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Triglyceride-glucose index is associated with all-cause mortality in critically ill patients with alcohol use disorder: a retrospective cohort study

Yu Pan[1], Yue-yue Huang[2], Lian-min Ye[2], Xiao-hua Zhang[1], Jing-ye Pan[2] and Yi-hua Dong[2*]

Abstract

Background The relationship between Triglyceride-glucose (TyG) index and clinical outcomes in patients with alcohol use disorder (AUD) is unclear. The aim of this study was to evaluate the association between TyG index and all-cause mortality in critically ill patients with AUD.

Methods We used data from the multi-parameter intelligent monitoring in intensive care IV (MIMIC-IV) database. The patients were equally divided into quartiles. Kaplan–Meier curves were used for survival analysis. The primary endpoint of the study was 28-day mortality, followed by 1-year mortality. We used Cox proportional hazard models to assess the relationship between TyG index and all-cause mortality at different endpoints.

Results A total of 537 AUD patients were included. Using TyG value as a continuous variable (HR 1.460, 95% CI 1.121–1.903, $p=0.005$) and categorical variable (HR 1.447–3.477 from Q2 to Q4, with Q1 as reference), elevated TyG value was significantly associated with increased 28-day mortality. TyG was positively associated with 1-year mortality in AUD patients with an HR of 1.295 (95% CI 1.011–1.659, $p=0.041$).

Conclusion TyG index is positively associated with different clinical outcomes of critically ill AUD patients.

Keywords TyG index, Critically ill, AUD, Mortality

Introduction

Alcohol consumption is a major cause of disability and death, with a survey revealing that alcohol is the seventh leading factor of morbidity and mortality worldwide, in addition to 3.8 percent of female deaths and 12.2 percent of male deaths in the 15–49 age range [1]. It is well known that chronic alcohol abuse often leads to persistent and recurring mental disorders. This is often referred to as alcohol use disorder (AUD) and is one of the most common mental illnesses in the world [2]. AUD patients are characterized by loss of control over their alcohol intake and compulsive heavy alcohol use, impaired control over their alcohol consumption, and exhibit escalating and heavy pattern of alcohol use over time, resulting in significant damage to their health [3]. There are approximately 17 million adult AUD patients in the United States [4] and an estimated 763 million worldwide [5]. Long-term alcohol consumption can have serious negative effects on organ impairments, family well-being and public health. In the United States, 88,000 people die from AUD each year [6], and about 5% of

*Correspondence:
Yi-hua Dong
dongyihua@126.com
[1] Department of Pharmacy, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou 325000, Zhejiang, China
[2] Department of Intensive Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China

registered deaths are blamed on AUD in most Western countries [7]. Patients with AUD often have severe symptoms, such as delirium, infection, liver cirrhosis, or gastrointestinal bleeding, and require admission to the ICU [8]. In any type of intensive care unit, AUD accounts for about 16–31% of all admissions [9]. These patients had a longer duration of mechanical ventilation, a longer ICU stay, and a higher mortality rate. The length of hospital stay was extended by an average of 2.4 days and the likelihood of re-hospitalization within 30 days of discharge was increased by 8% [10]. Despite the serious problems that AUD poses, it remains one of the most under treated diseases.

The triglyceride-glucose (TyG) index is an available index to evaluate glucolipid metabolism levels [11] based on the fasting blood glucose (FBG) and triglyceride (TG) concentrations of patients [12], and can be easily applied to clinical work. A study that showed that triglycerides in skeletal muscle are inversely correlated with skeletal muscle insulin sensitivity and systemic insulin action [13] proposed the concept of TyG index, which has now become a novel alternative marker for insulin resistance and related metabolic abnormalities and is gradually being accepted [12]. In recent years, many studies have shown that high TyG index is positively correlated with the risk of arterial stiffness [14], hypertensive stroke [15], myocardial infarction and other diseases [16]. In addition to the above diseases, this index is also associated with Alzheimer's disease [17] and metabolic syndrome [18]. Excessive alcohol consumption is associated with abnormal and impaired liver function [19], cardiovascular disease [20], hypertriglyceridemia [21] and diabetes [22]. Heavy alcohol consumption and the increased risk of AUD have been linked to metabolic factors such as glucose, cholesterol, triglycerides and high body mass index (BMI) [23–27]. We speculated that there might be some relationship between TyG and AUD. Therefore, we conducted this study to explore the potential relationship between TyG index and mortality of AUD patients in ICU.

Materials and methods

Data source

This was a retrospective observational study using publicly available data from the Medical Information Mart for Intensive Care IV database (MIMIC-IV). Access to the database has been approved by the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology (MIT) Affiliate Review Board. After completing the NIH web training course "Protecting Human Research Participants" (certification number: 22691479), we gained access to the database. All patient records in the MIMIC-IV database were completely de-identified and therefore do not require informed patient consent.

Study population

Patients were identified according to the ICD-9 diagnostic codes (291.xx, 303.xx, 305.0x, 357.5, 425.5, 535.30, 535.31, 571.0, 571.1, 571.2, and 571.3, except 303.03, 303.93, or 305.03) [28] and extracted from the database. The inclusion and exclusion procedures are shown in Fig. 1. Patients who met the AUD diagnosis were considered eligible for inclusion in the study. For readmitted patients, only the first ICU admission information was included. Patients younger than 18 years of age and those with deficient fasting blood glucose (FBG) or triglyceride (TG) values were excluded.

Variable extraction

Structured query language (SQL) was used to extract information such as age, sex, race, BMI index, important scoring systems, major comorbidities, and some laboratory parameters of patients admitted to ICU for the first time from MIMIC-IV. All laboratory parameters extracted from the MIMIC-IV database were measured on the first day of initial ICU admission. The TyG index was calculated as follows: TyG index = ln [fasting TG (mg/dl) × FBG (mg/dl)]/2 [29].

The primary endpoint was 28-day mortality, followed by 1-year mortality. The follow-up period was 1 year, where the date of admission was the start date of follow-up and the US government's Social Security Death Index was the confirmed date of death.

