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Triglyceride–glucose index and the risk of in-hospital and ICU all-cause mortality: a systematic review and meta-analysis of observational studies

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Several studies have illustrated the association of the triglyceride glucose (TyG) index with in-hospital and intensive care unit (ICU) mortality. However, no studies have compiled this evidence and reached a conclusion. This study aimed to quantify the association of the TYG index with the risk of in-hospital and ICU mortality. An extensive search of databases including PubMed, Scopus, and Web of Science, was performed up to 21 Jan 2024. Nineteen studies were included in the meta-analysis. The outcomes were in-hospital mortality in 18 studies and ICU mortality in 8 studies. Among the 42,525 participants, 5233 in-hospital and 1754 ICU mortality cases were reported. The pooled analysis revealed that each unit increase in the TYG index was associated with a 33% and 45% increase in the risk of in-hospital (RR = 1.33; 95% CI: 1.23, 1.43; *I squared* = 90.3%) and ICU (RR: 1.45; 95% CI: 1.25, 1.67; *I squared* = 44.8%) mortality, respectively. Subgroup analysis revealed a stronger association between the TYG index and the risk of in-hospital mortality in patients with cardiovascular diseases than in those with cerebrovascular diseases ($P_{heterogeneity\ between\ Groups} = 0.014$). The findings of this study showed a positive association between the TyG index and the risk of in-hospital and ICU mortality. (PROSPERO registration ID: CRD420245414390).

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INTRODUCTION

The prevalence of in-hospital mortality among patients in intensive care units (ICUs) is as high as 20–30% [1], and ICUs often account for 20–50% of all hospital deaths [2]. However, in general hospitals, the ICU accounts for 10%–15% of hospital beds, including 22% of the total costs [3]. Patients in the ICU typically experience an extended mean length of stay and face an exceptionally high mortality rate, imposing a substantial burden on families and society [4]. Hence, predicting risks in advance is crucial for providing medical treatment guidance. The ICU encompasses a spectrum of various diseases, from sepsis to trauma, comma, and ischemic stroke [5]. However, most ICU patients exhibit increased insulin resistance due to inflammatory stress, which is a marker of both systemic inflammatory responses and metabolic disorders [6]. Previous studies demonstrated a 50–70% reduction in insulin sensitivity in critically ill patients and reported that this reduction is associated with illness severity rather than various admission diagnoses [4, 7]. Furthermore, insulin resistance has been related to significant morbidities in intensive care [8]. Thus, changes in insulin resistance are considered useful indicators of stress response-associated inflammation [9]. The triglyceride-glucose (TyG) index, which contains two biomarkers, fasting triglyceride (TG) and fasting blood glucose (FBG), is an easily accessible, cost-effective, and reliable surrogate indicator of insulin resistance [10] that can facilitate its application in clinical practice. Several studies have shown that TyG has a positive relationship with many diseases, such as cardiovascular diseases [11], diabetes [12], bladder cancer [13], and hypertension [14]. In addition, an observational study reported that the TyG index could be used as a predictor of hospital and ICU mortality in critically ill stroke patients [15]. A recent study revealed a strong association between the TyG index and increased all-cause mortality in critically ill patients [10]. Another scholar reported that the TyG index could be a significant predictor of severe impairment of consciousness and in-hospital death in patients with cerebrovascular disease in the ICU [16]. Furthermore, many investigations have verified the positive relationship between the TyG index and coronary atherosclerosis progression [17]. This index is a valuable approach for simultaneously analyzing lipid metabolism and glucose status, which is why it has been widely assessed in many different diseases [18]. Although many studies have investigated the relationship between the TyG index and different diseases, no studies have compiled this evidence and reached a clear conclusion. Therefore, we performed this systematic review and meta-analysis to determine whether the TyG index is associated with the risk of in-hospital and ICU mortality.

METHODS

The current study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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(PRISMA) statement. The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID CRD42024541439.

Search strategy

A comprehensive and systematic literature search, with no restriction on publication date, was performed through online databases, including PubMed, Scopus, and Web of Science, up to 21 Jan 2024 to find related studies. The search terms "TYG" and "triglyceride-glucose index" in combination with "in-hospital" and "ICU"-related mortality were included in the search strategy (Supplementary Table 1). Furthermore, the reference lists of eligible studies, and the first 4 pages of Google Scholar, were manually checked to find other potentially relevant studies.

Study selection

EndNote software version 20.4.1 was used to manage all the retrieved articles. After removing duplicate studies, two reviewers independently assessed the eligibility of the remaining studies according to the PECOS (population, exposure, comparator, outcome and setting) scheme, which considered hospitalized patients aged >18 years old as the population; the "TYG" index as the exposure; the highest compared to lowest "TYG" index as a comparator; "in-hospital" or "ICU" all-cause mortality as the outcome; and all prospective or retrospective cohort studies as the setting. In this review, letters, comments, reviews, randomized controlled trials, case reports, cross-sectional and case-control studies, studies on Coronavirus disease 2019 (COVID-19) patients, and those with insufficient data were excluded. Two reviewers cross-checked the excluded articles, and any discrepancies were resolved through discussion.

Data extraction

Two researchers screened the titles, abstracts, and full texts of the obtained articles to identify eligible studies. Then, all necessary data were extracted according to an arranged screening form that included the following items: the first author's name, publication year, cohort-based population, study design, outcome, characteristics of participants, number of participants with mortality, mean or range of age, sex and any adjustment for confounding variables. If a study reported different risk estimates for mortality, the effect size in the fully adjusted model was selected and used in the meta-analysis. In cases where adequate data for outcomes were not reported, we contacted the corresponding author by email. Discrepancies between authors were resolved at any stage through consultation and discussion with the principal investigator.

