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Association between all-cause mortality and triglyceride glucose body mass index among critically ill patients with sepsis: a retrospective cohort investigation

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Abstract

Background We determined utilizing a sepsis participant cohort whether there is a significant association between TyG-BMI (triglyceride glucose body mass index) and mortality rates at any stage.

Methods Herein, a historical cohort investigation approach was adopted, using information provided by the Medical Information Mart for Intensive Care-IV (MIMIC-IV). We categorized the included individuals in accordance with their TyG-BMI data quartiles, and the primary outcomes were mortality during the hospital stay and death rate due to any reason at postadmission day 28, 90, and 365. To evaluate TyG-BMI mortality's relationship with sepsis-induced mortality risk, we employed restricted cubic spline regression (RCS) and Cox regression models. Additionally, we confirmed TyG-BMI's significant predictive value for mortality via machine learning methods. Furthermore, we performed subgroup analyses to investigate possible differences among various patient groups.

Results The cohort included 4759 individuals, aged 63.9 ± 15.0 years, involving 2885 males (60.6%). The rates of death that took place during hospital stay and at 28, 90 and 365 days postadmission were respectively 19.60%, 24.70%, 28.80%, and 35.20%. As reflected by Cox models, TyG-BMI was negatively associated with mortality risk at various intervals: in-hospital [hazard ratio (HR) 0.47 (0.39–0.56), $P = 0.003$], 28 days postadmission [HR 0.42 (0.35–0.49), $P < 0.001$], 90 days postadmission [HR 0.41 (0.35–0.48), $P < 0.001$], and 365 days postadmission [HR 0.41 (0.35–0.47), $P < 0.001$]. Additionally, the relationship between TyG-BMI and death rates was L-shaped, as reflected by the RCS, with a TyG-BMI of 249 being the turning point.

Conclusions Among sepsis patients in critical care, TyG-BMI is negatively correlated with mortality possibility at various intervals: during hospital stay and 28 days, 90 days, and one year postadmission. TyG-BMI is a beneficial parameter for categorizing risk levels among sepsis patients and for predicting their mortality risk within one year.

Keywords Retrospective design, Cohort investigation, TyG-BMI, Critical Illness, In-hospital Death

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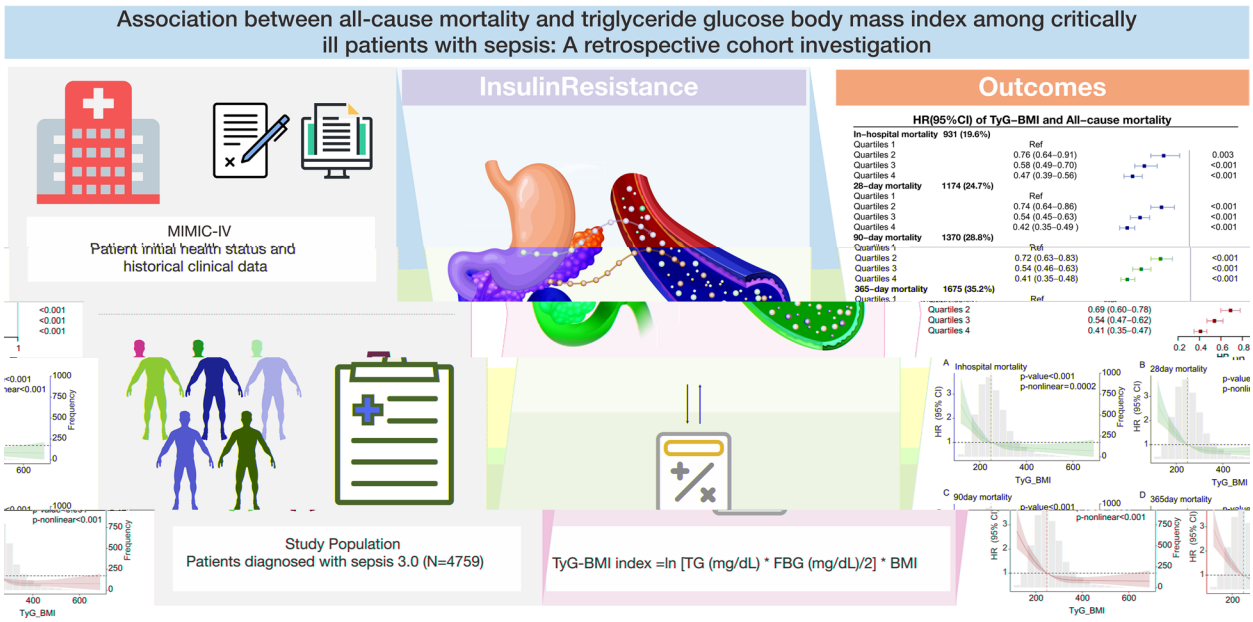
Graphical Abstract



Introduction

Infectious diseases are among the world's foremost health challenges. Sepsis is a critical sequela of infectious processes and is closely related to dysregulated immune reactions. Owing to its propensity to induce multiorgan dysfunction, sepsis poses a significant threat to patient survival [1]. Although there have been notable advancements in treating infectious diseases through the extensive use of antibiotics and medical technology, sepsis persists in its high incidence and mortality rates [2], underscoring the urgent need for improved understanding and management strategies.