Statistical analysis

The representation of continuous variables varies according to their distribution state, with the normal distribution expressed as mean ± standard deviation and the non-normal distribution expressed as the median (interquartile range (IQR)). Continuous variables were compared using Mann–Whitney *U* test, Kruskal–Wallis test or Wilcoxon signed rank test. Categorical variables are expressed as numbers and percentages and compared using Chi-square tests or Fisher's exact tests. The TyG index was converted into a categorical variable by quartiles, and Kaplan–Meier method with the log-rank test was used to estimate the cumulative incidence of 28-day mortality based on the TyG quartiles. Univariate and multivariate Cox proportional hazard models were applied to calculate hazard ratios (HR) with a 95% confidence interval (CI) to predict the relationship between the TyG index (as a continuous and categorical variable) and 28-day or 1-year risk of death [30]. Using the lowest quartile

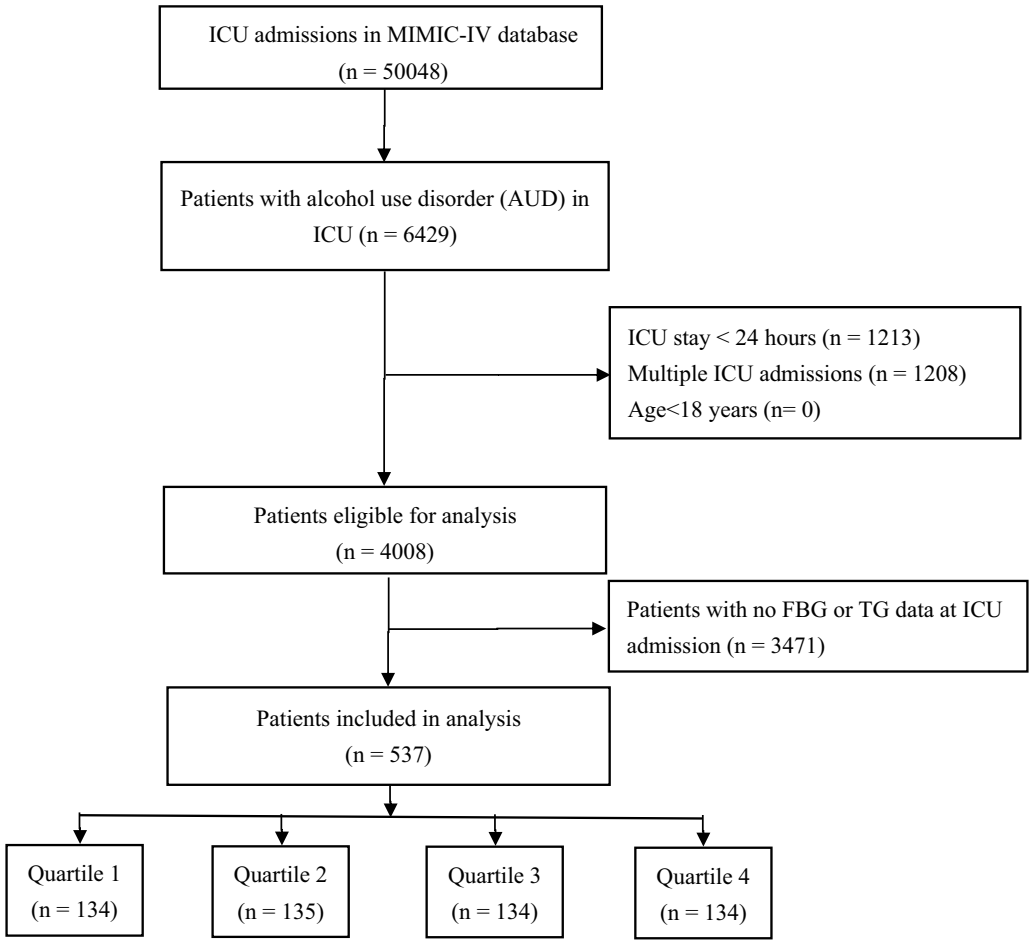


Fig. 1 Study flow chart

1 (Q1) as a reference, we observed the relationship between each level and the end point. Three models were constructed: Mode 1, no adjustment; Model 2, adjusted for age, race, sex and BMI index; Model 3, adjusted for Model 2 + length of ICU stay, spo2, major comorbidities (including metastatic solid tumor, liver disease, diabetes, malignant cancer, congestive heart failure, renal disease, paraplegia, peptic ulcer disease, rheumatic disease, chronic pulmonary disease, cerebrovascular disease, peripheral vascular disease and myocardial infarct), and laboratory parameters (including hematocrit, platelets, white blood cells and creatinine). Log-likelihood test was used to evaluate the interaction effect of TyG with subgroup variables. Subgroup analyses were performed based on age, sex, race, BMI index, and major complications to assess the robustness. All statistical analyses were performed with the statistical software SPSS (version 22.0) and R (version 3.5.2). A p value of less than 0.05 was considered to indicate statistical significance in all analyses.

Results

Characteristics of the studied population

A total of 537 AUD patients (median age: 54.07 years (IQR 45.49–63.65); median TyG index: 8.99 (IQR 8.52–9.63)) were included in the study according to inclusion and exclusion criteria. The demographic and biochemical characteristics of the study cohort are summarized in Table 1. There was no significant difference in blood glucose and potassium levels between the two groups ($p > 0.05$). However, the levels of triglyceride, white blood cells and creatinine in the 28-day death group were significantly higher than those in the 28-day survival group, while the levels of platelet, hematocrit, chloride and sodium were opposite ($P < 0.05$ for all). The median TyG of the patients who did not survive for 28 days was significantly higher than that of the patients who survived for 28 days ($p < 0.05$). According to TyG quartiles, patients with AUD were divided into four groups: Q1

Table 1 Basic characteristics of critically ill patients with alcohol use disorder