Quality assessment of the studies

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies. The current checklist includes three domains: (1) selection (population representativeness, which can take a maximum of 4 stars), (2) comparability (controlling appropriate confounders in study design or during statistical analyses with a maximum of 2 stars), and (3) outcomes, with a maximum of 3 stars. A maximum of 9 stars for each study indicates the highest quality. Likewise, studies with more than 6 stars were considered high-quality, those with 4–6 stars were rated as medium-quality, and studies with 0–3 stars were considered low-quality. The quality assessment was independently checked by two authors, and any disagreements between the researchers were resolved through discussion with the principal investigator.

Statistical analysis

In all included studies, the relative risks (RRs) and their 95% confidence intervals (CIs) were considered the main effect sizes. A random effects model taking the between-study heterogeneity into account was used to estimate the pooled effect size. The assessment of interstudy heterogeneity was based on Cochrane's Q test and the *I-squared test* (I^2). Additionally, subgroup analysis based on participants' disease (cardiovascular or cerebrovascular diseases) was performed to explore the possible source of heterogeneity among studies using the random effects model.

To calculate the linear dose-response relationship across categories of the TYG index, the methods proposed by Greenland and Longnecker [19] and Orsini et al. [20]. were applied where the number of mortality cases and the adjusted effect size (ORs, RRs, or HRs) for at least 3 categories of the TYG index were needed. Based on this method, the midpoint of exposure in each category of the TYG index was considered the relevant effect size for each study. In cases where the dose of the exposure was expressed in a range, the midpoint in each single category was calculated via the mean of the minimum and maximum values. To detect whether the overall pooled results might be affected by a specific study, a sensitivity analysis was performed by removing the studies from the analysis one by one. This also was the case for the study by Cheng et al., where we had to manually calculate the unadjusted effect size based on the reported crude data [21]. Likewise, publication bias tests were performed using visual examination of funnel plots and checked statistically by Egger's and Begg's regression tests. If the findings of publication bias were significant, a trim-and-fill analysis was performed to detect the effect of possible unpublished articles on the pooled results. All the statistical analyses were performed with Stata, version 14 (Stata Crop). Values < 0.05 were considered to indicate statistical significance.

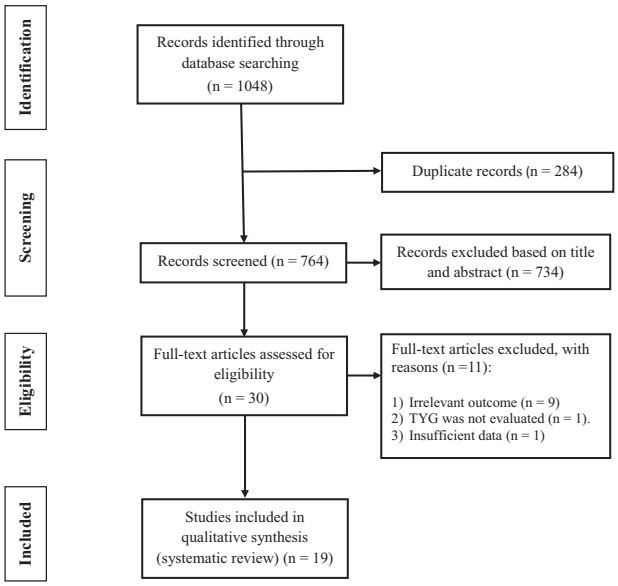

Fig. 1 The process of study selection.

RESULTS

Literature search

The detailed processes of the study selection are provided in Fig. 1. In our primary search, 1048 studies were identified. After excluding duplicates and irrelevant studies, 30 potentially eligible studies remained for further assessment. Finally, by reviewing the full texts, an additional 11 studies were removed for the following reasons: nine studies reported outcomes not relevant to the purpose of the current study, one did not assess the TYG index, and one study by Şaylık et al. [22]. did not provide sufficient data. Thus, 19 unique eligible cohort studies [4, 10, 15, 16, 21, 23–36] were included in the final meta-analysis.

Table 1. Main characteristics of studies examining the association between TYG index and the risk of in-hospital and ICU all-cause mortality.