A critical factor in sepsis management is the recognition of insulin resistance (IR), a common clinical feature among sepsis sufferers associating with increased death risk due to the abrupt imbalances in blood glucose levels [3]. During sepsis, an overabundance of inflammatory cytokines and oxidative stress are suspected to exacerbate IR, complicating patient outcomes. However, the clinical implications of IR in sepsis are not fully understood, partly due to the lack of convenient and non-invasive markers for assessing IR [4]. Pan et al. proposed that in-hospital mortality is positively correlated with triglyceride-glucose index (TyG) parameters among severe sepsis patients under intensive care [5]. Notably, TyG-BMI, an index that combines body mass index (BMI) and TyG, outperformed other methods in evaluating IR [6, 7]. This composite parameter not only captures obesity indicators but also more comprehensively reflects an individual's body composition and metabolic equilibrium [8, 9]. Various conditions, including metabolic dysfunction-associated fatty liver disease, hypertension, coronary heart disease (CHD), renal implications, and diabetes exhibit notable implications with TyG [10–14]. Despite these associations, the parameter's sepsis prognostic significance, particularly over extended periods, remains underexplored. Understanding its association with clinical outcomes could lead to more personalized and targeted therapies, improving patient management. It could enhance the predictive capability regarding patient survival, inform the development of novel therapeutic interventions, and guide clinical decision-making by providing a metric that reflects the intricate relationship between metabolic dysfunction and sepsis severity.

This retrospective cohort study aimed to explore whether TyG-BMI is associated with both immediate and extended survival rates in individuals with sepsis, shedding light on the prognostic significance of TyG-BMI and potentially pave the way for innovative therapeutic approaches that could enhance treatment outcomes in sepsis management. The findings from this study could lead to the establishment of innovative approaches benefiting sepsis therapeutic outcomes and highlight TyG-BMI's prognostic significance.

Method

Data source and ethics approval

Data were retrospectively attained from version 2.2 of the Medical Information Mart for Intensive Care IV (MIMIC-IV), an extensive dataset encompassing > 190,000 individuals treated in a US medical center during the 2008–2019 period [15]. It includes detailed patient profiles, clinical measurements, laboratory analysis results, diagnosis conditions classified under codes ICD-9 and −10, drug administration records, and patient survival data.

The original institution's review board permitted data sharing, waiving the need for participant consent. Author HJJ completed the human subject protection training and successfully met the criteria set by the Collaborative Institutional Training Initiative (approval No. 61632129).

Cohort selection

Individuals who satisfied the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) diagnostic standards, requiring no less than two points of increment in Sequential Organ Failure Assessment (SOFA) score relative to starting values, coupled with a suspected infection, were selected. Suspected infections were confirmed through the initiation of microbiological cultures or the clinical decision to administer antibiotics [1]. Individuals who (1) spent < 24 h in the Intensive Care Unit (ICU); (2) lacked necessary data, including triglyceride (TG) and fasting blood glucose (FBG) levels; and (3) were under the age of 18 years, were not subjected to selection. Furthermore, for those who were admitted into ICU > 1 time for sepsis, only the data from their first admission was used. In total, data from 4759 eligible ICU patients with sepsis were analysed, and the participants were categorized into TyG-BMI value quartiles (Supplementary Figure S1).

Data retrieval

Data were retrieved via Structured Query Language (SQL) through Navicat Premium software, v.16.1.12. A range of variables, including demographic details, clinical indicators, underlying health conditions, pharmaceuticals, and laboratory measurements, were collected. Clinical severity scores and patient outcomes were tracked for rates of mortality that occurred during the hospital stay and at 28, 90 and 365 days postadmission. Variables with > 20% missing information were discarded, as per the set standards. For variables containing < 20% missing data, imputation was conducted using a multivariable interpolation method. Assuming that the data were missing at random, we applied the "miss-Forest" R package for data imputation prior to analysis [16, 17].

TyG-BMI calculation

TG and FBG values (in mg/dL) used for the calculation of TyG-BMI were obtained during the initial ICU admission as part of the standard clinical assessment. This approach is consistent with previous studies [5, 18, 19]. FBG, BMI, and TG values were input into the equation $\text{TyG-BMI} = \ln[\text{TG} \times \text{FBG} \div 2] \times \text{BMI}$ [20].

Outcomes

This study's endpoints included mortality rates at different time points following hospitalization: in-hospital, 28 days postadmission, 90 days postadmission, and 365 days postadmission. Information on patient mortality after hospital release was obtained from the United States Social Security Administration's Death Master File.

Statistical analysis

Continuous variables' distribution normality was first assessed. Variables with a Gaussian distribution were subjected to one-way analysis of variance or t tests, and the data are reported as means ± SDs. For variables with skewed distribution, we implemented Kruskal–Wallis test, and utilized medians (interquartile ranges, IQRs) for data expression. The chi-square or Fisher's exact test was employed for comparisons among qualitative data, and the data are expressed as counts and proportions. To examine differences in survival outcomes among TyG-BMI groups, Mantel–Haenszel and Kaplan–Meier analyses were applied. Cox regression models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI). The initial model was based solely on TyG-BMI. The second model incorporated adjustments for age, sex, and ethnicity. The third model incorporated clinically relevant factors, previous findings [21], and feature selection via the Boruta and random forest methods, as shown in Figure S3. The Boruta algorithm is adept at managing high-dimensional data and has been a utilized in similar studies [18]. The algorithm's efficiency lies in its balanced selection process, combining the strengths of filter and wrapper methods, and its ability to minimize overfitting by focusing on key features. The visual representation of feature importance, with color-coded boxes for important, tentative, and unimportant variables, further aids in the interpretation of results. A reference group for all Cox models was set using the lowest TyG-BMI quartile. Variance inflation factors (VIFs) were utilized for assessment of multicollinearity. The association of mortality with TyG-BMI was explored with RCS, and nonlinear trends were analysed via Cox models with RCS. The placement of four knots within the RCS was

strategically determined by the Akaike Information Criterion, with knots positioned at the 5th, 35th, 65th, and 95th percentiles of the TyG-BMI distribution to capture the full spectrum of its relationship with mortality risk. The participants were stratified into subgroups according to age, sex, simplified acute physiology score (SAPS II), SOFA score, hypertension status, diabetes status, chronic kidney disease (CKD), acute pancreatitis (AP), septic shock and atrial fibrillation (AF) to determine whether the prognostic significance of TyG-BMI for mortality was robust across subgroups. Statistical analyses were conducted using R version 4.4.1, with significance defined as a two-tailed $P < 0.05$.