Variable	all patients (n = 537)	28-day survivors (n = 463)	28-day non-survivors (n = 74)	*P*-value
Age (years)	54.07 (45.49, 63.65)	53.84 (45.28, 63.58)	57.25 (47.45, 64.00)	0.212
Sex (Male), n (%)	396 (73.74%)	342 (73.87%)	54 (72.97%)	0.871
BMI (kg/m^2)	28.00 (24.00, 33.00)	28.00 (23.00–32.00)	31.50 (25.00–34.00)	0.003
Ethnicity, n (%)				0.009
White	317 (59.03%)	280 (60.48%)	37 (50.00%)	
Black	55 (10.24%)	50 (10.80%)	5 (6.76%)	
Asian	4 (0.74%)	4 (0.86%)	0 (0.00%)	
Hispanic/Latino	17 (3.17%)	16 (3.46%)	1 (1.35%)	
Others	24 (4.47%)	22 (4.75%)	2 (2.70%)	
Unkown	120 (22.35%)	91 (19.65%)	29 (39.19%)	
Vital signs				
Heart rate (bmp)	90.00 (77.00, 102.10)	89.73 (76.19, 102.08)	93.07 (83.16, 106.47)	0.029
MBP (mmHg)	84.64 (74.77, 93.59)	85.41 (76.34, 94.08)	75.03 (68.66, 85.84)	< 0.001
Respiratory rate	19.68 (17.31, 22.65)	19.41 (17.09, 22.11)	22.32 (19.50, 25.44)	< 0.001
Temperature	36.96 (36.72, 37.35)	36.97 (36.73, 37.36)	36.89 (36.65, 37.33)	0.070
SpO_2 (%)	96.95 (95.55, 98.38)	97.00 (95.58, 98.40)	96.70 (95.17, 97.95)	0.218
Scoring systems				
SOFA	5.00 (2.00, 8.00)	4.00 (2.00, 7.00)	10.50 (6.75, 15.00)	< 0.001
LODS	4.00 (2.00, 7.00)	4.00 (2.00, 6.00)	7.00 (5.00, 10.00)	< 0.001
SAPSII	30.00 (22.00, 42.00)	28.00 (21.00, 38.00)	44.50 (35.00, 60.00)	< 0.001
OASIS	32.00 (26.00, 39.00)	31.00 (26.00, 37.00)	39.50 (31.75, 46.00)	< 0.001
SIRS	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	3.00 (3.00, 4.00)	< 0.001
Laboratory tests				
Blood glucose (mg/dL)	120.00 (100.00, 159.00)	119.00 (100.00, 156.00)	130.00 (101.50, 173.50)	0.358
TG (mg/dL)	127.00 (85.00, 211.50)	122.00 (83.00, 198.00)	159.50 (101.75, 320.50)	0.004
Platelet (K/uL)	179.50 (113.25, 237.25)	184.00 (125.00, 243.33)	108.42 (63.63, 183.25)	< 0.001
Hematocrit (mg/dL)	35.73 (30.00, 40.46)	36.25 (31.15, 40.67)	29.75 (25.23, 37.08)	< 0.001
WBC (K/uL)	10.07 (7.24, 13.74)	9.90 (7.17, 13.60)	11.64 (9.08, 15.74)	0.006
Serum potassium (mEq/L)	4.04 (3.73, 4.40)	4.03 (3.73, 4.37)	4.19 (3.70, 4.65)	0.232
BUN (mg/dL)	16.00 (10.58, 27.50)	15.00 (10.25, 23.40)	26.29 (16.00, 43.38)	< 0.001
Chloride (mEq/L)	103.00 (98.92, 106.50)	103.00 (99.33, 106.50)	101.25 (95.16, 105.88)	0.014
Scr (mg/dL)	0.95 (0.70, 1.51)	0.90 (0.70, 1.28)	1.81 (0.98, 2.83)	< 0.001
Serum sodium (mEq/L)	138.00 (135.00, 140.93)	138.00 (135.00, 141.00)	136.50 (130.79, 140.85)	0.017
TyG index	8.99 (8.52, 9.63)	8.96 (8.49, 9.51)	9.37 (8.70, 10.06)	0.007
Major comorbidities, n(%)				
Myocardial infarct	67 (12.48%)	62 (13.39%)	5 (6.76%)	0.109
Congestive heart failure	89 (16.57%)	79 (17.06%)	10 (13.51%)	0.446
Peripheral vascular disease	25 (4.66%)	21 (4.54%)	4 (5.41%)	0.742
Cerebrovascular disease	136 (25.33%)	117 (25.27%)	19 (25.68%)	0.941
Peptic ulcer disease	18 (3.35%)	14 (3.02%)	4 (5.41%)	0.291
Mild liver disease	213 (39.66%)	158 (34.13%)	55 (74.32%)	< 0.001
Rheumatic disease	7 (1.30%)	6 (1.30%)	1 (1.35%)	0.969
Chronic pulmonary disease	103 (19.18%)	89 (19.22%)	14 (18.92%)	0.951
Renal disease	48 (8.94%)	38 (8.21%)	10 (13.51%)	0.137
Paraplegia	67 (12.48%)	57 (12.31%)	10 (13.51%)	0.771
Diabetes	102 (18.99%)	92 (19.87%)	10 (13.51%)	0.196
Severe liver disease	103 (19.18%)	62 (13.39%)	41 (55.41%)	< 0.001
Metastatic solid tumor	10 (1.86%)	6 (1.30%)	4 (5.41%)	0.015
Malignant cancer	21 (3.91%)	16 (3.46%)	5 (6.76%)	0.174
Events				
Los ICU (days)	3.27 (1.75, 7.42)	2.97 (1.68, 6.76)	5.47 (2.83, 11.20)	< 0.001
Los hospital (days)	8.91 (4.46, 16.06)	9.21 (4.63, 16.65)	7.83 (3.99, 14.58)	0.089

Table 1 (continued)

TyG index triglyceride glucose index; *BMI* body mass index; *MBP* mean blood pressure; *SpO_2* pulse blood oxygen saturation; *SOFA* sequential organ failure assessment; *LODS* logistic organ dysfunction system; *SAPSII* simplified acute physiological score II; *OASIS* Oxford acute severity of illness; *SIRS* systemic inflammatory response syndrome; *WBC* white blood cell; *TG* triglyceride; *Scr* serum creatinine; *BUN* blood urea nitrogen; *LOS* length of stay; *ICU* intensive care unit

(< 8.5201, n = 134), Q2 (8.5201 ≤ TyG < 8.9863, n = 135), Q3 (8.9863 ≤ TyG < 9.6276, n = 134), and Q4 (≥ 9.6276, n = 134). The baseline characteristics of each group are shown in Table 2.

Overall, patients with higher TyG level were more likely to be male, had a history of faster heart rate and respiratory rate, higher values of blood glucose, triglyceride, BUN, SOFA, SAPSII, diabetes, and 28-day mortality. According to the TyG index quartiles, Kaplan–Meier survival analysis curves of the incidence of 28-day mortality among groups are shown in Fig. 2. The 28-day mortality rate among groups was statistically significant (log-rank $P = 0.044$). The cumulative 28-day mortality rate of the 74 patients was 7.46% in Q1 (n = 10), 13.33% in Q2 (n = 18), 14.93% in Q3 (n = 20), and 19.40% in Q4 (n = 26), respectively.

TyG index and 28-day mortality and 1-year mortality

Of the 537 patients, 74 (13.78%) and 79 (14.71%) died during the 28-day and 1-year follow-up, respectively. Univariate and multivariate Cox regression models were established to observe the effect size of the association between TyG index and 28-day and 1-year mortality.

