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Associations of the triglyceride-glucose index with mortality mediated by blood urea nitrogen among critically ill patients: a cohort study

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Previous studies have shown that an elevated triglyceride-glucose (TyG) index is associated with all-cause mortality in patients. However, the potential mediating effect of blood urea nitrogen (BUN) within these associations has not been reported. The focus of this study was to investigate the potential mediating effect of BUN within these associations. This was a retrospective cohort study of patients in the eICU Collaborative Research Database (eICU-CRD) from 208 different ICUs in the United States between 2014 and 2015 that explored. The primary endpoint of the study was all-cause mortality within 28 days of ICU admission. In addition, the following formula was used to calculate the TyG index: Ln [fasting TG (mg/dL) × FBG (mg/dL)/2]. Cox regression model and subgroup analysis were performed to assess the associations of TyG index with 28-day mortality. The mediating effect of BUN was assessed to investigate the potential mechanism of the associations between TyG index and mortality using the mediation package in R 4.2.0. Of the 14,414 patients with a mean age of 64.1 years, 809 (5.61%) died within 28 days of ICU admission. The proportion of women was 57.9% and the mean TyG index was 8.97 ± 0.82. In the multivariable-adjusted model, the high tertile showed an even stronger association with 28-day ICU mortality than the low tertile, with a hazard ratio (HR) of 1.27 (95% CI: 1.05, 1.53; *P* = 0.014). Mediation analysis showed that BUN mediated 12.4% of the association between the TyG index and mortality. Our study showed that an elevated TyG index was associated with an increased risk of mortality in critically ill patients. The association appeared to be partially mediated by BUN.

Keywords Triglyceride glucose index, Insulin resistance, Prognosis, Mortality, Critically ill patients, Mediation, Blood urea nitrogen

The global population is ageing, resulting in an increasing number of elderly patients, aged 60 years and older being admitted to intensive care units (ICU)[1]. This trend is expected to continue, with a particular increase in the number of extremely elderly patients, aged 85 years and older, requiring ICU care[2]. As the population ages, the number of people aged 80 years and over is increasing rapidly, impacting on the demand for critical care services[3]. Understanding the outcomes of patients admitted to the ICU and the factors influencing these outcomes is crucial due to the increasing demand from the ageing population[4].

The triglyceride-glucose (TyG) index has emerged as a reliable biomarker for assessing insulin resistance (IR), which is a critical factor in the development of several metabolic disorders and cardiovascular diseases[5–9].

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This index is calculated using the formula that incorporates both fasting triglyceride levels and fasting glucose levels, providing a simple yet effective means of assessing an individual's metabolic health[6–10]. In recent years, the TyG index has emerged as a novel and cost-effective marker of insulin resistance and has attracted considerable attention in the field of cardiovascular disease research.

A substantial body of evidence from numerous studies has demonstrated a close association between the TyG index and traditional risk factors for all-cause mortality, including obesity, hypertension, and dyslipidemia[6–9,11]. A number of studies have demonstrated that an elevated TyG index is associated with all-cause mortality in a variety of patient populations, including those with acute kidney injury[12], paediatrics[10], and acute pancreatitis[13]. Furthermore, insulin resistance is associated with chronic low-grade inflammation, oxidative stress, and impaired endothelial function, all of which can accelerate the progression of diseases[14]. Therefore, elevated TyG index values have been linked to an increased risk of mortality, highlighting its potential utility in clinical settings for risk stratification and management of patients at high risk for cardiovascular diseases and other related health issues.

The TyG index has been demonstrated to be associated with not only insulin resistance but also linked to an increased risk of mortality in critically ill patients. This association may be mediated through factors such as blood urea nitrogen (BUN)[12]. BUN serves as a reliable indicator of kidney function, and its levels are closely associated with the prognosis of critically ill patients. This association is significant as the TyG index reflects the equilibrium between glucose and lipid metabolism, which is essential for the supply of energy and materials to the body. A lower TyG index in critically ill patients may be indicative of inadequate energy and material resources, which could result in poor nutrition and an elevated mortality risk[12].

The association between the TyG index and BUN and its role in the prognosis of critically ill patients is a complex and multi-factorial process that requires further investigation to clarify its specific mechanisms and clinical utility.

However, no prior study has examined the potential mediating role of BUN within the TyG index in relation to the risk of mortality in critically ill patients. To the best of our knowledge, although the relationship between the TyG index and mortality has been a topic of concern, the mediating effect of BUN remains unclear. This prompted us to conduct the present study.

We hypothesised that the potential mediating effect of BUN within the TyG index would be associated with the risk of 28-day mortality after intensive care unit (ICU) admission in critically ill patients. In this retrospective multicentre cohort study, we used the eICU Collaborative Research Database (eICU-CRD) from the Philips Healthcare eICU programme was used, comprising data from 208 different ICUs in the United States. The objective was to examine the potential mediating effect of BUN within the TyG index, which has been demonstrated to significantly increase the risk of death and is a high priority in critically ill patients.

Methods

Data source and ethical statement

Our study was designed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines[15]. The eICU Collaborative Research Database is a multicenter intensive care unit (ICU) resource that includes data from over 200,000 patient admissions across 335 ICUs in 208 hospitals in the United States during the years 2014 and 2015[16]. To access this database, researchers must pass an examination and obtain certification in line with the data use agreement set by the PhysioNet Review Board. It is released under the Safe Harbor provision of HIPAA, ensuring compliance with privacy standards. Access approval requires completing the Collaborative Institutional Training Initiative (CITI) program specific to data-only research. Because the study is retrospective and involves no direct patient interaction, it is exempt from the Massachusetts Institute of Technology's Institutional Review Board (IRB) approval (Record ID: 40859994), as it adheres to Privacert's certified security scheme for minimizing re-identification risk. Informed consent is similarly waived for these reasons. The study aligns with the Declaration of Helsinki and follows all relevant ethical guidelines and regulations. The eICU-CRD has been utilised in observational research studies[6–9,17–19].