First author/ year	Cohort-based population	Study Design/ database	Outcome	Patients characteristic	Participants/ Cases Hospital mortality	Participants/ Cases ICU mortality	Age (y) (Mean or range)	Sex	Adjustment
Boshen et al. [23]	USA	Retrospective cohort study /eICU Collaborative Research Database	In-hospital& ICU all-cause mortality	Critically ill patients post-CA	1021/379	1021/314	67	F/M	Age, gender, BMI, CHF, Cardiogenic shock, ARF, AF, diabetes, hypertension, CKD, MI, Platelet, SBP, DBP, HR, WBC, HDL, LDL, TC, RBC, BUN, Creatinine, HB, temperature, SpO_2, epinephrine, dobutamine, dopamine, amiodarone, statin, non-shockable rhythm, arterial pH, bystander CPR, CPR > 15 min, CPR < 15 min, unwitnessed status, enteral nutrition
Cai et al. [10]	USA	Retrospective cohort study /MIMIC-IV	In-hospital all-cause mortality	Critically ill patients with ischemic stroke	733/139	733/109	69	F/M	Age, sex, BMI, heart failure, atrial fibrillation, diabetes, sepsis, IV-tPA, mechanical thrombectomy, white blood cell, red blood cell, platelet, serum creatinine
Chen et al. 2023.A	USA	Retrospective cohort study /.MIMIC-IV	In-hospital& all-cause mortality	Patients with nontraumatic cerebral hemorrhage	537/99	-----	40–79	F/M	Age, sex, BMI, race, CPK, CKMB, IDH, ALP, AST, INR, ALT, Creatinine, PT, PTT, HbA1c, anemia, cancer, CKD, hyperlipemia, hypertension, respiratory failure, diabetes, alcohol abuse, long-term use of antiplatelet agents/anticoagulants, tobacco use
Chen et al.2023.B	USA	Retrospective cohort study /.MIMIC-IV	In-hospital& all-cause mortality	Patients with cerebral infarction	872/129		40–79	F/M	Age, sex, BMI, race, CPK, CKMB, IDH, ALP, AST, INR, ALT, Creatinine, PT, PTT, HbA1c, anemia, cancer, CKD, hyperlipemia, hypertension, respiratory failure, diabetes, alcohol abuse, long-term use of antiplatelet agents/anticoagulants, tobacco use
Cheng et al. [21]	USA	Retrospective cohort study /MIMIC-IV2.0	In-hospital all-cause mortality	Critically ill patients	8392/1224	-----	64.4	F/M	---------
Dai et al. [25]	USA	Retrospective cohort study /MIMIC	In-hospital all-cause mortality	Adult patients of first hospital and ICU admission	3902/587	-----	63.1	F/M	Age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPS II, WBC, platelet, creatine, ventilation, vasopressors, and dialysis
Liao et al. [4]	USA	Retrospective cohort study /MIMIC-III	In-hospital& ICU all-cause mortality	Critically ill patients	3026/350	3026/258	65.4	F/M	Age, sex, ethnicity, first care unit, SOFA score, LODS score, white blood cell, red blood cell, hemoglobin, serum sodium, serum potassium, total cholesterol, low-density lipoprotein, high-density lipoprotein, albumin, serum creatinine, coronary heart disease, heart failure, hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, respiratory failure, liver disease, chronic kidney disease, acute kidney injury, sepsis, cancer
Zhai et al. [33]	USA	Retrospective cohort study /eICU Collaborative Research Database	In-hospital all-cause mortality	Critically ill patients with heart disease	4839/413	-----	65.2	F/M	Age, gender, ethnicity, systolic blood pressure, diastolic blood pressure, respiration, congestive heart failure, STEMI, cardiac arrest, acute kidney injury, respiratory failure, stroke, malignancy, white blood cell, neutrophil percentage, oral anticoagulants, ACEI/ARB, APACHE IV, length of ICU stay and length of hospital stay.

Table 1. continued

First author/ year	Cohort-based population	Study Design/ database	Outcome	Patients characteristic	Participants/ Cases Hospital mortality	Participants/ Cases ICU mortality	Age (y) (Mean or range)	Sex	Adjustment
Zhang et al.2020.A	USA	Retrospective cohort study /eICU Collaborative Research Database	In-hospital& ICU all-cause mortality	Critically ill stroke patients	4570 /469	4570 /229	66.3	F/M	Gender, age, ethnicity, stroke types, coronary heart disease, diabetes mellitus, heart failure, plasma glucose, TC, LDL-C, triglyceride, mechanical ventilation, APACHE IV score, LOS.
Zhang et al.2023.B	USA	Retrospective cohort study /MIMIC-III	In-hospital& ICU all-cause mortality	Critically ill patients with coronary heart disease	1618/156	1618/123	68.05	F/M	Adjusted for age, sex, BMI, dyslipidemia, hypertension, diabetes, chronic kidney disease, respiratory failure, white blood cell, red blood cell, hemoglobin, serum creatinine, SIRS score
Zheng et al. [36]	USA	Retrospective cohort study /MIMIC-IV	In-hospital& ICU all-cause mortality	Critically ill patients with sepsis:	1257/269	1257/194	62.2	F/M	Age; Gender; BMI; SOFA score; Hemoglobin; Sodium; WBC; RDW; LDL; PT; PTT; ALT; ALP; AST; CRP; NLR; Atrial Fibrillation; Hypertension; Myocardial Infarction; CHF; COPD; CAD; AKI; Low_HDL
Cheng et al. [21]	China	Retrospective cohort study	In-hospital all-cause mortality	Consecutive AHF patients	889/81	-----	70.6	F/M	Age, cardiogenic shock, NT-proBNP, serum albumin, total cholesterol, low-density lipoprotein cholesterol, serum bilirubin, ALT, comorbidities of hypertension, CHD, AF, cerebrovascular accident, COPD, and left ventricular end-diastolic diameter, left atrial diameter, EFFECT score, and use of vasoactive drugs.
Zhang et al. [35]	China	Retrospective cohort study	In-hospital all-cause mortality	Patients with severe fever with thrombocytopenia syndrome (SFTS)	79/17	-----	64.9	F/M	Age and gender, hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, and neurological manifestations, NEU%, PLT, CD4 + T-LYM, AST, BUN, CK, and LDH.
Fu et al. [27]	China	Prospective cohort study/CAMI	In-hospital all-cause mortality	Patients with STsegment elevation myocardial infarction	2190/46	-----	59.6	F/M	Age, sex, anterior myocardial infarction, Killip class III/IV, primary PCI, current smoking, previous stroke, chronic kidney disease, heart rate, systolic blood pressure, LVEF, serum creatinine, low-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, β-blockers and statins.
Ye et al. [32]	USA	Retrospective cohort study /MIMIC-IV	In-hospital all-cause mortality	CKD patients with CAD	639/102	-----	75	F/M	Age, sex, ACS, dialysis, HT, SOFA, eGFR, RBC_mean, hematocrit_min, platelet_mean, ALT_mean, bilirubin_total_mean, creatinine_ mean, potassium_max, sodium_mean, total_calcium_max, free_calcium_min, phosphate_min, INR_mean, PT_mean, HR_mean, SpO_2_min, statin, aspirin, warfarin
Gu et al.2022	China	Retrospective cohort study	In-hospital all-cause mortality	AMI patients	1648/85	-----	75.6	F/M	Age,ALB, ALT,BUN,SBP,WBC,