Results

Basic information of the participants

Among the 32,971 sepsis patients from the MIMIC-IV database, 4,759 met the inclusion criteria and were included for analysis. Table 1 outlines their baseline features categorized by TyG-BMI quartiles. The mean age at admission was 63.9 ± 15.0 years, with male participants accounting for 60.6% of the cohort. Those in the lowest TyG-BMI quartile tended to be male, have a reduced prevalence of diabetes and hypertension, and have unique patterns in terms of medication use and physiological measurements compared with those in higher quartiles, including less frequent use of insulin and statins but more frequent use of aspirin. Those in the lowest TyG-BMI quartile also presented with lower heart rates, respiratory rates, carbon dioxide pressures, urea nitrogen, creatinine, and potassium levels, white blood cell, platelet, and oxygen saturation levels. Furthermore, compared with the higher TyG-BMI quartiles, mortality rates for the lowest TyG-BMI quartile were significantly higher at each time point: in-hospital (23.1% versus 19.6%, 17.0%, and 18.6%, $P = 0.001$), 28 days postadmission (30.1% versus 25.4%, 20.8%, and 21.6%, $P < 0.001$), 90 days postadmission (36.6% versus 29.2%, 24.6%, and 24.8%, $P < 0.001$), and 365 days postadmission (45.4% versus 34.6%, 30.8%, and 30.1%, $P < 0.001$).

Associations between TyG-BMI and mortality risk

The established Kaplan–Meier curves revealed significant variations in survival probabilities across different groups classified by TyG-BMI for mortality that occurred during the hospital stay and at 28, 90 and 365 days postadmission (Supplementary Figure S2). The survival probabilities of individuals in the quartile with the lowest TyG-BMI were markedly lower than those of individuals in the higher quartiles, with corresponding log-rank test P values of 0.0003, < 0.0001, < 0.0001, and < 0.0001.

Prior to examining the link between TyG-BMI and mortality risk among sepsis patients, a feature selection process was applied via Boruta's method [22]. This method evaluates the relevance of features by assessing their Z scores against a set of shadow features, selecting features with Z scores that surpass those of the shadow features for inclusion in the model (Supplementary Figure S3).

The Cox proportional hazards models revealed a steady decrease in mortality risk across different follow-up periods with increasing TyG-BMI quartiles, achieving statistical significance at the $P < 0.001$ level after controlling for demographics, comorbidities, and laboratory values (Table 2). Notably, the HR and 95% CI for in-hospital mortality ranged from 1.00 to 0.76 (0.64–0.91), 0.58 (0.49–0.70), and 0.47 (0.39–0.56) as TyG-BMI values increased. Similarly, for 365-day mortality, the HR was 1.00, 0.69 (0.60–0.78), 0.54 (0.47–0.62), and 0.41 (0.35–0.47), respectively. Patients with the highest TyG-BMI presented a markedly decreased mortality rates at 365 days (59% reduction) compared with a 53% reduction observed for in-hospital mortality. Consistent with these findings, the associations between TyG-BMI and mortality risk at 28 and 90 days postadmission are also detailed in Table 2.

Furthermore, to ensure the reliability of the findings, RCS analysis was performed and revealed a nonlinear reduction in mortality risk at the various time points mentioned above as TyG-BMI values increased, suggesting that the association of TyG-BMI with mortality risk was inversely L-shaped (Fig. 1). The threshold value of TyG-BMI that demarcates the two segments of the L-shaped curve was identified at approximately 249. For TyG-BMI values below this threshold, mortality risks in both the short and long term increased precipitously as TyG-BMI decreased. Conversely, above the threshold of 249, the mortality risk slowly decreased when TyG-BMI increased, with significant nonlinearity ($P < 0.001$).

Subgroup analysis

To further validate the associations of TyG-BMI with various mortality endpoints at the evaluation time points mentioned above, this study performed subgroup analyses based on age, sex, hypertension, diabetes mellitus, CKD, AF, AP, septic shock and SAPS II and SOFA scores (Fig. 2). The subgroup analyses consistently revealed a similar pattern between TyG-BMI and mortality risk across most subgroups, regardless of whether the endpoint was short-term mortality or long-term mortality. Specifically, the mortality risk was inversely and significantly correlated with TyG-BMI. However, for AP participants, no significant association was found between TyG-BMI and mortality risk during hospital stay or one-year follow-up.