Study population

Individuals falling within the following categories were excluded from participation: (1) patients who remained in the ICU for a period of less than 24 h, (2) those for whom no recorded triglyceride or glucose levels were available following admission, or in the event of a system error, (3) patients under the age of 18 years, and (4) those for whom BUN level data was unavailable following ICU admission. The study process is outlined in a flowchart, as shown in Fig. 1.

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Variables

Triglyceride glucose index (TyG index)

The TyG index was calculated using the formula ln [fasting triglycerides (mg/dl)×fasting blood glucose (mg/dl)/2][20]. The first measurements were taken within 24 h after admission to the ICU.

Outcomes

The outcome of the study was all-cause ICU mortality within 28 days after admission to the ICU. In the supplemental analysis. In the supplemental analysis, we also analysed the in-hospital 28-day mortality rate after admission to the ICU.

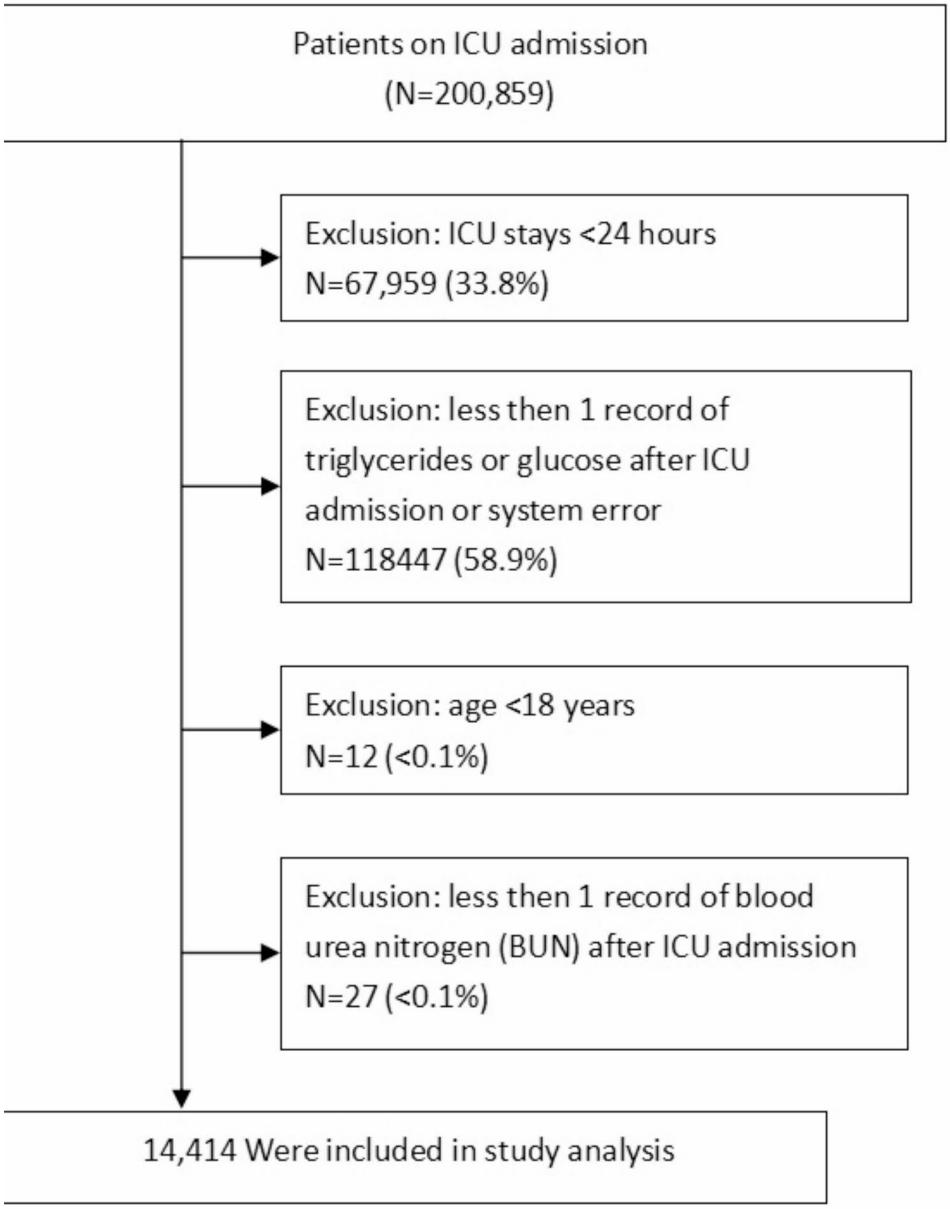

Fig. 1. Flow chart of study population. ICU, intensive care unit

Covariates

The data were extracted from the database using structured query language (SQL) with PostgreSQL (version 9.6). The code that supported the eICU documentation and website was publicly available (https://github.com/mit-lcp/eicu-code). The eICU database comprises patient demographics, bedside monitor physiological data, diagnostic information determined by ICD-9-CM codes, and laboratory results collected during routine medical care. Information from the initial 24 h following ICU admission was retrieved from the eICU-CRD. Physiological measurements such as body temperature, respiratory rate, and heart rate were sourced from the apacheApsVar table. Basic patient data, including age, sex, ethnicity, and body weight, were obtained from the patient and apachePatientResult tables. Laboratory parameters like sodium, BUN, creatinine, triglycerides, C-reactive protein (CRP) and glucose originated from the laboratory tables. The TyG index was derived using the formula: ln [fasting triglycerides (mg/dl)×fasting blood glucose (mg/dl)/2][20]. Diagnoses such as COPD, CHF, AMI, acute renal failure, and sepsis were retrieved from the diagnosis table. Admission severity was evaluated using the SOFA score and Acute Physiology Score III. Dialyses was retrieved from the apacheApsVar table. The SOFA score utilized lab data recorded within the first 24 h post-ICU entry. If measurements were recorded multiple times during this period, the one linked to the highest Acute Physiology Score III was utilized.