Table 1. continued

First author/ year	Cohort-based population	Study Design/ database	Outcome	Patients characteristic	Participants/ Cases Hospital mortality	Participants/ Cases ICU mortality	Age (y) (Mean or range)	Sex	Adjustment
Liao et al. [4]	USA	Retrospective cohort study /MIMIC-IV	In-hospital& ICU all-cause mortality	Patients with severe SAH	352/59	352/46	65	F/M	Age, gender, sodium, INR, sapsii, platelets, cerebrovascular disease, diabetes.
Miao et al. [31]	China	Prospective cohort study	In-hospital all-cause mortality	Patients with acute ischemic stroke	3216/105	-----	68.6	F/M	Age, sex, current smoking, alcohol consumption, admission NIHSS score, and stroke syndrome. systolic blood pressure, diastolic blood pressure, medical history (hypertension, diabetes mellitus, and atrial fibrillation), use of antihypertensive medications and lipid-lowering medications, time from onset to hospital, ischemic stroke subtype, and total cholesterol.
Ding et al. [26]	China	Retrospective cohort study	In-hospital all-cause mortality	Liver transplantation recipients	780/43	-----	49	F/M	Age, sex, BMI, ASA classification, hypertension, diabetes, renal insufficiency, HE, MELD score, hemodialysis, HB, WBC, platelet, day-or-night surgery, surgery duration, massive transfusion, massive blood losing, urinary oliguria, and intraoperative cardiac arrest
Jiang et al. [29]	USA	Retrospective cohort study /MIMIC-IV	ICU all-cause mortality	Patients with CVD	----	1965/481	71.97	F/M	Sex, admission age, weight, ethnicity, INR, PT, PTT, WBC, chloride, RBC, platelet, heart rate, respiratory rate, SBP, DBP, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, paraplegia, renal disease, atrial fibrillation, diabetes, soft, antihyperglycemic, and antihyperlipidemic drugs

CA cardiac arrest, *BMI* body mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, SpO_2 saturation of peripheral oxygen, *MI* myocardial infarction, *AF* atrial fibrillation, *CHF* chronic heart failure, *CKD* chronic kidney disease, ARF acute renal failure, *RBC* red blood cell, *WBC* white blood cell, *HB* hemoglobin, *BUN* blood urea nitrogen, FBG fast blood glucose, *TyG index* triglyceride-glucose index, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CPR* cardiopulmonary resuscitation, *MIMIC-IV* Medical Information Mart for Intensive Care, *IV-tPA* intravenous tissue plasminogen activator, *CPK* Creatine phosphokinase, *CKMB* Creatine kinase isoenzyme MB, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *INR* International normalized ratio, *ALT* alanine aminotransferase, *PT* prothrombin time, *PTT* active partial thromboplastin time, *HbA1c* glycated hemoglobin A 1c, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *HBP* hypertension, *ICU* intensive care unit, *LOS* length of stay, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment, *LODS* logistic organ dysfunction system, *STEMI* ST-elevation myocardial infarction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *APS* acute physiology score, *APACHE IV* Acute Physiology and Chronic Health Evaluation IV, *SIRS* systemic infammatory response syndrome, *AKI_48 h* Acute Kidney Injury within 48 h, *CRP* C-reactive protein, *NLR* Neutrophil-to-Lymphocyte Ratio, *RDW* Red Cell Distribution Width, *NT-proBNP* N-terminal B-type, *EFFECT* Enhanced Feedback for Effective Cardiac Treatment, *CHD* coronary heart, *NEU%* neutrophil percentage, *LYM%* lymphocyte percentage, *PLT* platelet, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *ACS* acute coronary syndrome, *HT* hypertension, *eGFR* estimated glomerular fltration rate, *SAH* Ssubarachnoid hemorrhage, *AMI* Acute myocardial infarction, *ALB* Albumin, *NIHSS* National Institutes of Health Stroke Scale, *ASA* American Society of Anesthesiologists, *MELD* model for end-stage liver disease score, *HE* hepatic encephalopathy.