Cox proportional risk analysis showed that when the TyG index was a continuous variable, higher TyG value in the unadjusted model was positively associated with 28-day mortality (HR, 1.260 [95%CI 1.033–1.537] $P = 0.022$). After TyG index was converted into a quartile variable, it was significantly associated with 28-day mortality in the unadjusted model, and it showed an upward trend with the increase of TyG index (Q2: HR, 1.818 [95%CI 0.839–3.939] $P = 0.129$; Q3: HR, 2.105 [95%CI 0.985–4.497] $P = 0.055$; Q4: HR, 2.754 [95%CI 1.328–5.711] $P = 0.006$; P for trend = 0.006) (Table 3). In Model 2, after adjusting for demographic variables (age; ethnicity; gender; BMI), the correlation between TyG and 28-day and 1-year mortality was strong significant, and the correlation remaining strong regardless of the adjustment for multiple confounders in Model 3. In adjusted Model 3, the same tendency was also shown with the increase of TyG index (Q2: HR, 1.447 [95%CI 0.638–3.282] $P = 0.376$; Q3: HR, 1.982 [95%CI 0.866–4.535] $P = 0.105$; Q4: HR, 3.477 [95%CI 1.514–7.985] $P = 0.003$; P for trend = 0.002) (Table 3). Considering TyG as a continuous variable, this association still exists (HR: 1.460; 95% CI, 1.121–1.903, $p = 0.005$). The observation was consistent in the relationship between TyG value and 1-year mortality (Table S1).

Subgroup analyses

The risk stratification values of TyG index on 28-day mortality and 1-year mortality were further evaluated by subgroups. Stratification factors included age, sex, race, BMI, liver disease, myocardial infarct, congestive heart failure, cerebrovascular disease, and so on (Table S2). In the following subgroups, TyG index was significantly associated with a higher risk of 28-day mortality: > 65 years old (HR: 2.197, 95% CI: 1.330–3.630), without diabetes (HR: 1.448, 95% CI: 1.173–1.788), myocardial infarct (HR: 1.883, 95% CI: 1.129–3.141), congestive heart failure (HR: 1.816, 95% CI: 1.028–3.208), and malignant tumors (HR: 4.439, 95% CI: 1.629–12.099) (all $P < 0.05$, Fig. 3). It is worth noting that the predictive value of TyG index for 28-day mortality in AUD patients was more significant in patients with BMI < 30 kg/m^2 [1.318 (0.960, 1.810) vs. 1.073 (0.817, 1.409)]. The same trend was seen for non-diabetic patients [1.448 (1.173, 1.788) vs. 0.679 (0.337, 1.366)]. Stratified analysis showed that the association of TyG levels was similar in most sub-populations (Fig. 4). Regardless of whether the outcome variable is 28-day or 1-year mortality, the effect size of patients with peripheral vascular disease, cerebrovascular disease, or malignant cancer were more than in patients without these diseases (p value for interaction < 0.05). Similar results were obtained in a stratified analysis of TyG index and 1-year mortality (Figs. S1, S2).

Discussion

Our study is the first to show that elevated levels of TyG are significantly associated with all-cause mortality in critically ill AUD patients. The main finding of the study was that TyG levels were positively associated with 28-day and 1-year mortality in critically ill AUD patients. This finding persisted after adjusting for possible confounding factors.

Insulin resistance (IR) is defined as a diminished response to insulin, and previous studies have shown that it is significantly associated with serious cardiovascular and cerebrovascular events [31, 32]. In critically ill patients, insulin sensitivity is reduced by up to 70% [33]. As we know, IR plays a key role in the development of diabetes mellitus (DM). As a product of FBG and TG, TyG index is a reliable and convenient indicator for assessing IR in high-risk populations. David et al. found that the TyG index was better at predicting DM (AUC: 0.75, 95% CI 0.70–0.81) than FBG (AUC: 0.66, 95% CI 0.60–0.72) and TG (AUC: 0.71, 95% CI 0.65–0.77) [34].

Table 2 Baseline characteristics of critically ill patients with alcohol use disorder grouped according to TyG index quartiles[a]