Statistical analysis

Categorical variables were assessed using Fisher's exact test or the chi-square test and are reported as frequencies (percentages). For continuous variables, we used the Wilcoxon rank-sum test, Student's t-test, or one-way ANOVA.

To assess the relationship between the TyG index and 28-day mortality risk, we utilized a Cox proportional hazards regression model. The findings are reported as hazard ratios (HR) along with their 95% confidence intervals (95% CI). We provided the results in two formats: initially as unadjusted regression estimates and subsequently as estimates adjusted for various covariates. These confounding variables were chosen based on their known associations with the outcome or if they altered the effect estimates by more than 10%[21]. After considering their clinical relevance, we adjusted for covariates including age, sex, ethnicity, weight, heart rate, COPD, CHF, AMI, diabetes mellitus, sodium levels, use of mechanical ventilation, CRP, acute renal failure, dialyses, and SOFA score. Additionally, in exploring the link between the TyG index and mortality, we considered serum creatinine and BUN as part of our adjustments.

To determine whether the effect of the TyG index on the outcome variable (mortality) was mediated by the mediator variable (BUN), a mediation analysis was conducted. Mediation analyses could quantify the total effect (association between TyG index and mortality), natural direct effect (total effect without the influence of BUN), and natural indirect effect (effect of TyG index on mortality attributed to BUN). To measure the adjusted mediation effect, the covariates age, sex, ethnicity, weight, heart rate, COPD, CHF, AMI, diabetes mellitus, sodium, mechanical ventilation use, CRP, acute renal failure, dialyses, and SOFA score were adjusted for in the mediation analysis through three different models.

To assess the robustness of our findings, we carried out sensitivity analyses, starting with several subgroup analyses. For any continuous variables missing over 1% of their values, dummy variables were created to denote these missing entries. We set the two-sided alpha level at 0.05 for statistical significance. All analyses were conducted using EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R version 4.2.0 (http://www.r-project.org).

Results

Baseline characteristics

A total of 14,414 patients who were critically ill were subjected to analysis. The median age of the cohort was 65 years (interquartile range 54–76 years). Of the total number of patients, 8,348 (57.92%) were female. Table 1 presents a comparison of the patient demographics, vital signs, laboratory results, and severity of illness across the tertiles (Tertile 1: <8.58, Tertile 2: 8.58–9.19, Tertile 3: ≥9.19) of the TyG index. A significant increase in age was observed with rising TyG index levels ($P<0.001$), with Tertile 1 averaging 64.04 ± 15.40 years, Tertile 2 at 66.94 ± 15.96 years, and Tertile 3 at 65.05 ± 14.81 years. There were no notable differences in sex distribution among the tertiles ($P=0.264$), with males constituting 42.08% of the total sample. In laboratory parameters, a significant difference in weight was noted, with Tertile 1 at 86.04 ± 25.96 kg, Tertile 2 at 80.19 ± 24.00 kg, and Tertile 3 at 91.92 ± 26.56 kg ($P<0.001$). Other biochemical indicators such as blood urea nitrogen and triglycerides also displayed significant differences among the groups. Regarding the severity of illness, APACHE IV scores significantly increased with the TyG index ($P<0.001$). Comorbidities such as congestive heart failure, acute renal failure and diabetes were notably higher in the high TyG index group, particularly diabetes, which accounted for 17.40% in Tertile 3 ($P<0.001$). Additionally, the rate of mechanical ventilation usage was significantly elevated in the high TyG group ($P<0.001$).

Data are expressed as the mean ± SD, median (interquartile range), or percentage; TyG triglyceride-glucose; COPD Chronic Obstructive Pulmonary Disease; CHF Chronic Heart Failure; AMI Acute Myocardial Infarction; CRP C-reactive protein; SOFA Sequential Organ Failure Assessment. Among the 14,414 patients, the amount of missing values for the covariates were 349 (2.4%) for admission weight, 1276 (8.9%) for temperature, 775 (5.4%) for respiratory rate, 700 (4.9%) for heart rate, 16 (0.1%) for creatinine, 14,094 (97.7%) for CRP, 696 (4.8%) for dialyses, 696 (4.8%) for mechanical ventilation use, 1 for SOFA score, 1862 (12.9%) for Apache IV score, and 1862 (12.9%) for Acute Physiology Score III.

ICU 28-Day Mortality

The 28-day ICU mortality rate was 809/13,605 = 5.61% (95% CI; 5.55–6.34) in our cohort. Furthermore, the 28-day mortality rate exhibited a notable variation across TyG index tertiles, with a rate of 3.9% observed in Tertile 1 and 7.2% in Tertile 3 ($P<0.001$).

The association between the TyG index and 28-day mortality

Table 2 presents the association between the TyG index and ICU 28-day mortality in critically ill patients. In the non-adjusted model, the HR for the TyG index was 1.11 (95% CI: 1.02, 1.20; $P=0.013$). After adjusting for gender, age, and ethnicity (Adjust I), the HR increased to 1.18 (95% CI: 1.09, 1.29; $P<0.001$). However, in the fully adjusted model (Adjust II), which included additional covariates such as weight, mechanical ventilation use, heart rate, and various comorbidities, the association was attenuated (HR = 1.04, 95% CI: 0.96, 1.14; $P=0.339$).