Table 1 Patient characteristics

Variable	Overall (*n* = 4759)	Quartiles1 (*n* = 1190)	Quartiles2 (*n* = 1189)	Quartiles3 (*n* = 1190)	Quartiles4 (*n* = 1190)	*P* value
TyG-BMI	248.9 (211.7–294.3)	188.8 (171.2–201.4)	230.8 (221.6–239.5)	269.5 (259.1–281.9)	339.0 (311.9–386.7)	< 0.001
Demographics						
Age, years	63.9 ± 15.0	63.8 ± 15.3	64.4 ± 15.1	63.7 ± 14.8	63.6 ± 14.7	0.111
Men, n (%)	2885 (60.6)	768 (64.5)	788 (66.3)	663 (55.7)	666 (56.0)	< 0.001
Race/ethnicity, n (%)						< 0.001
Asian	142 (3.0)	64 (5.4)	49 (4.1)	19 (1.6)	10 (0.8)	
White	3202 (67.3)	787 (66.1)	802 (67.5)	833 (70.0)	780 (65.5)	
Black	537 (11.3)	132 (11.1)	117 (9.8)	125 (10.5)	163 (13.7)	
Others	878 (18.4)	207 (17.4)	222 (18.7)	212 (17.8)	237 (19.9)	
Vital signs						
Height, m	1.70 (1.63, 1.78)	1.70 [1.63, 1.78]	1.73 [1.63, 1.78]	1.70 [1.60, 1.78]	1.68 [1.60, 1.75]	< 0.001
Weight, kg	80.30 (67.80, 96.80)	75.10 [68.40, 81.80]	87.90 [79.85, 96.00]	108.86 [97.50, 122.57]	60.10 [53.40, 68.24]	< 0.001
Body mass index, kg/cm2	27.85 (24.18, 32.58)	26.00 [25.08, 26.93]	29.94 [28.87, 31.09]	37.13 [34.48, 41.96]	21.69 [19.85, 22.96]	< 0.001
Mean heart rate, beats/min	86 (76, 97)	85 (76–97)	85 (75–96)	86 (76–97)	87 (77–99)	0.006
Systolic blood pressure, mmHg	112.48 (104.69 122.32)	112.75 [104.67, 122.24]	113.11 [105.32, 122.47]	112.94 [105.21, 122.30]	111.01 [103.43, 122.19]	0.012
Diastolic blood pressure, mmHg	60.15 (54.39, 66.57)	60.28 [54.12, 66.41]	60.14 [54.46, 66.63]	59.96 [54.91, 66.04]	60.20 [54.18, 67.40]	0.919
Respiratory rate, times/min	19 (17, 22)	18.72 [16.48, 21.82]	19.12 [16.80, 21.86]	19.68 [17.28, 22.86]	19.05 [16.61, 22.21]	< 0.001
Saturation of pulse oxygen, %	98 (96, 99)	98 [96, 99]	97 [96, 99]	97 [96, 98]	98 [96, 99]	< 0.001
Comorbidities						
Hypertension, n (%)	2148 (45.1)	540 (45.4)	600 (50.5)	549 (46.1)	459 (38.6)	< 0.001
Diabetes mellitus, n (%)	243 (5.1)	52 (4.4)	61 (5.1)	91 (7.6)	39 (3.3)	< 0.001
Acute myocardial infarction, n (%)	186 (3.9)	50 (4.2)	43 (3.6)	48 (4.0)	45 (3.8)	0.522
Heart failure, n (%)	284 (6.0)	62 (5.2)	73 (6.1)	81 (6.8)	68 (5.7)	0.115
Chronic obstructive pulmonary disease, n (%)	196 (4.1)	42 (3.5)	39 (3.3)	64 (5.4)	51 (4.3)	0.116
Liver disease, n (%)	156 (3.3)	29 (2.4)	40 (3.4)	40 (3.4)	47 (3.9)	0.076
Acute kidney injury, n (%)	4059 (85.7)	982 (82.5)	1030 (86.6)	1129 (94.9)	938 (78.8)	< 0.001
Atrial fibrillation, n (%)	467 (9.8)	110 (9.2)	113 (9.5)	118 (9.9)	126 (10.6)	0.797
Stroke, n (%)	161 (3.4)	54 (4.5)	35 (2.9)	34 (2.9)	38 (3.2)	0.270
Peripheral vascular disease, n (%)	105 (2.2)	26 (2.2)	26 (2.2)	30 (2.5)	23 (1.9)	0.810
Severity scores						
SOFA	3 (2, 5)	3 (2, 4)	3 (2, 5)	3 (2, 5)	3 (2, 5)	< 0.001
SAPS-II	40 (32, 50)	39.00 [31.00, 49.00]	40.00 [31.00, 50.00]	40.00 [32.00, 51.00]	40.00 [32.00, 50.00]	0.652
SIRS	3 (2, 3)	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	0.124
OASIS	35 (29, 41)	34.00 [29.00, 40.00]	34.00 [29.00, 40.00]	35.00 [30.00, 41.00]	35.00 [30.00, 41.00]	0.120
Laboratory parameters						
Hemoglobin, g/L	10.30 (9.00, 11.85)	10.25 [9.10, 11.75]	10.30 [9.00, 11.90]	10.50 [9.10, 12.00]	10.15 [8.85, 11.70]	0.015
Platelet, 10^9/L	178 (127, 243)	172.50 [124.50, 230.25]	170.50 [123.00, 233.50]	185.00 [137.62, 249.38]	184.25 [123.50, 260.38]	< 0.001

Table 1 (continued)