Variable	TyG index				*p*-value
	Q1 (n = 134)	Q2 (n = 135)	Q3 (n = 134)	Q4 (n = 134)	
Age (years)	55.32 (39.99, 65.52)	57.94 (49.64, 66.58)	54.54 (46.58, 63.57)	50.44 (43.96, 59.76)	< 0.001
Sex (Male), n (%)	84 (62.69%)	101 (74.81%)	105 (78.36%)	106 (79.10%)	0.007
BMI (kg/m2)	27.00 (22.75, 30.00)	27.00 (23.00, 32.00)	29.00 (26.00, 33.00)	30.00 (24.75, 35.00)	< 0.001
Ethnicity, n (%)					0.390
White	80 (59.70%)	77 (57.04%)	74 (55.22%)	86 (64.18%)	
Black	17 (12.69%)	16 (11.85%)	10 (7.46%)	12 (8.96%)	
Asian	0 (0.00%)	2 (1.48%)	1 (0.75%)	1 (0.75%)	
Hispanic	2 (1.49%)	1 (0.74%)	8 (5.97%)	6 (4.48%)	
Others	7 (5.22%)	6 (4.44%)	7 (5.22%)	4 (2.99%)	
Unkown	28 (20.90%)	33 (24.44%)	34 (25.37%)	25 (18.66%)	
Vital signs					
Heart rate (bmp)	89.00 (75.15, 99.86)	83.41 (74.46, 97.96)	90.65 (76.52, 100.00)	98.69 (85.73, 108.99)	< 0.001
MBP (mmHg)	84.86 (74.46, 95.19)	84.56 (76.52, 93.52)	84.31 (74.29, 92.77)	84.79 (74.96, 93.44)	0.985
Respiratory rate	18.52 (16.59, 20.40)	19.58 (17.32, 21.94)	19.93 (17.42, 23.12)	21.34 (17.99, 24.77)	< 0.001
Temperature	36.88 (36.65, 37.23)	36.95 (36.72, 37.28)	37.04 (36.71, 37.34)	37.08 (36.79, 37.63)	0.002
SpO_2 (%)	96.81 (95.60, 98.18)	97.04 (95.68, 98.56)	96.91 (95.48, 98.43)	96.94 (95.12, 98.20)	0.682
Scoring systems					
SOFA	3.00 (2.00, 7.00)	4.00 (2.00, 7.00)	5.00 (2.00, 9.00)	6.00 (3.00, 10.00)	0.001
LODS	3.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (3.00, 7.00)	5.00 (2.00, 8.00)	< 0.001
SAPSII	27.00 (20.00, 37.25)	30.00 (22.00, 40.00)	32.00 (23.00, 43.00)	33.50 (22.00, 44.50)	0.012
OASIS	30.00 (24.75, 36.00)	31.00 (26.00, 37.00)	34.00 (28.00, 40.00)	34.00 (27.75, 41.00)	0.003
SIRS	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	3.00 (2.00, 4.00)	0.002
Laboratory tests					
Blood glucose (mg/dL)	102.00 (87.75, 113.25)	118.00 (102.00, 144.00)	124.00 (104.75, 162.00)	170.50 (124.00, 232.75)	< 0.001
TG (mg/dL)	75.00 (61.00, 86.00)	106.00 (89.00, 131.00)	163.50 (125.75, 202.50)	358.00 (223.50, 807.00)	< 0.001
Platelet (K/uL)	181.75 (115.13, 249.50)	183.00 (139.75, 232.00)	182.50 (111.56, 238.13)	150.25 (100.38, 229.14)	0.141
Hematocrit (mg/dL)	36.37 (30.95, 40.65)	36.37 (32.00, 41.15)	35.50 (28.90, 40.74)	34.93 (29.21, 39.32)	0.174
WBC (K/uL)	9.50 (6.83, 13.21)	10.45 (7.55, 13.70)	9.89 (7.44, 13.78)	10.56 (7.19, 15.41)	0.526
Serum potassium (mEq/L)	3.96 (3.73, 4.27)	4.10 (3.77, 4.45)	4.01 (3.73, 4.40)	4.05 (3.62, 4.44)	0.407
BUN (mg/dL)	12.67 (9.37, 20.70)	15.50 (10.50, 27.00)	17.00 (11.67, 30.00)	17.50 (11.00, 35.40)	0.001
Chloride (mEq/L)	103.42 (98.55, 107.08)	104.00 (99.50, 107.00)	102.20 (99.00, 105.81)	102.42 (98.00, 105.69)	0.060
Scr (mg/dL)	0.80 (0.63, 1.05)	0.95 (0.70, 1.37)	1.00 (0.70, 1.54)	1.13 (0.76, 2.42)	< 0.001
Serum sodium (mEq/L)	137.67 (134.38, 141.00)	138.50 (136.00, 141.00)	138.50 (135.24, 141.00)	136.45 (132.94, 139.60)	< 0.001
TyG index	8.25 (8.05, 8.37)	8.78 (8.67, 8.89)	9.26 (9.13, 9.40)	10.39 (9.94, 10.96)	< 0.001
Major comorbidities, n (%)					
Myocardial infarct	15 (11.19%)	16 (11.85%)	22 (16.42%)	14 (10.45%)	0.447
Congestive heart failure	25 (18.66%)	29 (21.48%)	22 (16.42%)	13 (9.70%)	0.061
Peripheral vascular disease	5 (3.73%)	11 (8.15%)	4 (2.99%)	5 (3.73%)	0.167
Cerebrovascular disease	39 (29.10%)	41 (30.37%)	39 (29.10%)	17 (12.69%)	0.002
Peptic ulcer disease	2 (1.49%)	5 (3.70%)	5 (3.73%)	6 (4.48%)	0.559
Mild liver disease	44 (32.84%)	53 (39.26%)	50 (37.31%)	66 (49.25%)	0.044
Rheumatic disease	1 (0.75%)	3 (2.22%)	2 (1.49%)	1 (0.75%)	0.666
Chronic pulmonary disease	29 (21.64%)	26 (19.26%)	23 (17.16%)	25 (18.66%)	0.826
Renal disease	11 (8.21%)	14 (10.37%)	12 (8.96%)	11 (8.21%)	0.916
Paraplegia	19 (14.18%)	22 (16.30%)	19 (14.18%)	7 (5.22%)	0.030
Diabetes	7 (5.22%)	22 (16.30%)	30 (22.39%)	43 (32.09%)	< 0.001
Dementia	5 (3.73%)	1 (0.74%)	1 (0.75%)	1 (0.75%)	0.106
Severe liver disease	20 (14.93%)	20 (14.81%)	30 (22.39%)	33 (24.63%)	0.083

Table 2 (continued)

Variable	TyG index				*p*-value
	Q1 (n = 134)	Q2 (n = 135)	Q3 (n = 134)	Q4 (n = 134)	
Metastatic solid tumor	0 (0.00%)	2 (1.48%)	5 (3.73%)	3 (2.24%)	0.150
Malignant cancer	1 (0.75%)	6 (4.44%)	7 (5.22%)	7 (5.22%)	0.179
Events					
28-day mortality	10 (7.46%)	18 (13.33%)	20 (14.93%)	26 (19.40%)	0.041
Los ICU (days)	2.68 (1.40, 5.18)	3.94 (1.86, 7.53)	3.46 (1.74, 6.95)	3.81 (1.85, 10.94)	0.008
Los hospital (days)	7.13 (3.61, 14.67)	9.90 (5.46, 14.95)	9.60 (4.62, 16.13)	9.53 (4.49, 18.29)	0.121

TyG index: Q1 (< 8.5201), Q2 (8.5201 ≤ TyG < 8.9863), Q3 (8.9863 ≤ TyG < 9.6276), Q4 (≥ 9.6276)

TyG index triglyceride glucose index; *BMI* body mass index; *MBP* mean blood pressure; *SpO_2* pulse blood oxygen saturation; *SOFA* sequential organ failure assessment; *LODS* logistic organ dysfunction system; *SAPSII* simplified acute physiological score II; *OASIS* Oxford acute severity of illness; *SIRS* systemic inflammatory response syndrome; *WBC* white blood cell; *TG* triglyceride; *Scr* serum creatinine; *BUN* blood urea nitrogen; *LOS* length of stay; *ICU* intensive care unit