When stratified by TyG index tertiles, the middle tertile (Tertile 2) demonstrated a significantly higher mortality risk compared to the low tertile (Tertile 1), with HRs of 1.27 (95% CI: 1.06, 1.53; $P=0.014$) in the non-adjusted model, 1.32 (95% CI: 1.09, 1.59; $P=0.003$) in Adjust I, and 1.21 (95% CI: 1.00, 1.46; $P=0.049$) in Adjust II. The high tertile (Tertile 3) showed an even greater association with ICU 28-day mortality, with HRs of 1.42 (95% CI: 1.19, 1.70; $P<0.001$) in the non-adjusted model, 1.58 (95% CI: 1.32, 1.90; $P<0.001$) in Adjust I, and 1.27 (95% CI: 1.05, 1.53; $P=0.014$) in Adjust II. The P for trend was significant across all models, indicating a trend between higher TyG index tertiles and increased mortality risk (P-values < 0.05). These findings suggest that,

Parameters	Total	TyG index			*P* value
		Tertile 1 <8.58 *n* = 4804	Tertile 2 8.58–9.19 *n* = 4805	Tertile 3 ≥ 9.19 *n* = 4805	
Demographics					
Age (yr)	64.04 ± 15.40	66.94 ± 15.96	65.05 ± 14.81	60.12 ± 14.59	< 0.001
Sex					
Male	6066 (42.08)	2050 (42.67)	2039 (42.43)	1977 (41.14)	0.264
Female	8348 (57.92)	2754 (57.33)	2766 (57.57)	2828 (58.86)	
Ethnicity, n (%)					
Caucasian	10,573 (73.35)	3461 (72.04)	3574 (74.38)	3538 (73.63)	< 0.001
African American	1931 (13.40)	754 (15.70)	614 (12.78)	563 (11.72)	
Hispanic	872 (6.05)	267 (5.56)	267 (5.56)	338 (7.03)	
Asian	575 (3.99)	173 (3.60)	199 (4.14)	203 (4.22)	
Native American	78 (0.54)	31 (0.65)	18 (0.37)	29 (0.60)	
Other/Unknown	385 (2.67)	118 (2.46)	133 (2.77)	134 (2.79)	
Weight (kg)	86.04 ± 25.96	80.19 ± 24.00	85.97 ± 25.90	91.92 ± 26.56	< 0.001
Vital signs					
Temperature (°C)	36.41 ± 0.99	36.41 ± 0.94	36.42 ± 0.86	36.40 ± 1.14	0.544
Respiratory rate (bpm)	26.03 ± 15.27	25.87 ± 15.04	25.56 ± 15.28	26.66 ± 15.48	0.002
Heart rate (/min)	97.28 ± 32.35	93.60 ± 32.65	95.94 ± 32.31	102.30 ± 31.45	< 0.001
Laboratory data					
Glucose (mg/dl)	151.91 ± 87.54	112.1 ± 28.9	135.5 ± 42.2	208.0 ± 123.9	< 0.001
Blood urea nitrogen (mg/dL)	23.63 ± 18.80	17.0(12.0–25.0)	17.0(12.0–26.0)	19.0(13.0–31.0)	< 0.001
Creatinine (mg/dL)	0.98 (0.76–1.40)	0.91 (0.71–1.28)	0.98 (0.76–1.35)	1.05 (0.80–1.59)	< 0.001
Triglycerides (mg/dL)	107(75–160)	68(54–83)	112(91–134)	189(140–262)	< 0.001
Sodium (mmol/L)	138.27 ± 4.76	138.29 ± 4.81	138.50 ± 4.48	138.01 ± 4.96	< 0.001
CRP (mg/dL)	6.62 (1.50–20.30)	4.48 (1.05–13.80)	8.11 (2.70–21.23)	6.30 (1.64–22.92)	0.099
Severity of illness					
SOFA score	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	< 0.001
Acute Physiology Score III	44.30 ± 24.26	40.90 ± 21.56	42.61 ± 23.00	49.44 ± 27.07	< 0.001
Apache IV score	56.14 ± 25.66	54.11 ± 23.25	54.89 ± 24.54	59.44 ± 28.60	< 0.001
Comorbidities, n (%)					
COPD	823 (5.71)	288 (6.00)	286 (5.95)	249 (5.18)	0.154
CHF	1290 (8.95)	477 (9.93)	431 (8.97)	382 (7.95)	0.003
AMI	2575 (17.86)	729 (15.17)	905 (18.83)	941 (19.58)	< 0.001
Diabetes mellitus	1607 (11.15)	324 (6.74)	447 (9.30)	836 (17.40)	< 0.001
Acute renal failure	1553 (10.77)	404 (8.41)	458 (9.53)	691 (14.38)	< 0.001
Dialyses, n (%)					
No	13,358 (97.38)	4463 (97.66)	4463 (97.32)	4432 (97.15)	0.301
Yes	360 (2.62)	107 (2.34)	123 (2.68)	130 (2.85)	
Mechanical ventilation use, n (%)					
No	9878 (72.01)	3546 (77.5)	3312 (72.2)	3020 (66.2)	< 0.001
Yes	3840 (27.99)	1024 (22.5)	1274 (27.8)	1542 (33.8)	
ICU 28-day Mortality, n (%)					
No	13,605 (94.39)	4614 (96.1)	4534 (94.4)	4457 (92.8)	< 0.001
Yes	809 (5.61)	190 (3.9)	271 (5.6)	348 (7.2)	
Hospital 28-day Mortality, n (%)					
No	13,062 (90.62)	4447 (92.5)	4349 (90.5)	4266 (88.8)	< 0.001
Yes	1352 (9.38)	357 (7.5)	456 (9.5)	539 (11.2)	

Table 1. Baseline characteristics and ICU 28-day mortality according to the tertiles of the TyG index in critically ill patients (*n* = 14,414).