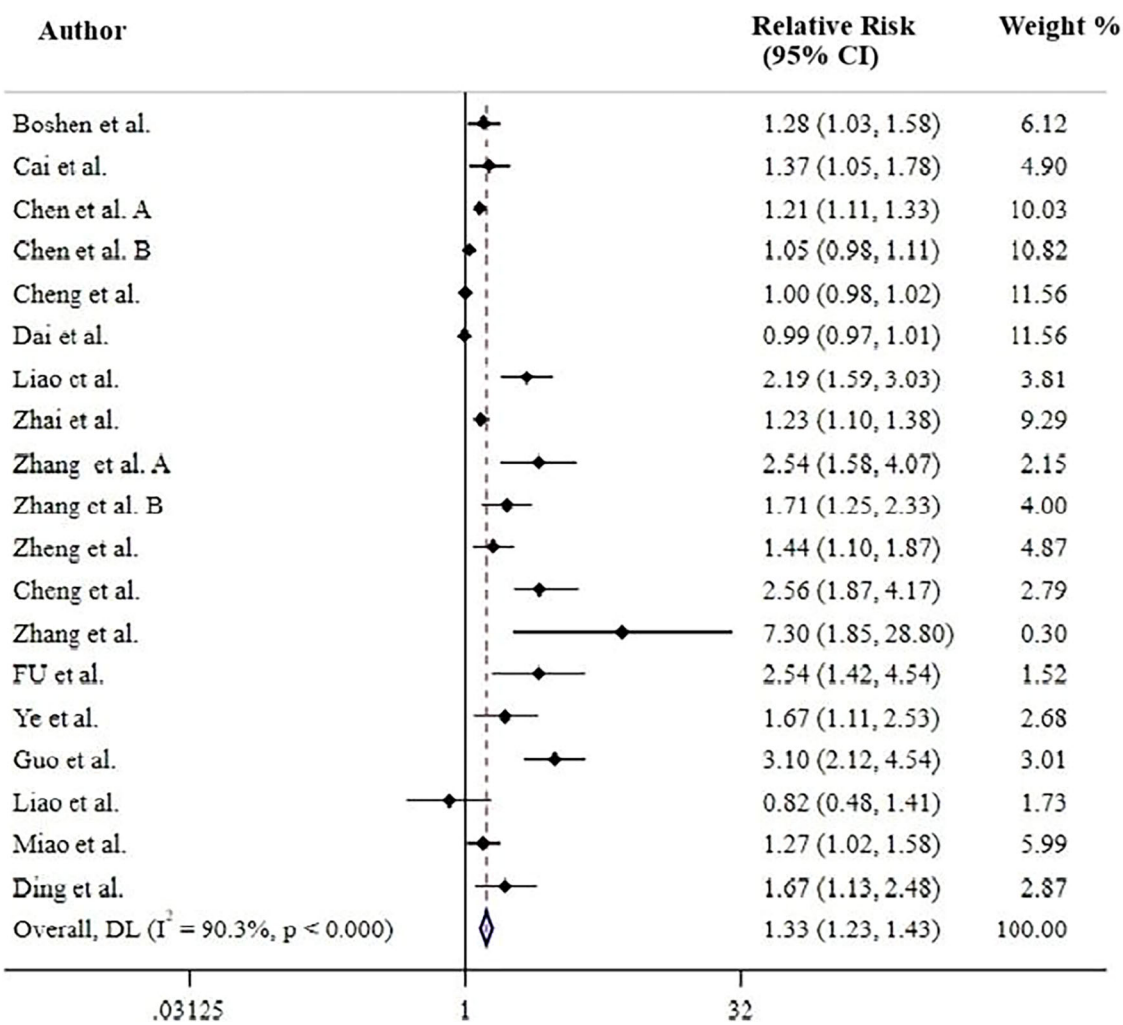

Fig. 2 TYG index and in-hospital all-cause mortality.

Study characteristics

Table 1 shows the characteristics of the included studies evaluating the associations of TYG with in-hospital and ICU mortality. The outcomes were in-hospital mortality in 18 studies [4, 10, 15, 16, 21, 30–36] and ICU mortality in 8 studies [4, 10, 15, 23, 29, 30, 34, 36]. Among the 42,525 participants, 5233 in-hospital and 1754 ICU mortality cases were reported by the included studies. All studies included both males and females with an age range of 40–79 years. Five studies included patients with cerebrovascular diseases [10, 15, 16, 30, 31], eight were conducted on patients with cardiovascular diseases (CVD) [21, 23, 32–34], two were performed on critically ill patients [4, 24], and individual studies were conducted on adult patients who were in their first hospital and ICU admission [25], patients with sepsis [36], patients suffering from severe fever with thrombocytopenia syndrome [35] and liver transplantation recipients [26].

Except for two studies [27, 31], all the included studies had a retrospective design. A study by Chen et al. [16] used two different populations (patients with nontraumatic cerebral hemorrhage and patients with cerebral infarction). Therefore, we considered this study to have two separate effect sizes (Chen et al. A and Chen et al. B). Of the included studies, 10 used data extracted from the Medical Information Mart for Intensive Care (MIMIC) [4, 10, 16, 21, 25, 29, 30, 32, 34, 36], and three used the eICU Collaborative Research Database [15, 23, 33]. Moreover, except for a study conducted by Cheng et al. [21], all included studies adjusted for potential confounders, including age, sex, smoking status, body mass index, and some conventional risk factors, including alcohol intake, chronic disease morbidity, diabetes, dyslipidemia, hypertension, and race. Generally, the included studies originated from China ($n = 6$) [24, 31, 35] and the United States of America (USA) ($n = 13$) [4, 10, 15, 16, 21, 23, 25, 29, 30, 36].

Meta-analysis

TYG index and in-hospital mortality. Nineteen effect sizes from 18 studies investigated the association between the circulating TYG index and in-hospital all-cause mortality. The pooled analysis revealed a significant positive association between the TYG index and in-hospital mortality; in this way, each one-unit increase in the TYG index was associated with a 33% increase in the risk of in-hospital mortality (RR = 1.33; 95% CI: 1.23, 1.43). However, high heterogeneity was detected among studies (Cochrane's Q test, I squared = 90.3%; $P < 0.001$) (Fig. 2). Similarly, subgroup analysis revealed that the TYG index was more strongly associated with the risk of in-hospital mortality in patients with cardiovascular disease compared to those with cerebrovascular disease ($p_{\text{for heterogeneity between groups}} = 0.014$) (Fig. 3).

TYG index and ICU mortality. The association between the TYG index and all-cause mortality in the ICU was assessed in eight studies. Overall, each unit increase in the TYG index was significantly associated with a 45% increase in the risk of all-cause mortality in the ICU (RR: 1.45; 95% CI: 1.25, 1.67). The results of Cochrane's Q test revealed a low level of heterogeneity among