Variable	Overall (*n* = 4759)	Quartiles1 (*n* = 1190)	Quartiles2 (*n* = 1189)	Quartiles3 (*n* = 1190)	Quartiles4 (*n* = 1190)	*P* value
White blood cell, 10^9/L	11.85 (8.75, 15.75)	11.53 [8.75, 15.29]	12.20 [8.95, 15.75]	12.40 [9.20, 16.62]	11.40 [7.95, 15.45]	< 0.001
Lactate, mmol/L	1.90 (1.35, 2.80)	1.90 [1.40, 2.80]	1.95 [1.40, 2.90]	1.90 [1.35, 2.80]	1.80 [1.30, 2.70]	0.004
PH	7.37 (7.32, 7.42)	7.38 [7.33, 7.42]	7.37 [7.32, 7.40]	7.36 [7.31, 7.40]	7.38 [7.33, 7.42]	< 0.001
PO_2, mmHg	167 (104, 250)	179 [111, 260]	176 [109, 250]	152 [102, 236]	158 [100, 251]	< 0.001
PCO_2, mmHg	41 (36, 45)	40 [36, 44]	41 [37, 45]	42[37, 47]	39 [35, 45]	< 0.001
Creatinine, mg/dL	1.1 (0.8, 1.7)	1.05 [0.80, 1.60]	1.10 [0.80, 1.75]	1.15 [0.85, 1.95]	1.00 [0.70, 1.55]	< 0.001
Blood urea nitrogen, mg/dL	21.5 (14.5, 36.0)	20.50 [14.00, 32.88]	21.00 [14.50, 35.50]	23.00 [16.00, 38.00]	21.25 [13.50, 35.88]	< 0.001
Sodium, mmol/L	138.5 (136, 141)	138.50 [136.00, 141.00]	138.50 [136.00, 141.00]	138.50 [136.00, 141.00]	138.50 [135.50, 141.00]	0.579
Potassium, mmol/L	4.20 (3.90, 4.65)	4.20 [3.85, 4.55]	4.30 [3.90, 4.70]	4.30 [3.90, 4.75]	4.15 [3.80, 4.55]	< 0.001
Fasting blood glucose, mg/dL	132.61 (115.8, 160.8)	130.73 [116.53, 155.55]	135.05 [119.75, 166.38]	139.24 [120.33, 174.32]	124.03 [105.76, 148.00]	< 0.001
Triglyceride, mg/dL	112,00 (82.00, 151.00)	110.00 [80.00, 147.00]	118.00 [86.00, 158.00]	125.00 [93.00, 164.00]	95.00 [71.00, 135.00]	< 0.001
Prothrombin time, s	14.70 (13.1, 17.55)	14.80 [13.10, 17.69]	14.65 [13.30, 17.60]	14.60 [13.15, 17.50]	14.60 [12.80, 17.40]	0.119
Activated partial thromboplastin time, s	32.95 (28.30, 43.33)	33.23 [28.56, 44.09]	33.20 [28.60, 45.50]	31.90 [27.85, 41.80]	33.30 [28.35, 42.04]	0.002
Medication						
Aspirin	2694 (56.6)	724 (60.8)	730 (61.4)	661 (55.5)	579 (48.7)	< 0.001
Insulin	3416 (71.8)	788 (66.2)	833 (70.1)	881 (74.0)	914 (76.8)	< 0.001
Statin	3383 (71.1)	780 (65.5)	870 (73.2)	874 (73.4)	859 (72.2)	< 0.001
Dobutamine	162 (3.4)	32 (2.7)	38 (3.2)	47 (3.9)	45 (3.8)	0.306
Dopamine	240 (5.0)	52 (4.4)	60 (5.0)	71 (6.0)	57 (4.8)	0.330
Epineprine	470 (9.9)	92 (7.7)	122 (10.3)	127 (10.7)	129 (10.8)	0.038
Norepineprine	1897 (39.9)	477 (40.1)	450 (37.8)	459 (38.6)	511 (42.9)	0.055
Heparin	4577 (96.2)	1150 (96.6)	1135 (95.4)	1135 (95.4)	1157 (97.2)	0.046
Outcome						
In-hospital mortality, n (%)	931 (19.6)	275 (23.1)	233 (19.6)	202 (17.0)	221 (18.6)	0.001
28-day mortality, n (%)	1174 (24.7)	368 (30.1)	302 (25.4)	247 (20.8)	257 (21.6)	< 0.001
90-day mortality, n (%)	1370 (28.8)	435 (36.6)	347 (29.2)	293 (24.6)	295 (24.8)	< 0.001
365-day mortality, n (%)	1675 (35.2)	540 (45.4)	411 (34.6)	366 (30.8)	358 (30.1)	< 0.001

Data: N (%), mean (Q1–Q3), or mean ± standard deviation

Abbreviations: *PaCO2* carbon dioxide partial pressure, *PaO2* partial pressure of arterial oxygen, *SOFA* sequential organ failure assessment, *SAPS II* simplified acute physiology score, *SIRS* systemic inflammatory response syndrome, *OASIS* organ dysfunction and acute injury

Discussion

This is the first study to examine the association of short-term and long-term mortality risk with TyG-BMI among individuals with sepsis. This study revealed three key insights: (a) a notably elevated TyG-BMI is correlated with a reduced risk of mortality both during the hospital stay and within 365 days following discharge among sepsis patients, similar to the trends observed for mortality risk at 28 and 90 days; (b) an inverse L-shaped association was identified for mortality risk during the hospital stay and within 365 days following discharge and TyG-BMI, with a threshold value of approximately 249, thus highlighting the importance of detailed analysis at different time intervals; (c) this association was consistently strong across most subgroups, especially among those with hypertension, those with lower SOFA scores, and those without CKD, where a higher TyG-BMI seemed advantageous. By applying TyG-BMI to critically ill populations,

Table 2 Cox proportional hazard models for in-hospital, 28-day, 90-day, and 365-day all-cause mortality

Variable	Model 1		Model 2		Model 3	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
In-hospital mortality						
TyG-BMI (Quartiless)						
Quartiles 1	Ref		Ref		Ref	
Quartiles 2	0.82 (0.69–0.98)	0.028	0.83 (0.70–0.99)	0.043	0.76 (0.64–0.91)	0.003
Quartiles 3	0.70 (0.58–0.83)	< 0.001	0.71 (0.59–0.86)	< 0.001	0.58 (0.49–0.70)	< 0.001
Quartiles 4	0.77 (0.64–0.91)	0.003	0.76 (0.64–0.91)	0.003	0.47 (0.39–0.56)	< 0.001
28-day mortality						
TyG-BMI (Quartiless)						
Quartiles 1	Ref		Ref		Ref	
Quartiles 2	0.79 (0.68–0.92)	0.003	0.80 (0.69–0.94)	0.005	0.74 (0.64–0.86)	< 0.001
Quartiles 3	0.63 (0.54–0.73)	< 0.001	0.65 (0.55–0.76)	< 0.001	0.54 (0.45–0.63)	< 0.001
Quartiles 4	0.66 (0.56–0.78)	< 0.001	0.66 (0.56–0.78)	< 0.001	0.42 (0.35–0.49)	< 0.001
90-day mortality						
TyG-BMI (Quartiless)						
Quartiles 1	Ref		Ref		Ref	
Quartiles 2	0.76 (0.66–0.88)	0.0002	0.77 (0.67–0.89)	0.0004	0.72 (0.63–0.83)	< 0.001
Quartiles 3	0.63 (0.54–0.73)	< 0.001	0.64 (0.55–0.74)	< 0.001	0.54 (0.46–0.63)	< 0.001
Quartiles 4	0.64 (0.55–0.74)	< 0.001	0.63 (0.54–0.73)	< 0.001	0.41 (0.35–0.48)	< 0.001
365-day mortality						
TyG-BMI (Quartiless)						
Quartiles 1	Ref		Ref		Ref	
Quartiles 2	0.72 (0.63–0.82)	< 0.001	0.73 (0.64–0.83)	< 0.001	0.69 (0.60–0.78)	< 0.001
Quartiles 3	0.62 (0.54–0.70)	< 0.001	0.63 (0.55–0.72)	< 0.001	0.54 (0.47–0.62)	< 0.001
Quartiles 4	0.60 (0.53–0.69)	< 0.001	0.60 (0.53–0.69)	< 0.001	0.41 (0.35–0.47)	< 0.001