Exposure	HR (95%CI) *P* value		
	Non-adjusted	Adjust I	Adjust II
TyG index	1.11 (1.02, 1.20) 0.013	1.18 (1.09, 1.29) < 0.001	1.04 (0.96, 1.14) 0.339
TyG index tertile			
Low (Tertile 1)	1.0	1.0	1.0
Middle (Tertile 2)	1.27 (1.06, 1.53) 0.010	1.32 (1.09, 1.59) 0.003	1.21 (1.00, 1.46) 0.049
High (Tertile 3)	1.42 (1.19, 1.70) < 0.001	1.58 (1.32, 1.90) < 0.001	1.27 (1.05, 1.53) 0.014
P for trend	0.001	< 0.001	0.017

Table 2. The association between TyG index and ICU 28-day mortality in critically ill patients ($n = 14,414$). Non-adjusted model adjust for: None. Adjust I model adjust for: gender, age (years), and ethnicity. Adjust II model adjust for: gender, age (years), ethnicity, weight, mechanical ventilation use, heart rate, COPD, CHF, AMI, DM, BUN (mg/dL), serum creatinine (mg/dL), sodium(mmol/L), CRP, acute renal failure, dialyses, and SOFA score. TyG triglyceride-glucose; BUN, Blood urea nitrogen; COPD Chronic Obstructive Pulmonary Disease; CHF Chronic Heart Failure; CRP C-reactive protein; AMI Acute Myocardial Infarction; DM Diabetes mellitus; SOFA Sequential Organ Failure Assessment. CI, confidence interval; HR, hazard ratio; ICU intensive care unit.

Exposure	HR (95%CI) *P* value		
	Non-adjusted	Adjust I	Adjust II
BUN (per 10 mg/dL)	1.09 (1.06, 1.11) < 0.001	1.08 (1.05, 1.10) < 0.001	1.02 (0.99, 1.05) 0.284
BUN tertile			
Low (Tertile 1)	1.0	1.0	1.0
Middle (Tertile 2)	1.44 (1.15, 1.80) 0.001	1.34 (1.07, 1.68) 0.010	1.20 (0.96, 1.51) 0.111
High (Tertile 3)	2.28 (1.87, 2.78) < 0.001	2.06 (1.68, 2.53) < 0.001	1.50 (1.20, 1.87) 0.004
P for trend	< 0.001	< 0.001	< 0.001

Table 3. The association between BUN levels and ICU 28-day mortality in critically ill patients ($n = 14,414$). Non-adjusted model adjust for: None. Adjust I model adjust for: gender, age (years), and ethnicity. Adjust II model adjust for: gender, age (years), ethnicity, weight, mechanical ventilation use, heart rate, COPD, CHF, AMI, DM, sodium(mmol/L), CRP, acute renal failure, dialyses, and SOFA score. TyG triglyceride-glucose; BUN, Blood urea nitrogen; COPD Chronic Obstructive Pulmonary Disease; CHF Chronic Heart Failure; AMI Acute Myocardial Infarction; DM Diabetes mellitus; SOFA Sequential Organ Failure Assessment. CI, confidence interval; HR, hazard ratio; ICU intensive care unit.

while the TyG index is associated with an increased risk of ICU 28-day mortality, the association is particularly pronounced in the unadjusted and partially adjusted models, but remains significant even after comprehensive adjustment for potential confounders.

The association between BUN levels and 28-day mortality

Table 3 outlines the association between BUN levels and ICU 28-day mortality in critically ill patients. In the non-adjusted model, each 10 mg/dL increase in BUN was linked to a significant increase in mortality risk, with a HR of 1.09 (95% CI: 1.06, 1.11; $P < 0.001$).

When examining BUN by tertiles, the middle tertile (Tertile 2) had an adjusted HR of 1.34 ($P = 0.010$) compared to the low tertile, while the high tertile (Tertile 3) showed a significant HR of 2.06 ($P < 0.001$) in the Adjust I model. In Adjust II, the high tertile's HR was 1.50 ($P = 0.001$), confirming its association with increased mortality risk. The trend across all models was significant ($P < 0.001$), indicating that higher BUN levels are linked to greater mortality risk in ICU settings, although this association was influenced by additional clinical factors in the fully adjusted analysis.

Subgroup analysis

To evaluate the relationships of TyG index with 28-day mortality, subgroup analyses were performed. The findings remained consistent with the primary results in subgroup analyses. The relationship between the TyG index and 28-day mortality was investigated in greater depth in different subgroups. The association was consistent across the majority of subpopulations (Fig. 2).

Mediating role of inflammationrelated indicators

As shown in Fig. 3, mediation analysis indicated that the TyG index had a significant direct effect on 28-day mortality ($P = 0.03$), and BUN partly mediated the indirect effect of the TyG index on 28-day mortalityD ($P = 0.008$). Therefore, approximately 12.4% of the TyG index effect on 28-day mortality was mediated through