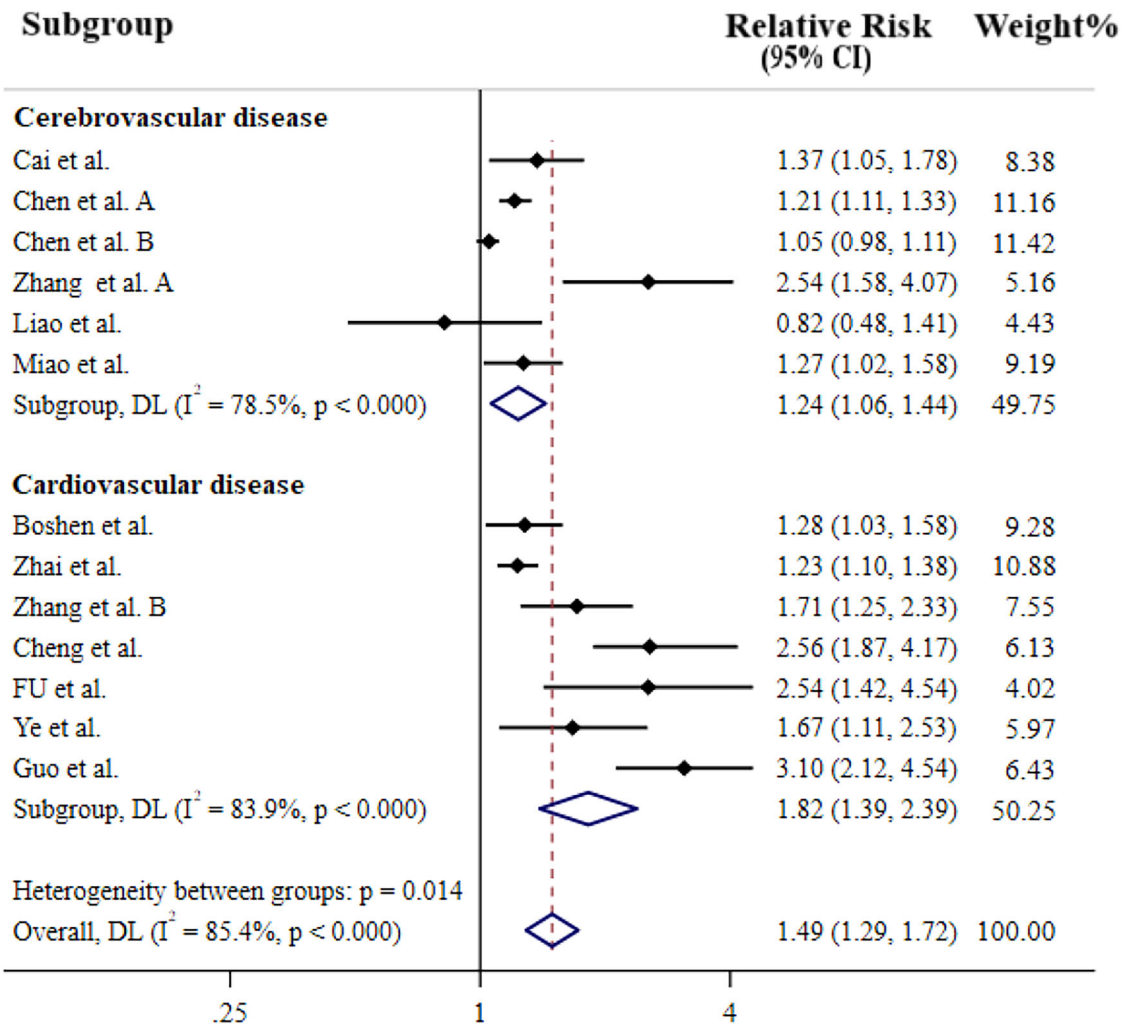

Fig. 3 Subgroup analysis for TYG index and in-hospital all-cause mortality.

studies (Cochrane's Q test, I squared = 44.8%; $P = 0.08$) (Fig. 4). Subgroup analysis showed no significant interstudy heterogeneity ($p_{\text{heterogeneity between groups}} = 0.069$) (Fig. 5).

Quality assessment. Table 2 shows the detailed quality assessment of the included studies. The quality scores were 9 in 8 studies, 7 in one study, and 8 in 10 studies. Hence, the overall quality of all the studies was rated as high.

Publication bias. Although visual inspection of the funnel plot for studies on the association between TYG and in-hospital mortality showed asymmetry, Begg's regression test indicated no significant publication bias ($P = 0.11$). Regarding ICU mortality, funnel plot examination and Egger's regression test showed some evidence of possible publication bias. Therefore, the trim-and-fill method was used, and the results showed that the overall effect size did not change with the addition of missing studies (RR: 1.31, 95% CI: 1.123, 1.527).

Sensitivity analysis. Sensitivity analysis revealed that the overall association of TYG with in-hospital (95% CI: 1.23, 1.43) and ICU (95% CI: 1.44, 1.67) mortality was not affected by a single study.

DISCUSSION

To the best of our knowledge, the present study was the first to pool the results of previous studies to provide a quantitative measure of the association between the TYG index and the risk of in-hospital and ICU all-cause mortality. Our findings showed that each one-unit increase in the TYG index was positively associated with a 33% and 45% increase in the risk of in-hospital and ICU mortality, respectively. As the primary studies were heterogeneous in terms of their participants, besides applying the random model effects, a subgroup analysis based on participants' health status was performed to find the source of heterogeneity. Notably, the subgroup analysis indicated a stronger association between the TYG index and the risk of in-hospital mortality in patients with cardiovascular diseases compared to those with cerebrovascular diseases.

These results indicate that the TyG index could serve as a valuable marker for risk stratification and predicting outcomes in critically ill patients. In critical illness, the metabolic response is an integral part of the body's adaptive response and encompasses various organ systems, wherein energy resources are shifted to the area of utmost necessity [21]. Multiple mechanisms are triggered to increase the provision of energy to vital tissues, including the stimulation of the sympathetic nervous system, the release of pituitary hormones, and an increase in peripheral resistance to the impacts of anabolic factors [37]. During the early phase of the metabolic response, the oxidation of carbohydrates is significantly more enhanced than the oxidation of fats and proteins [38]. Subsequently, there is a decrease in glucose oxidation, an increase in fat turnover, and a reduction in muscle and visceral protein mass, resulting in wasting [39]. The final