HR, hazard ratio

Model 1: Unadjusted

Model 2: Adjusted for age; gender

Model 3: Adjusted For age a; gender; SOFA score; SAPSII score; potassium; PLT; WBC; PH; SaO_2; atrial fibrillation; hypertension; diabetes; AKI; Plasma osmolality

this study highlights the significance of TyG-BMI in guiding the formulation of sepsis management strategies.

Previous investigations revealed the possibility of the use of TyG-BMI for diagnosing or forecasting the outcomes of various health issues, such as metabolic syndrome, heart disease, cerebrovascular events, renal conditions, and COVID-19 [10, 21, 23–26]. Numerous clinical investigations have examined how TyG-BMI is correlated with mortality risk among different demographic groups. Previous investigations on stroke sufferers under lethal conditions revealed that TyG-BMI may effectively predict extended clinical outcomes, irrespective of reperfusion treatment [19, 27]. Moreover, Hou et al.'s study of patients with hypertension and CHD revealed that the relationship between TyG-BMI and all-cause mortality was U-shaped, demonstrating the index's predictive power for this particular demographic [14]. Within the broader community, a reduced TyG-BMI value was found to be correlated with increased likelihood of respiratory issues, a greater chance of being affected by persistent lung disorders, and poorer respiratory capacity [28]. Additionally, elevated TyG-BMI values have been associated with a greater risk of sudden cardiac arrest in a nonlinear manner [29]. Collectively, these studies suggest a possible link between TyG-BMI and medical outcomes, underscoring its prognostic value across various health care scenarios and healthy population. Nevertheless, there is a lack of research exploring its association with all-cause mortality, especially among critically ill patients with sepsis.

As reflected by the findings of this investigation, TyG-BMI predicts prolonged survival in sepsis patients, with an inverse L-shaped association with mortality rates. This finding is vital for pinpointing high-risk individuals in intensive care units. Analysis within specific subgroups revealed that among severely ill sepsis patients, regardless of whether comorbid high blood pressure, AF, CKD, or varying degrees of organ dysfunction, a decreased

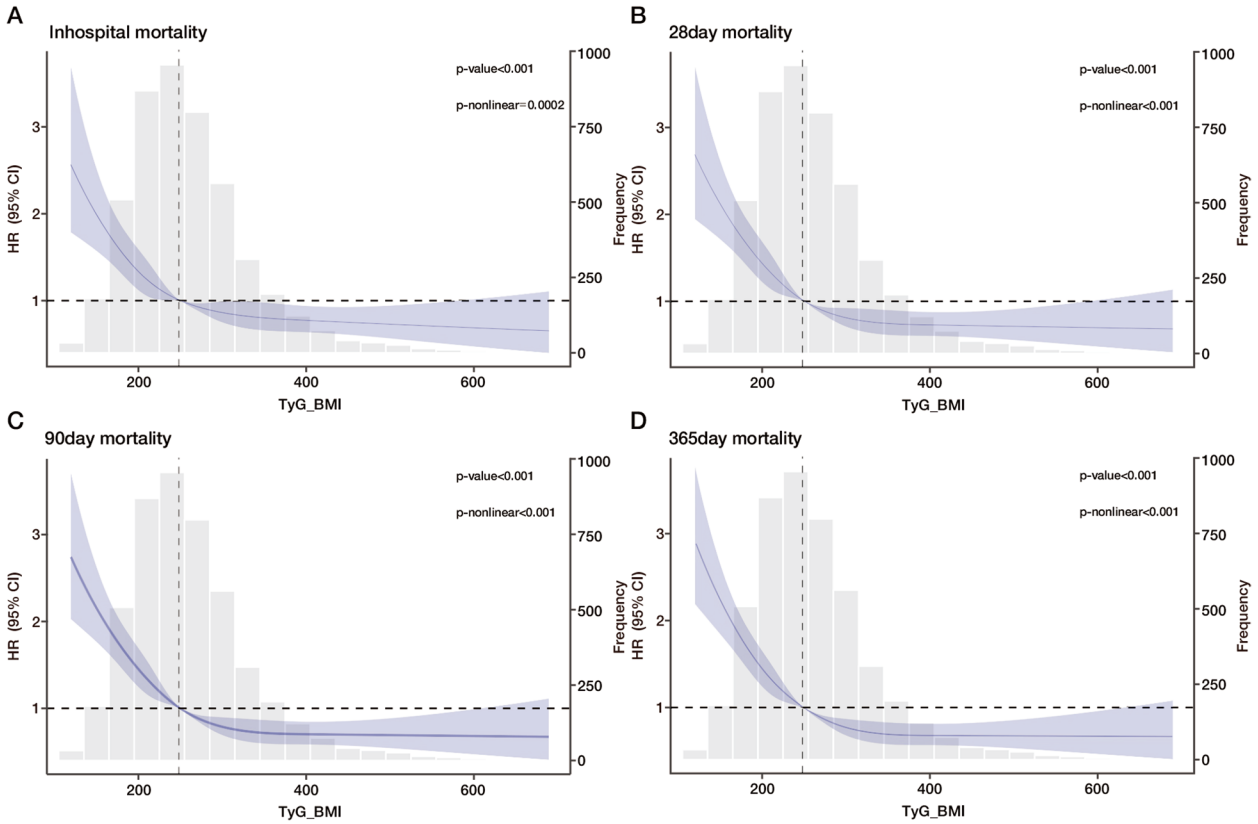


Fig. 1 Restricted cubic spline regression analysis of the TyG-BMI index with all-cause mortality. Restricted cubic spline regression analysis of the TyG-BMI index with (**A**) in-hospital; **B** 28-day; **C** 90-day; **D** 365-day all-cause mortality