Strarified variable		No. (%) With Outcome	HR(95%CI)	*P* value
Gender	Male	336 (41.5%)	1.30 (1.16, 1.47)	<0.001
	Female	473 (58.5%)	1.20 (1.08, 1.33)	0.0007
Age (years)	<64	334 (41.3%)	1.15 (1.03, 1.29)	0.0122
	≥65	475 (58.7%)	1.54 (1.36, 1.74)	<0.001
Ethnicity	Caucasian	588 (72.7%)	1.30 (1.19, 1.43)	<0.001
	Other	221 (27.3%)	1.11 (0.96, 1.29)	0.1699
Admission weight (kg)	<81.76	420 (52.6%)	1.33 (1.19, 1.50)	<0.001
	≥81.8	379 (47.4%)	1.19 (1.07, 1.34)	0.002
Mechanical ventilation use	No	247 (31.3%)	1.14 (0.99, 1.31)	0.071
	Yes	542 (68.7%)	1.18 (1.05, 1.32)	0.004
Temperature	<36.4	450 (59.1%)	1.31 (1.17, 1.46)	<0.001
	≥36.5	312 (40.9%)	1.18 (1.04, 1.34)	0.0099
Respiratory rate (bpm)	<28	291 (37.1%)	1.31 (1.14, 1.50)	0.0001
	≥28	493 (62.9%)	1.19 (1.08, 1.31)	0.0006
Heart rate (/min)	<101	244 (30.9%)	1.43 (1.22, 1.68)	<0.001
	≥102	545 (69.1%)	1.11 (1.01, 1.22)	0.0258
Acute Physiology Score III	<37	72 (9.8%)	1.06 (0.78, 1.44)	0.6973
	≥38	666 (90.2%)	1.15 (1.05, 1.25)	0.0027
Apache IV score	<50	66 (8.9%)	1.19 (0.90, 1.56)	0.225
	≥51	672 (91.1%)	1.25 (1.14, 1.37)	<0.001
SOFA score	<2	90 (11.1%)	1.12 (0.88, 1.42)	0.3641
	≥2	719 (88.9%)	1.24 (1.14, 1.36)	<0.001
COPD	No	763 (94.3%)	1.25 (1.16, 1.36)	<0.001
	Yes	46 (5.7%)	0.98 (0.64, 1.48)	0.9127
CHF	No	719 (88.9%)	1.23 (1.13, 1.33)	<0.001
	Yes	90 (11.1%)	1.51 (1.14, 2.00)	0.0038
AMI	No	703 (86.9%)	1.22 (1.12, 1.33)	<0.001
	Yes	106 (13.1%)	1.47 (1.15, 1.87)	0.002
DM	No	723 (89.4%)	1.29 (1.19, 1.40)	<0.001
	Yes	86 (10.6%)	1.02 (0.81, 1.29)	0.8377
Blood urea nitrogen (mg/dL)	<17.8	220 (27.2%)	1.17 (1.01, 1.37)	0.0405
	≥18	589 (72.8%)	1.22 (1.11, 1.34)	<0.001
Serum creatinine (mg/dL)	<0.97	241 (29.9%)	1.14 (0.98, 1.32)	0.0928
	≥0.98	566 (70.1%)	1.22 (1.11, 1.35)	<0.001
sodium(mmol/L)	<137	327 (40.4%)	1.08 (0.96, 1.21)	0.2302
	≥138	482 (59.6%)	1.43 (1.28, 1.59)	<0.001

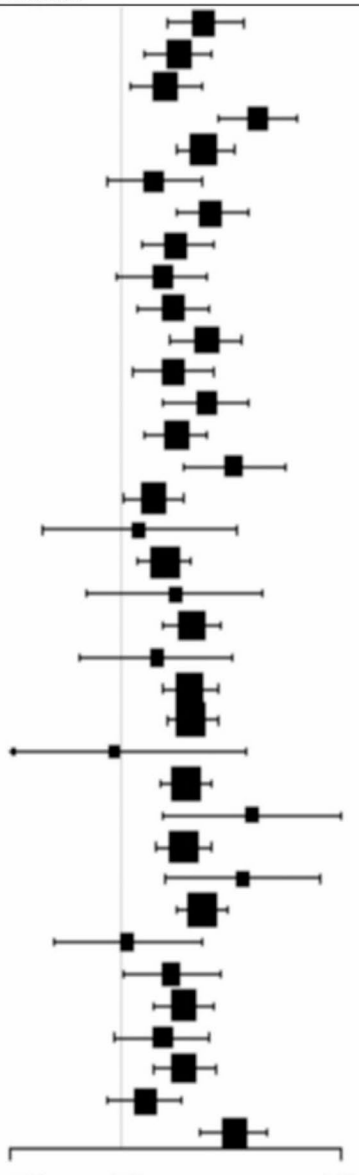

Fig. 2. Stratified analyses by potential modifiers of the association between TyG index and 28-day mortality in elderly critically ill patients. TyG triglyceride-glucose, HR hazard ratio, CI confidence interval. COPD Chronic Obstructive Pulmonary Disease; CHF Chronic Heart Failure; AMI Acute Myocardial Infarction; SOFA Sequential Organ Failure Assessment.

BUN levels. The above results were obtained after adjusting for factors such as gender, age, ethnicity, weight, mechanical ventilation use, heart rate, COPD, CHF, AMI, DM, sodium(mmol/L), CRP, acute renal failure, dialyses, and SOFA score. The results were consistent with the above results when no confounding factors or only some demographic variables were adjusted.

TyG triglyceride-glucose; BUN Blood urea nitrogen; CI confidence interval. Adjust for: gender, age (years), ethnicity, weight, mechanical ventilation use, heart rate, COPD, CHF, AMI, DM, sodium(mmol/L), CRP, acute renal failure, dialyses, and SOFA score.

In the supplementary analysis, the in-hospital 28-day mortality rate was also evaluated, and the results were found to be generally consistent with those of the primary analysis (see Table S1). Approximately 8.16% of the TyG index effect on in-hospital 28-day mortality was mediated through BUN levels (see Table S1). In instances where a covariate value was absent, a dummy variable was employed to indicate this. The influence of missing data was similarly accounted for in the results (data not shown).