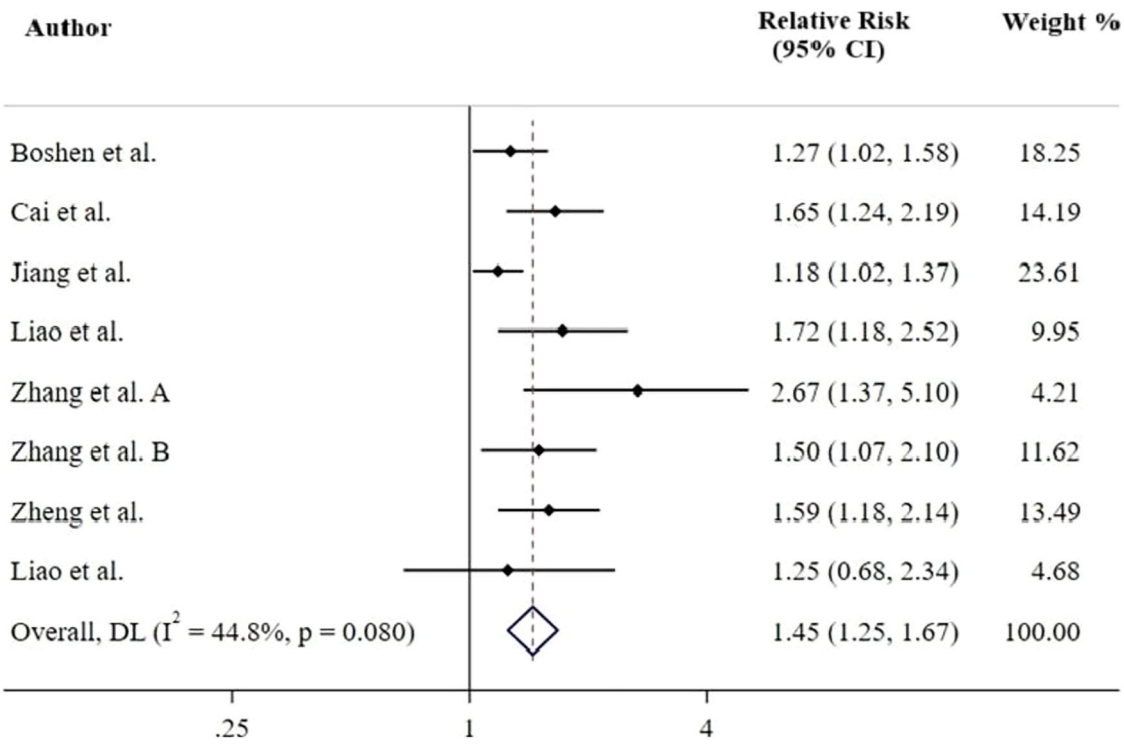

Fig. 4 TYG index and ICU all-cause mortality.

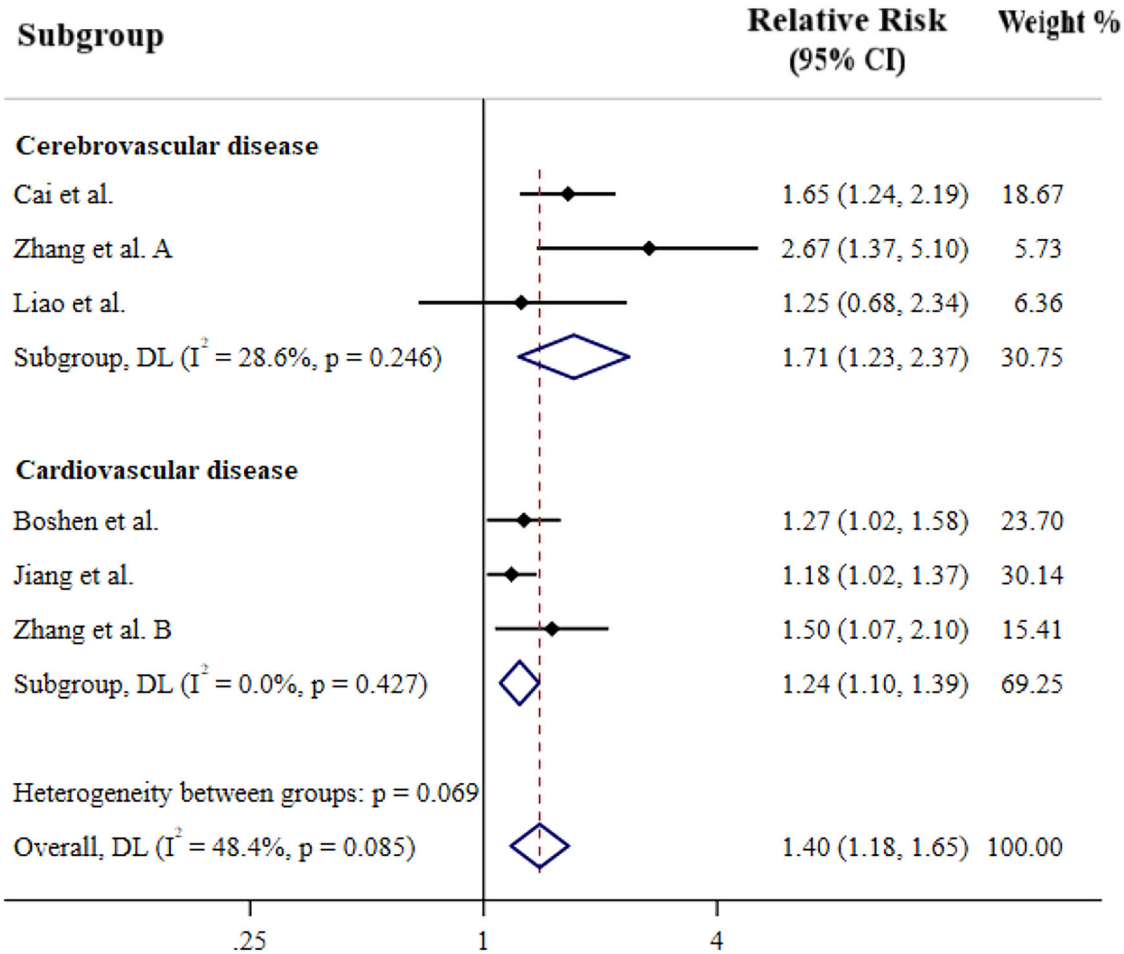

Fig. 5 Subgroup analysis for TYG index and ICU all-cause mortality.