TyG-BMI is linked to increased all-cause mortality during the hospital stay and 365-day follow-up periods, where TyG-BMI is negatively correlated with all-cause mortality, thus serving as a protective factor. Similarly, previous study focusing on patients with AF have demonstrated that elevated TyG-BMI levels are associated with improved prognoses for AF patients within the ICU setting [30]. This research echoes these results, reinforcing TyG-BMI's value as a prognostic indicator for AF patients under intensive care. In the analysis of the National Health and Nutrition Examination Survey (NHANES) cohort, Shen et al. discovered that TyG-BMI exhibits a U-shaped association with mortality risk among patients with CKD [31]. Another study from the same NHANES survey indicates that in women and individuals under the age of 60, TyG-BMI is positively correlated with the incidence of CKD [13]. This study revealed that TyG-BMI is associated with the risk of mortality in sepsis patients, irrespective of the presence of comorbid CKD, furthermore, no interaction effect between TyG-BMI and CKD was observed. The observed differences in outcomes may be attributed to inconsistencies in the demographic composition of the study populations. Notably, the subgroup analysis revealed a consistent negative association between TyG-BMI and all-cause mortality in sepsis patients, irrespective of the presence of septic shock, with a stronger association observed in non-shock patients. Similarly, TyG-BMI effectively stratified risk across all SOFA and SAPS II score levels. In the present study, no significant association was detected between TyG-BMI and mortality risk among patients with concurrent sepsis and AP. This finding may be attributed to the predominance of biliary etiology in the cases of AP enrolled in this study. It is hypothesized that TyG-BMI may exhibit a association with lipogenic pancreatitis. Nevertheless, the constrained sample size of sepsis patients with AP in this study could impair statistical power, potentially masking significant associations between TyG-BMI and mortality risk.

Based on the concept of the "obesity paradox," TyG serves as a dependable, easy-to-use, and economical alternative indicator for IR [32]. Various investigations