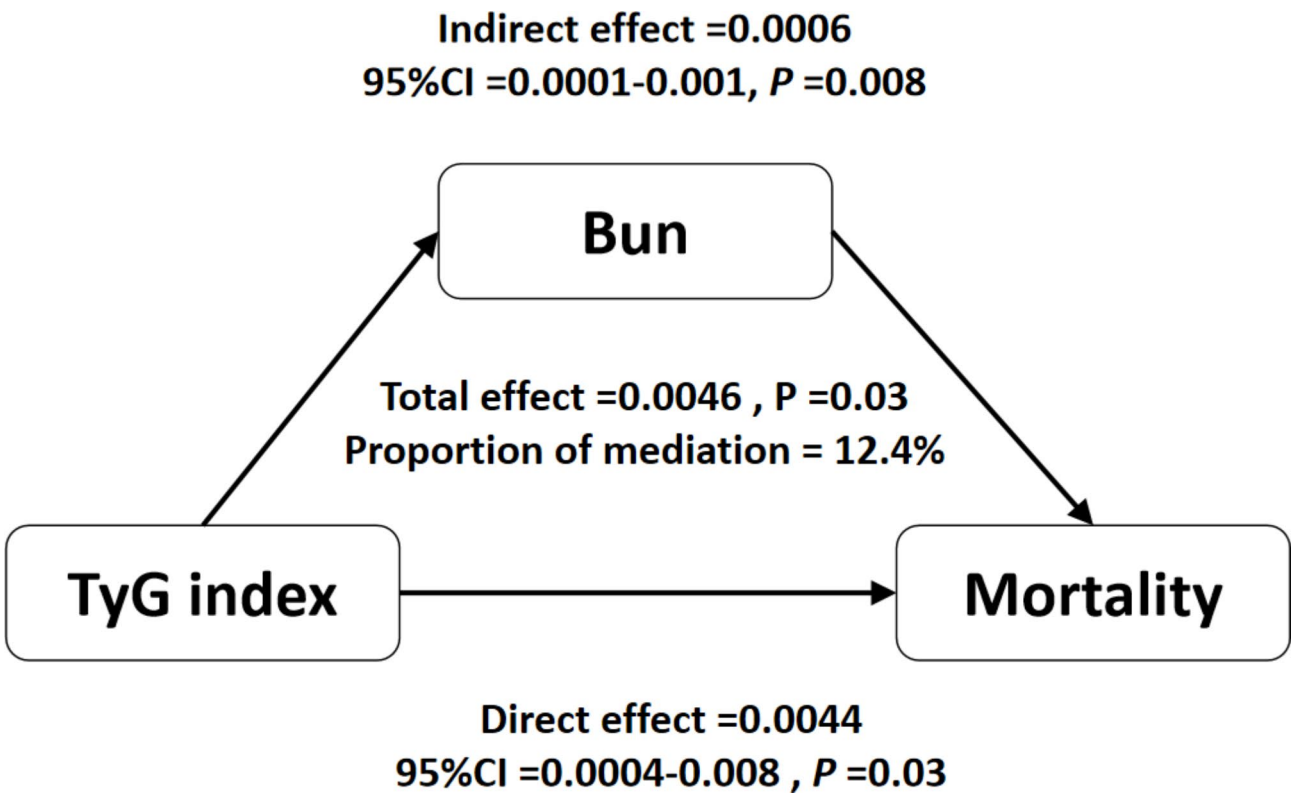

Fig. 3. Analysis of the mediation by BUN of the associations of TyG index with 28-day mortality.

Discussion

This large multicentre cohort study included 14,414 critically ill patients from the eICU-CRD database. The results of our study demonstrated that an elevated TyG index was associated with an increased risk of mortality in critically ill patients and the findings persisted significantly in the comprehensively adjusted model. After the positive correlations of BUN with mortality and TyG index were demonstrated, mediation analysis was performed and highlighted the significant roles of BUN in linking TyG index and 28-day mortality, proposing BUN as a potential underlying mechanism in these associations.

The results of our study demonstrated that an elevated TyG index was associated with an increased risk of mortality in critically ill patients. Furthermore, these findings remained significant even after comprehensive adjustments were made. Following the identification of a positive correlation between BUN and mortality, as well as between the TyG index and BUN, mediation analysis was conducted. This analysis revealed that BUN plays a crucial role in mediating the relationship between the TyG index and 28-day mortality. Consequently, BUN can be proposed as a potential underlying mechanism in these associations.

A number of recent studies have investigated the relationship between TyG index and the risk of mortality. In a recent study by Liu, D., et al., 2103 surgical and trauma ICU patients was investigated, revealing a significant correlation between elevated TyG index levels and increased 28-day mortality rates[11]. The research indicated that for every unit increase in the TyG index, there was a 19% heightened risk of mortality at 28 days. Notably, the association was pronounced in patients younger than 60 years, those with stroke or cardiovascular diseases, and non-diabetic individuals[11]. As an indicator of insulin resistance, the TyG index has been demonstrated to be significantly associated with the long-term prognosis of elderly patients with acute coronary syndrome. In a cohort study of 662 patients aged 80 and above with acute coronary syndrome (ACS), the TyG index was found to be associated with all-cause mortality and major adverse cardiac events[6]. Furthermore, another study demonstrated that the TyG index was significantly associated with the risk of first stroke in individuals with hypertension, with age identified as a significant effector modifier for this association[7]. The results of this study align with the hypothesis that elevated TyG index levels are associated with an increased risk of mortality. Our study identified an association between an elevated TyG index and an increased risk of mortality in critically ill patients.

In critically ill patients, the high mortality rate and poor prognosis have drawn significant attention. Multiple studies have demonstrated a positive correlation between elevated BUN levels and mortality rates in critically ill patients. For instance, a study on patients with acute myocardial infarction found that an admission BUN level greater than 8.95 mmol/L was significantly associated with a 30-day mortality rate, with BUN proving to be a better prognostic indicator than other renal function markers[22]. A multicenter retrospective study conducted in Zhenjiang, China, demonstrated that COVID-19 patients with higher BUN levels had a significantly increased 28-day mortality rate[23].