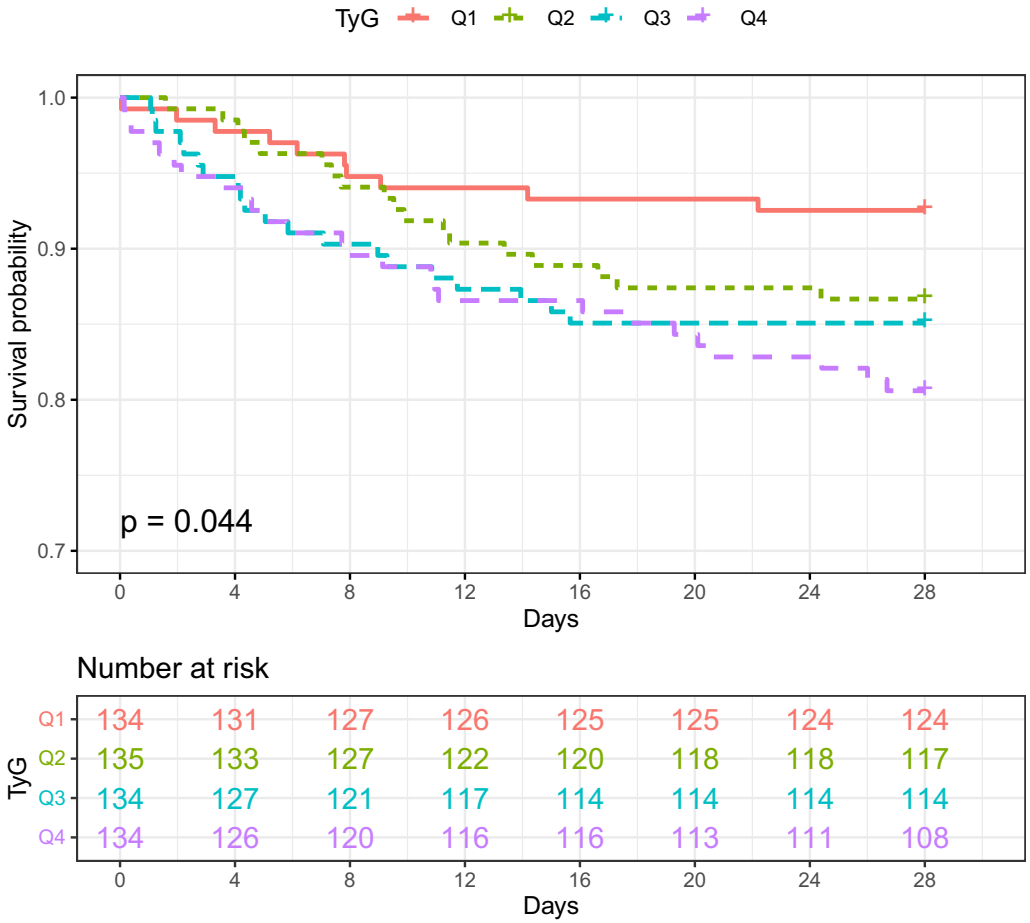


Fig. 2 Kaplan–Meier curves indicating the association between TyG quartiles and 28-day mortality

In addition to helping to assess the progression of people with diabetes, recent studies have shown that TyG index was associated with many diseases. The study by Jin et al. revealed that TyG index was closely associated with the development and poor prognosis of cardiovascular events (HR: 1.364, 95% CI 1.100–1.691, $P = 0.005$) [35]. A study of 5014 patients with a median follow-up of 10 years showed that higher levels of TyG index were significantly correlated with an increased risk of cardiovascular disease, with an HR value of 2.32

Table 3 Cox proportional hazard ratios (HR) for 28-day all-cause mortality

	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TyG	1.260 (1.033, 1.537)	0.022	1.309 (1.058, 1.619)	0.013	1.460 (1.121, 1.903)	0.005
$TyG^{Quartile}$						
Q1	Ref		Ref		Ref	
Q2	1.818 (0.839, 3.939)	0.129	1.614 (0.737, 3.533)	0.231	1.447 (0.638, 3.282)	0.376
Q3	2.105 (0.985, 4.497)	0.055	1.978 (0.919, 4.257)	0.081	1.982 (0.866, 4.535)	0.105
Q4	2.754 (1.328, 5.711)	0.006	2.752 (1.300, 5.825)	0.008	3.477 (1.514, 7.985)	0.003
P for trend	1.346 (1.091, 1.661)	0.006	1.368 (1.096, 1.707)	0.006	1.517 (1.168, 1.971)	0.002

TyG index ^{quartile}: Q1 (< 8.5201), Q2 (8.5201 ≤ TyG < 8.9863), Q3 (8.9863 ≤ TyG < 9.6276), Q4 (≥ 9.6276)

Model 1: unadjusted

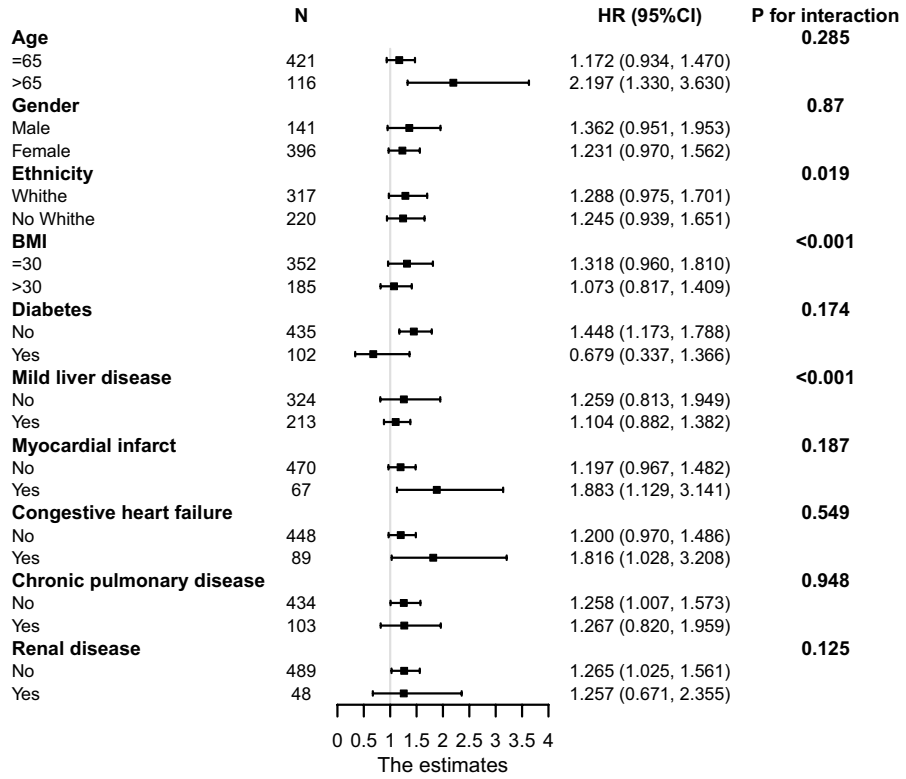
Model 2: adjusted for age, ethnicity, gender, BMI

Model 3: adjusted for age, gender, BMI, ethnicity, los in ICU, spo2, Co-morbidities (metastatic solid tumor, severe liver disease,, mild liver disease, diabetes, malignant cancer, congestive heart failure, renal disease, paraplegia, peptic ulcer disease, rheumatic disease, chronic pulmonary disease, cerebrovascular disease, peripheral vascular disease, myocardial infarct), hematocrit, platelets, wbc, creatinine, ref, reference

