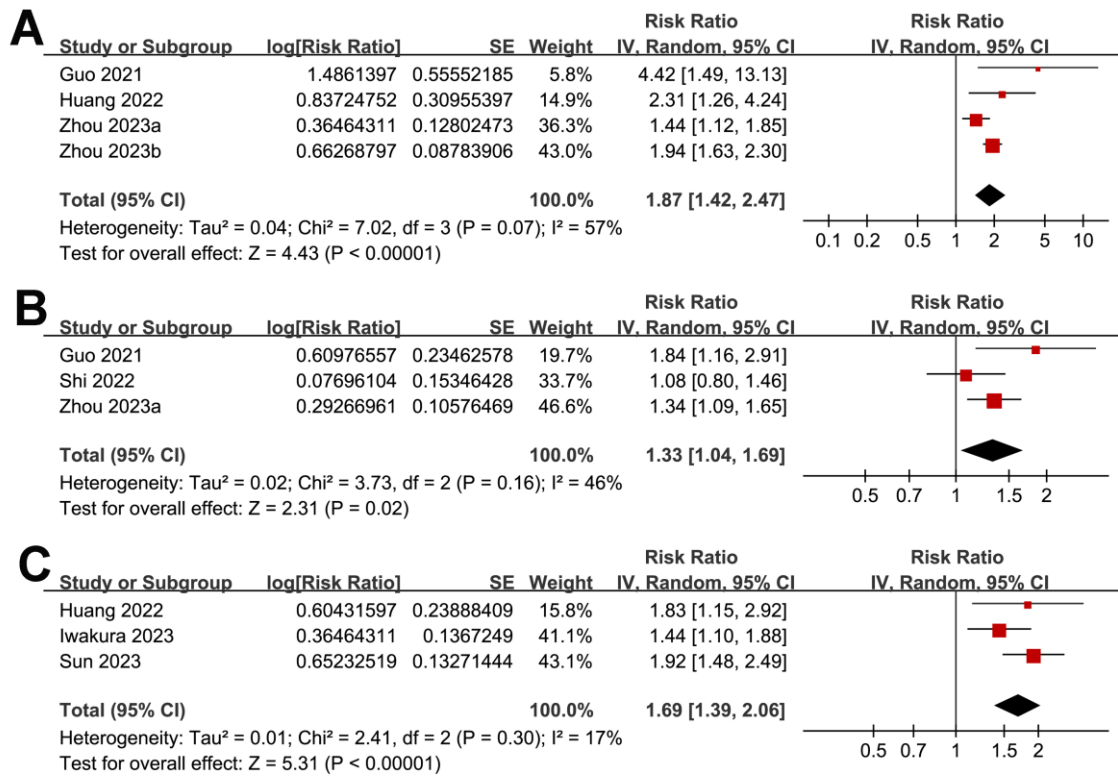
A

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guo 2021	1.4861397	0.55552185	5.8%	4.42 [1.49, 13.13]
Huang 2022	0.83724752	0.30955397	14.9%	2.31 [1.26, 4.24]
Zhou 2023a	0.36464311	0.12802473	36.3%	1.44 [1.12, 1.85]
Zhou 2023b	0.66268797	0.08783906	43.0%	1.94 [1.63, 2.30]
Total (95% CI)			**100.0%**	**1.87 [1.42, 2.47]**

Heterogeneity: Tau² = 0.04; Chi² = 7.02, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 4.43 (P < 0.00001)

Risk Ratio IV, Random, 95% CI — scale: 0.1 0.2 0.5 1 2 5 10

B

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Guo 2021	0.60976557	0.23462578	19.7%	1.84 [1.16, 2.91]
Shi 2022	0.07696104	0.15346428	33.7%	1.08 [0.80, 1.46]
Zhou 2023a	0.29266961	0.10576469	46.6%	1.34 [1.09, 1.65]
Total (95% CI)			**100.0%**	**1.33 [1.04, 1.69]**

Heterogeneity: Tau² = 0.02; Chi² = 3.73, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 2.31 (P = 0.02)

Risk Ratio IV, Random, 95% CI — scale: 0.5 0.7 1 1.5 2

C

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Huang 2022	0.60431597	0.23888409	15.8%	1.83 [1.15, 2.92]
Iwakura 2023	0.36464311	0.1367249	41.1%	1.44 [1.10, 1.88]
Sun 2023	0.65232519	0.13271444	43.1%	1.92 [1.48, 2.49]
Total (95% CI)			**100.0%**	**1.69 [1.39, 2.06]**

Heterogeneity: Tau² = 0.01; Chi² = 2.41, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 5.31 (P < 0.00001)

Risk Ratio IV, Random, 95% CI — scale: 0.5 0.7 1 1.5 2

FIGURE 6. Forest plots for the meta-analysis of the association between TyGI and the other clinical outcomes of patients with HF. (A) forest plots for the meta-analysis of the association between TyGI and CV death; (B) forest plots for the meta-analysis of the association between TyGI and HF-rehospitalization; (C) forest plots for the meta-analysis of the association between TyGI and MACE.
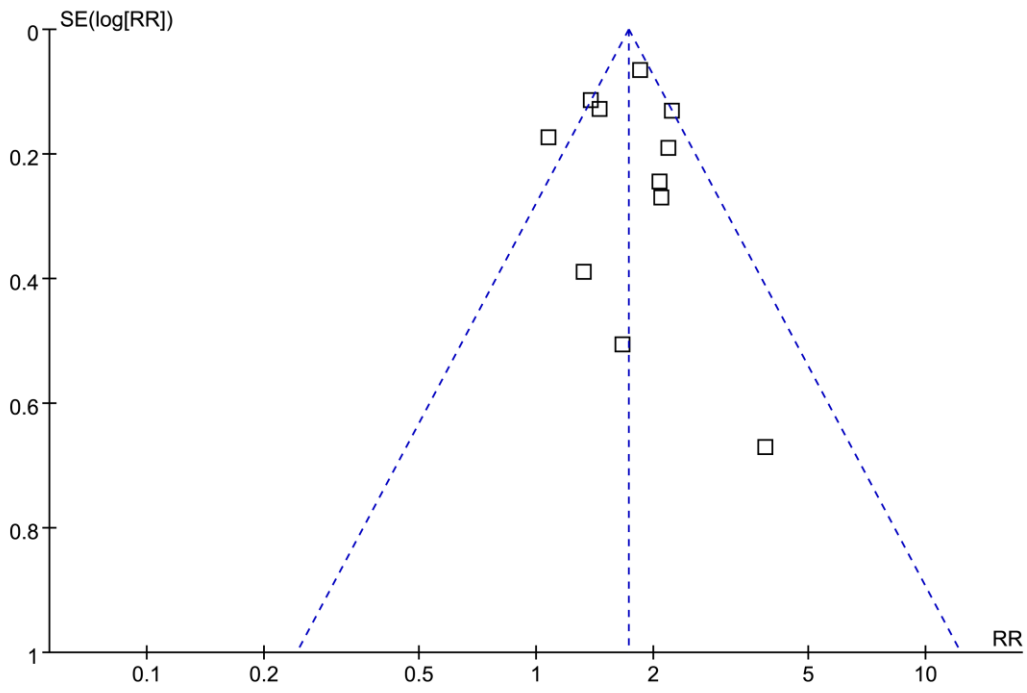
FIGURE 7. Funnel plots for the publication bias underlying the meta-analysis of the association between TyGI and all-cause mortality of patients with HF.