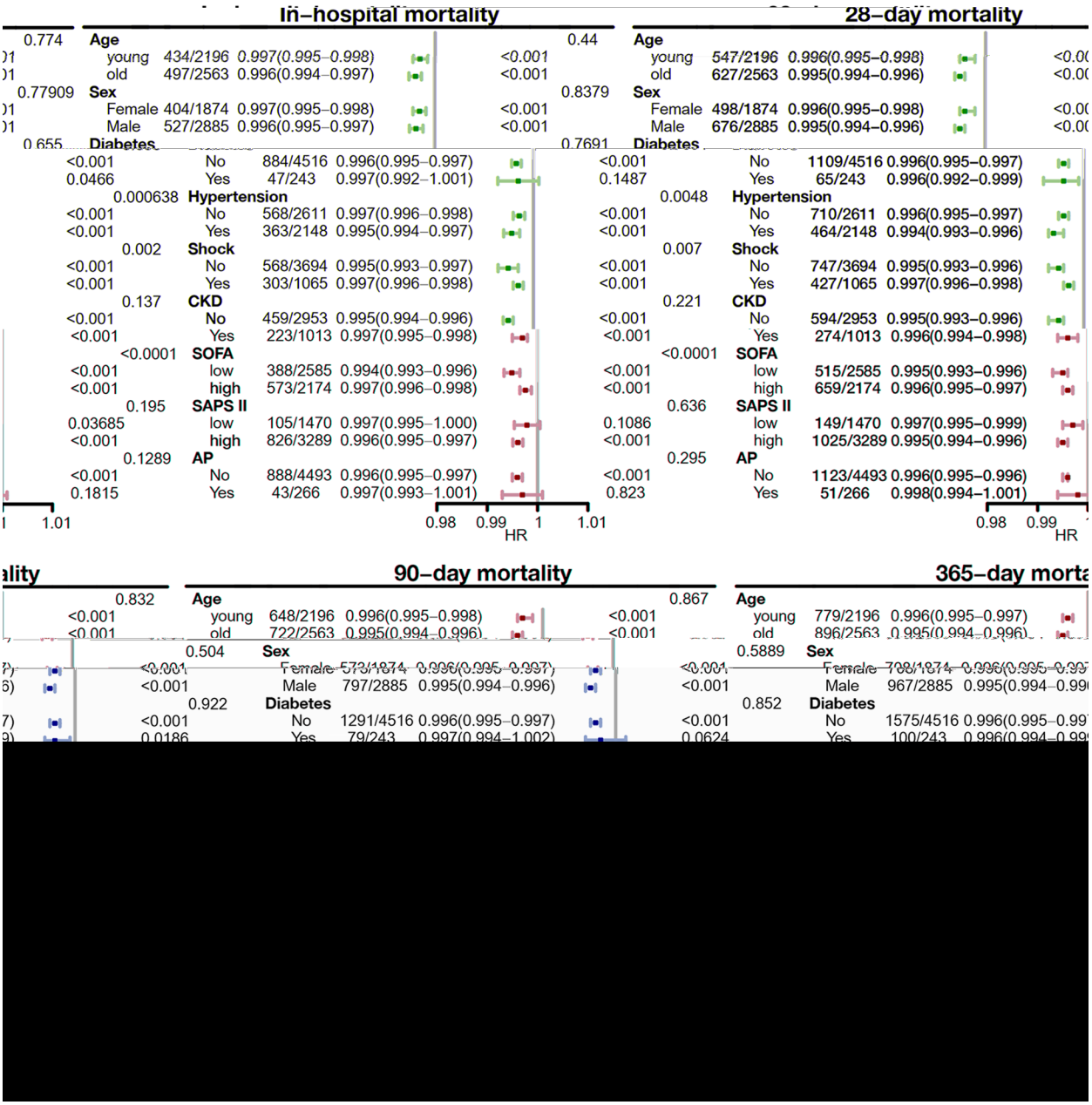


Fig. 2 Forest plots illustrating stratified analyses of the associations between TyG-BMI and (**A**) in-hospital, **B** 28-day, **C** 90-day, and **D** 365-day all-cause mortality. Abbreviations: SOFA: sequential organ failure assessment; SAPS II, simplified acute physiology score

have demonstrated that the association of BMI with clinical outcomes among sepsis sufferers displays a notable U shape, which is frequently used to evaluate obesity levels [33, 34]. The combined TyG-BMI is connected to IR, a state that is commonly related to issues such as blood vessel lining dysfunction, oxidative stress, immune system imbalance, blood clotting irregularities, and inflammatory responses [35–37]. Patients with severe sepsis suffer from abnormal metabolic states and complicated pathological implications, which may further result in risk factors distinguishable from those affecting their health counterparts. Moreover, TyG-BMI can indicate the level of insulin resistance and metabolic health. A decreased TyG-BMI in survivors of sepsis might indicate extreme malnourishment or metabolic exhaustion, both of which are intimately connected to the intensity

of the disease and an elevated mortality risk. Within this research, a substantial inverse and nonlinear connection with increased mortality risk was observed. This study also revealed a substantial inverse and nonlinear relationship between all-cause mortality and TyG-BMI.

The specific ways through which TyG-BMI affects sepsis prognosis are not yet completely understood. The complex interplay between sepsis occurrence and IR has yet to be clearly elucidated. This initial analysis revealed that the four TyG-BMI quartiles presented significantly different SOFA scores, indicating a progressive impact on disease severity. Additionally, it showed that a strong association between TyG-BMI and SOFA score could influence the short-term and long-term mortality risk, highlighting the complex link between TyG-BMI and sepsis severity. IR alterations during the acute phase of sepsis may reveal the severity of inflammation and the overall condition. TyG-BMI could be applied to reliably predict sepsis severity, possibly because it reflects IR among patients. It is believed that IR participates in disease development by increasing blood vessel stiffness and decreasing the availability of nitric oxide (NO), which can lead to multiple organ failure [38, 39].

Within the scope of this research, for certain patient cohorts exhibiting better survival rates, higher TyG-BMI values were observed, suggesting the broad applicability of this parameter in assessing sepsis prognosis across diverse populations. This study confirms that TyG-BMI may be applied clinically to identify sepsis patients with lethal illness effectively. Providing professional health care services to ICU patients is critical, and TyG-BMI, which is easily obtainable at ICU admission, could assist medical professionals in promptly recognizing those at higher risk, thus potentially reducing death rates and optimizing patient prognosis.

Study strengths and limitations

The highlights of the current scientific inquiry include the following: First, this work introduces a novel exploration of the prognostic value of TyG-BMI, particularly in terms of assessing long-term mortality outcomes in sepsis patients, thereby providing innovative perspectives within the critical care field. Methodologically rigorous, in-depth subgroup analyses demonstrated robustness across various demographics. Second, this study focused on sepsis patients, providing insights that are relevant to the pathophysiology of IR and potentially involving more targeted treatment strategies for decision-making in the ICU. Additionally, the use of information from the famous MIMIC-IV database bolsters this conclusions' credibility, whereas visual aids such as survival curves and spline plots effectively elucidate complex data, thus enhancing the interpretability of this analysis.

This study has certain limitations. First, while this study provides valuable insights into the relationship between TyG-BMI and mortality in sepsis, the index was only measured at the time of initial ICU admission. Repeated measurements throughout the follow-up period are needed to further examine the dynamic metabolic changes associated with the progression of sepsis. Second, potential confounders, such as metabolic syndrome indicators, nutritional status, and inflammatory biomarkers, were not comprehensively accounted for, which could influence the interpretation of these results. Third, the provision of nutritional substances, either parenterally or enterally, can modulate glucose and lipid abundances and therefore might have biased TyG-BMI. However, this potential bias is likely attenuated by the large cohort size in this study. Fourth, the use of a cohort design, though beneficial for observational research, inherently limits its ability to infer causality. Additionally, these findings are derived from the MIMIC-IV dataset, which, while rich in critical care data, may not fully represent the diversity of global healthcare settings. This could affect the generalizability of these results. Fifth, there is the potential for unmeasured confounders that could influence the observed associations. Despite these considerations, the study contributes meaningfully to the existing body of knowledge by offering a detailed analysis within a well-characterized dataset. Future research in diverse populations will be instrumental in validating and extending the findings.

Conclusions

The current investigation identified TyG-BMI may serve as a potentially clinical biomarker for assessing mortality due to any reason during a 365-day follow-up period for sepsis sufferers with lethal illness. An L-shaped association was identified between mortality risk and this parameter. TyG-BMI offers a valuable tool for clinicians to promptly recognize patients at elevated risk, thereby potentially attenuating mortality rates and optimizing prognostic outcomes.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
HJ, XH, CM, and JL were responsible for designing and conceptualizing the research. HJ wrote the first draft of the article, with further contributions from XF, CM, XH, and JL. HJ did the statistical analysis. All authors interpreted the data,carefully revised the manuscript,and agreed to have its final version published.

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Data availability
Any requirements regarding dataset or method sharing can be directed toward the corresponding author. Publicly MIMIC datasets are available at https://mimic.mit.edu/.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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