(95% CI: 1.65–3.26) [36]. Another study also found that patients with higher TyG index had a higher incidence of AMI (21.2% vs. 15.2%), and a higher rate of vascular recanalization (8.9% vs. 5.0%) [37]. Yang et al. found that TyG index was an independent risk factor for all-cause mortality and hospitalization in patients with heart failure (HR: 2.01, 95% CI 1.03–4.01) [38]. The results completed by Wang et al. showed that the higher the TyG index, the greater the likelihood of albuminuria (OR: 1.283, 95%CI, 1.138–1.446) [39]. A study encompassing a combined sample size of 20,972 participants revealed a positive correlation between an elevated TyG index and an increased likelihood of developing nephrolithiasis and recurrence. The incidence of kidney stones increased by 12% (OR: 1.12, 95% CI: 1.02–1.22; $p = 0.02$), and the recurrence rate increased by 26% (OR: 1.26, 95% CI: 1.08–1.46; $p < 0.01$) with each unit increase in TyG index [40]. Elevated TyG levels were associated with increased risk of death at 3 and 12 months in ischemic stroke patients younger than 65 years, but not in patients older than 65 years [41]. A recent study found an association between TyG index and all-cause mortality in ICU patients. The results showed that with the increase of the index, length of stay in ICU (3.68 days, 3.78 days, 4.16 days, 5.49 days), length of stay in hospital (7.68 days, 7.83 days, 8.82 days, 10.50 days), ICU mortality (5.6% vs. 7.8% vs. 10.2% vs. 10.6%), in-hospital mortality (7.5% vs. 11.3% vs. 13.5% vs. 14.0%), and long-term follow-up mortality (35.1% vs. 35.8% vs. 40.4% vs. 40.6%) showed a gradually increasing trend [30].

TyG index can be used as a biomarker to predict the potential mechanism of prognosis in AUD patients. AUD often causes insulin resistance and cardiovascular and cerebrovascular diseases. It is composed of glucose-related and lipid-related factors, reflecting IR situation in human body [42]. IR often occurs in AUD patients and leads to a series of problems. Firstly, IR can induce an imbalance in glucose metabolism, leading to hyperglycemia, which ultimately leads to inflammation and oxidative stress. Secondly, IR causes the body's lipid metabolism system to be disturbed, resulting in the increase of TG and the decrease of high-density lipoprotein [43]. In addition, IR elevates TG levels and promotes the increase of free fatty acids (FFA), which are transferred from adipose tissue to non-adipose tissue, ultimately leading to atherosclerosis [44]. Thirdly, IR can activate mitochondrial function and induce excessive activation of reactive oxidative stress (ROS) [45]. IR can also increase the production of glycosylated products and free products, resulting in the inactivation of nitric oxide (NO) [46], which can lead to impaired endothelial function. Furthermore, the effects of prostaglandin I2 (PGI2) and NO are also regulated by IR, affecting platelet function, thereby causing thrombosis and inflammation [47]. Nakagawa et al. found in animal models that IR led to a decrease in nitric oxide synthesis in glomerular endothelial cells, thus promoting the expression of renal vascular endothelial growth factor and significantly increasing macrophage infiltration, ultimately leading to renal dysfunction [48]. IR can also induce adipose tissue inflammation, thereby increasing the release of IL-6, TNF-α and other cytokines, and ultimately causing endothelial dysfunction [49].

Previous studies have explored the relationship between several useful indicators and adverse events in AUD patients. RDW was proved to be an effective prognostic indicator of 28-day mortality in critically ill AUD patients (HR: 1.964, 95%CI 1.429–2.698) [50]. A retrospective study revealed a linear relationship between