Table 2. Quality assessment of included studies on the association between TYG and in-hospital and ICU mortality.

Author/year (Reference)	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Boshen et al. [23]	*	*	*	*	**	*	*	*	9
Cai et al. [10]	*	*	*	*	**	*	*	*	9
Chen et al. [16]	*	*	*	*	**	*	*	*	9
Cheng et al. [21]	*	*	*	*	---	*	*	*	7
Dai. et al. [25]	*	*	*	*	**	*	*	*	9
Liao et al. [4]	*	*	*	*	*	*	*	*	8
Zhai et al. [33]	*	*	*	*	*	*	*	*	8
Zhang et al. [15]	*	*	*	*	*	*	*	*	8
Zhang et al. [34]	*	*	*	*	**	*	*	*	9
Zheng et al. [36]	*	*	*	*	**	*	*	*	9
Cheng et al. [21]	*	*	*	*	*	*	*	*	8
Zhang et al. [35]	*	*	*	*	*	*	*	*	8
Fu et al. [27]	*	*	*	*	*	*	*	*	8
Ye et al. [32]	*	*	*	*	*	*	*	*	8
Gu et al.2022	*	*	*	*	*	*	*	*	8
Liao et al. [4]	*	*	*	*	*	*	*	*	8
Miao et al. [31]	*	*	*	*	*	*	*	*	8
Ding et al. [26]	*	*	*	*	**	*	*	*	9
Jiang et al. [29]	*	*	*	*	**	*	*	*	9

Each star (*) represents one score.

common metabolic pathways activated in response to critical illness include uncontrolled catabolism and the development of resistance to anabolic signals such as insulin. This process aims to reset the hierarchy of energy supplies by prioritizing the allocation of energy substrates to vital tissues over insulin-dependent organs [40].

The TyG index has been well identified as an available and reliable substitute for insulin resistance (IR) since it does not necessitate insulin levels and can be utilized by all individuals, including both patients and healthy subjects [25]. Concurrently, the fasting levels of triglycerides and glucose, which are essential for calculating the TyG index, can be easily obtained clinically [16]. In a recently published meta-analysis, a significantly higher TyG index was observed in patients with obstructive sleep apnea, compared to the healthy subjects [41].

Moreover, in a study involving 6091 patients, the TyG index was reported to be a stronger predictor of metabolic syndrome than the homeostatic model assessment of insulin resistance (HOMAIR) [42].

The relationship between the TYG index and the risk of cardiovascular or cerebrovascular diseases has also been investigated in several studies [11, 43]. Findings from a meta-analysis indicated a potential linear dose-response association between TYG and the risk of cerebrovascular disease [43]. Likewise, another meta-analysis conducted by Khalaji et al. revealed a significant positive association between the TYG index and the risk of heart failure [44]. Furthermore, Tao et al. demonstrated [11] that the TyG index can serve as a reliable and available substitute for IR and can be improved for risk classification and prognostication of CVD outcomes. However, data regarding critically ill patients are limited. According to a study on critically ill stroke patients, the TyG index could predict in-hospital and ICU mortality [15]. Moreover, a recent study by Zhang et al. reported a significant linear correlation between the baseline TYG index and in-hospital and ICU mortality in critically ill patients suffering from coronary heart disease [34]. Similarly, our findings indicated linear dose-response associations between the TYG index and in-hospital and ICU mortality. Additionally, findings from the subgroup analysis showed that the TYG index had a stronger association with the risk of in-hospital mortality in patients with cardiovascular diseases compared to those with cerebrovascular diseases. Recent epidemiologic studies have indicated that the TyG index can serve as an independent predictor for the risk of cardiovascular diseases and consequent outcomes related to both cardiovascular and cerebrovascular diseases [23, 45, 46]. In this study, the greater association of TYG with cardiovascular diseases might be due to the larger effect sizes (7 vs 6 effect sizes) and a greater number of total participants in this subgroup than in the "cerebrovascular diseases" subgroup (20,347 vs 12,954 patients).

Notably, ICU patients are typically confronted with unstable and progressive disorders, and the progression of acute illnesses such as sepsis, shock, or trauma can result in stress-induced hyperglycemia. Therefore, this condition may bias the diagnostic value of the TyG index [11]. In addition, the TyG index is influenced by several factors, such as race and alcohol intake [16]. Since the majority of the included studies in this meta-analysis used the baseline TYG index as a biofactor to predict mortality and did not control for potential confounders such as race and alcohol intake, our findings should be interpreted with caution.

Strengths and limitations

The strengths of the current study include a meticulous and comprehensive systematic search in online databases, the use of a thorough and rigorous methodology to pool the results of the available studies, the use of subgroup analysis to determine the source of heterogeneity, the assessment of the impact of a separate study on the overall effect measured by sensitivity analysis, and the examination of the effect of unpublished studies on the overall result using publication bias tests. However, it should be noted that the present study has certain limitations that have the potential to undermine our results. As the majority of the included studies had a retrospective design, the dynamic measures of TYG, to control the effect of unstable stress-induced hyperglycemia throughout the studies, were not assessed. Although all the included studies controlled for confounding variables such as age, sex, smoking status, and body mass index, most of them did not adjust for other potential confounders such as race and alcohol intake.

CONCLUSION

The outcome of this meta-analysis demonstrated that the TYG index had a significant relationship with the risk of in-hospital and ICU mortality. Furthermore, subgroup analysis revealed a stronger association between the TYG index and the risk of in-hospital mortality. Based on these findings, the TyG index has the potential to predict the risk of in-hospital and ICU mortality in hospitalized patients.

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AUTHOR CONTRIBUTIONS

ESZ, NN, and MS: Contributed to the study design and data collection, interpretation, and drafting of the manuscript. FHS: Performed the statistical analysis and drafting of the manuscript. AS: Participated in the study conception, revised the paper critically, and approved the version of the manuscript being submitted. All the authors read the final content of the manuscript before submission.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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