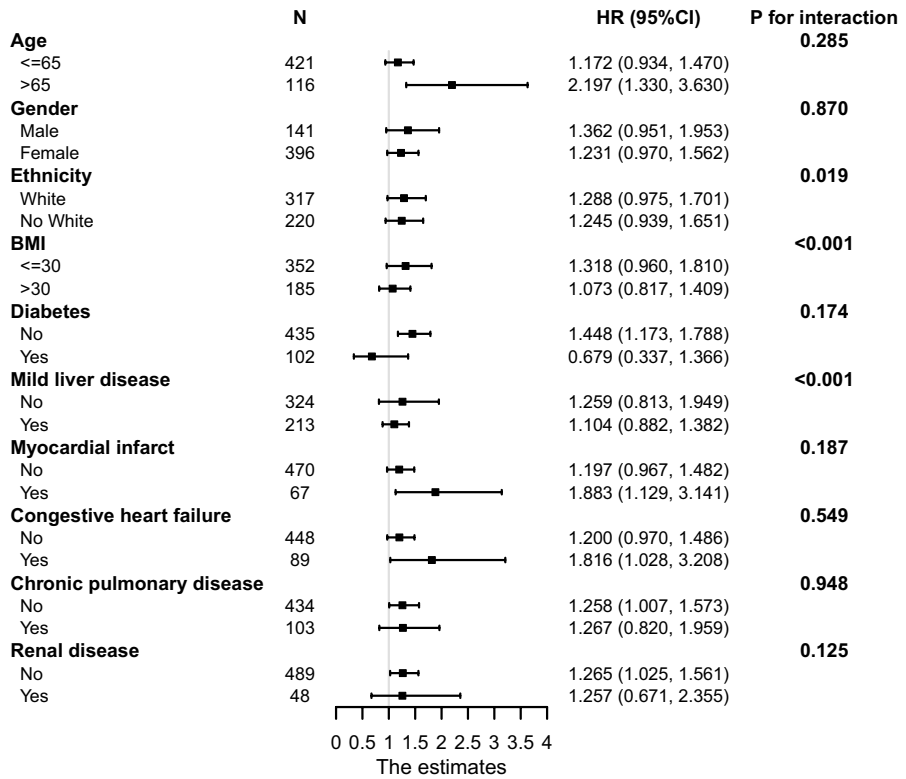


Fig. 3 Subgroup analysis of TyG value in 28-day mortality

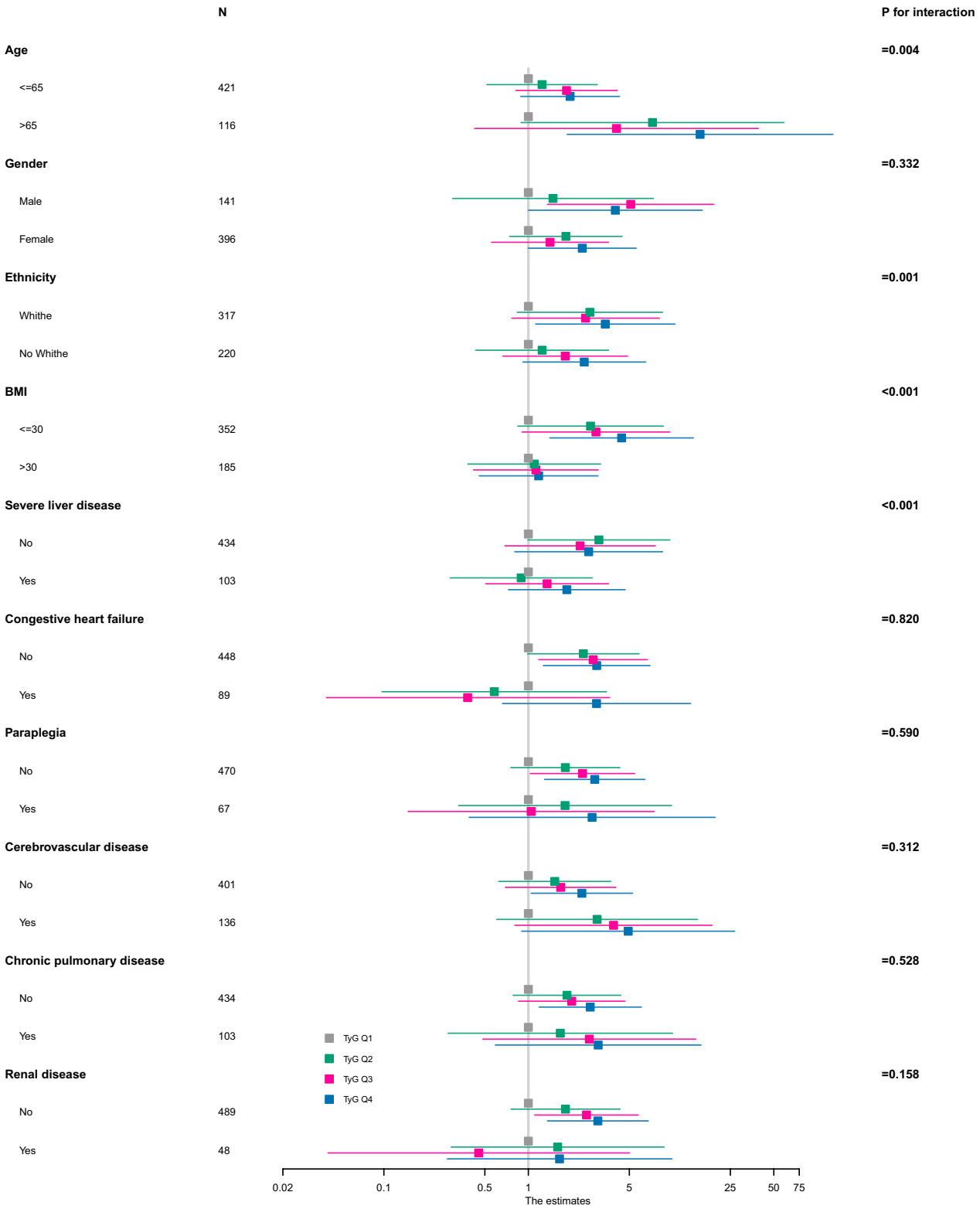


Fig. 4 Subgroup analysis of 28-day mortality according to TyG quartiles

AG and 28-day and 1-year all-cause mortality in critically ill AUD patients. Compared with AG < 12 mmol/L, the HR (95% CI) of 28-day mortality in patients with 12 ≤ AG < 14 mmol/L, 14 ≤ AG < 17 mmol/L, 17 ≤ AG < 20 mmol/L, and AG ≥ 20 mmol/L was 1.105 (0.906, 1.347), 1.171 (0.981, 1.398), 1.320 (1.108, 1.573), 1.487 (1.254, 1.763), respectively. The HR (95% CI) of 1-year all-cause mortality was 1.037 (0.898, 1.196), 1.091 (0.955, 1.246), 1.201 (1.052, 1.371), and 1.3093 (1.149, 1.492), respectively (all $p < 0.05$) [51]. Another study evaluated the association between anemia, fibrinogen and ferritin levels and all-cause mortality in alcohol-dependence patients, and anemia at admission was associated with all-cause mortality in alcohol-dependent patients (HR: 1.67, 95% CI 1.11–2.52) [52].

This study confirmed that TyG index could be used as a clinically reliable indicator and an independent risk predictor for evaluating all-cause mortality in AUD patients. However, there are still some limitations to our study. Firstly, this was a retrospective analysis derived from an observational study based on patients who were admitted to Beth Israel Deaconess Medical Center, and selection bias cannot be excluded, which could not definitively establish causation between TyG index and mortality outcomes. But we have carried out a rigorous and careful statistical analysis in order for the results to be reliable and valid. Secondly, all enrolled patients in the database were from the United States, and the results may not be completely applicable to ICUs in other countries, but the included patients were ethnically diverse. Therefore, it had a certain representative. Additionally, the sample size of this study was relatively small, and the validation of our data on a large cohort is needed. Thirdly, due to the limitation of the database, we did not include some potential confounders, such as dietary patterns, eating habits, energy intake conditions and physical activity, nor could we confirm that all glucose and triglyceride are the results of fasting. Despite adjustment for multivariate and subgroup analyses, residual confounders may inevitably affect prognosis. In addition to validation in a larger cohort, the results of this study require prospective cohort studies to verify our findings. Whether there is a relationship between the dynamic change of TyG index and clinical prognosis needs to be further studied.

Conclusions

Our findings demonstrated the utility of the TyG index in critically ill AUD patients, with a significant positive association between the TyG index and the risk of 28-day and 1-year all-cause mortality in these patients. Elevated TyG level was significantly associated with increased 28-day and 1-year mortality in AUD patients. The TyG index is a readily available risk stratification marker associated with clinical outcomes in critically ill AUD patients.

Abbreviations

TyG	Triglyceride-glucose
AUD	Alcohol use disorder
MIMIC-IV	Multi-parameter intelligent monitoring in intensive care IV
IR	Insulin resistance
FBG	Fasting blood glucose
TG	Triglyceride
MIT	Massachusetts Institute of Technology
SQL	Structured query language
IQR	Interquartile range
HR	Hazard ratios
95% CI	95% Confidence interval
BMI	Body mass index
MBP	Mean blood pressure
SpO_2	Pulse blood oxygen saturation
SOFA	Sequential organ failure assessment
LODS	Logistic organ dysfunction system
SAPSII	Simplified acute physiological score II
OASIS	Oxford acute severity of illness
SIRS	Systemic inflammatory response syndrome
WBC	White blood cell
Scr	Serum creatinine
BUN	Blood urea nitrogen
LOS	Length of stay
ICU	Intensive care unit

Supplementary Information

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Additional file1

Additional file2

Additional file3

Additional file4

Additional file5

Acknowledgements

Not applicable.

Author contributions

YHD and YP were responsible for the study concept. YYH and HXZ participated in data extraction and analysis. LMY and YHD drafted the manuscript. JYP made critical revision to important parts of the manuscript. All authors have read and approved the final manuscript.

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Data availability

The datasets supporting the findings of this study are available upon reasonable request by the corresponding author.

Declarations

Ethics approval and consent to participate

The use of the MIMIC-IV database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and the data in the database is publicly available, so the study did not require an ethical approval statement and informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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