Elevated BUN levels have been consistently associated with increased mortality across various patient populations, including those with acute exacerbations of chronic obstructive pulmonary disease (AECOPD)[24]and trauma-related acute respiratory distress syndrome (ARDS)[25].

In a recent study primarily investigates the relationship between elevated BUN levels upon admission and in-hospital mortality among patients experiencing acute exacerbations of chronic obstructive pulmonary disease (AECOPD)[24]. The research involved a cohort of 13,431 consecutive inpatients diagnosed with AECOPD. The study found that non-survivors had significantly higher BUN levels compared to survivors, with an optimal cutoff identified at 7.30 mmol/L for predicting mortality. The conclusion drawn from this analysis is that a BUN level of ≥7.3 mmol/L serves as an independent risk factor for in-hospital mortality. These findings collectively emphasize the relationship between BUN and mortality risk in critically ill patients[24]. This is similar to our result showing that higher BUN levels are linked to greater mortality risk.

The results of our mediation analysis indicated that BUN mediated 13.9% of the association between the TyG index and mortality. The precise biological mechanisms that underpin the BUN-mediated relationship between the TyG index and an elevated risk of mortality in critically ill patients remain uncertain. A possible explanation for our findings was that elevated TyG index levels are indicative of underlying metabolic disturbances and systemic inflammation, which can significantly impact health outcomes[26,27]. The association between high levels of the TyG index and an increased risk of all-cause mortality is multifaceted and extends beyond causal effects alone. These disturbances often manifest as insulin resistance, a condition closely linked to various pathophysiological changes such as dyslipidemia, hypertension, and increased oxidative stress[26]. These alterations not only predispose individuals to cardiovascular diseases but also play a crucial role in contributing to all-cause mortality[28]. Moreover, the TyG index serves as a valuable marker capturing the intricate interplay between lipid metabolism and glucose homeostasis, both of which are pivotal in the context of metabolic syndrome and type 2 diabetes[29]. Studies have shown that the TyG index is strongly associated with cardiovascular risk factors and outcomes, emphasizing its significance in predicting adverse events in conditions like coronary artery disease and cerebrovascular disorders[28,30]. Additionally, the TyG index has been linked to conditions such as metabolic syndrome, type 2 diabetes, and even abnormal liver function, highlighting its broad utility in assessing overall metabolic health[29,31]. Our study did not examine the cause of death; however, we noted a slightly higher percentage of patients with a higher severity of illness score in those with a high TyG index. Whether conditions associated with an increased severity of illness score (infection and chronic inflammation) explain the increased risk of death in patients with a high TyG index deserves further investigation. Insulin resistance plays a crucial role in various metabolic disorders, significantly affecting kidney function and cardiovascular health. The TyG index, a recognized marker of insulin resistance, is intricately linked to kidney dysfunction and the onset of cardiovascular diseases. Elevated TyG index levels are associated with an inflammatory state and oxidative stress, which can negatively impact kidney function and contribute to poor outcomes in critically ill patients[32].

There are some strengths of our study, which are listed below (1). One strength of our study is the large sample size that allows such analysis (2). To the best of our knowledge, this is the first time to explore the contribution of BUN as a mediator factor to the relationship between the TyG index and mortality in critically ill patients (3). By using different statistical methods, we examined the internal relationship between TyG index, BUN, and mortality. This strengthened our understanding of their relationship (4). We conducted sensitivity analyses (target independent variable transformations, subgroup analyses) to assess the robustness of the findings.

Study limitations

The findings of this research must be considered in the context of certain limitations. A further limitation of observational studies is that they are susceptible to the influence of unmeasured confounding variables, which can affect the results obtained. As illustrated in Table 1, there was a notable discrepancy in age across the tertiles, with Tertile 3 exhibiting the youngest mean age (60.1 years). Individuals with elevated TyG indices frequently exhibited a greater prevalence of comorbidities, such as diabetes, and demonstrated more severe clinical manifestations. These discrepancies indicate the potential influence of unmeasured variables, such as income and insurance coverage, on the risk of mortality within a 28-day period. Despite the inclusion of a range of demographic and clinical data, it was not possible to estimate the impact of unmeasured factors on the hazard ratios. In order to account for potential confounding variables, we adjusted for a range of factors, including age, sex, ethnicity, weight, heart rate, COPD, CHF, AMI, diabetes, sodium levels, use of mechanical ventilation, and SOFA score. Additionally, serum creatinine and BUN were considered when linking the TyG index to mortality. Despite some data being missing, we employed modern techniques to handle these gaps and minimise bias. A potential limitation of this study is the absence of sepsis biomarkers, such as procalcitonin, which could influence the comprehensiveness of the findings. Sepsis has a significant impact on ICU mortality; however, procalcitonin was not collected in this database, which represents a limitation of this study. It would be beneficial for future studies to consider the inclusion of these biomarkers in order to gain a deeper understanding of their role in the relationship between the TyG index and mortality. Furthermore, although serum creatinine and BUN are significantly associated with mortality, it would be beneficial for future studies to also include the incidence of acute renal failure and dialyses. This would help to rule out acute renal failure as a potential cause of death. Notwithstanding the aforementioned adjustments, the results remained consistent.

Another limitation of the study is related to the reliance on ICD-9 coding for diagnoses, determined by the attending physician. This means that the accuracy and comprehensiveness of diagnoses could vary depending on the physician's judgment and experience. Additionally, we did not have access to detailed information about the specific causes of death for the patients involved in the study. This lack of detailed mortality data prevents a thorough understanding of the underlying reasons leading to patient deaths. Considering that the study focused on mortality occurring shortly after ICU admission, distinguishing between cardiovascular-related deaths and those from other causes was not prioritized. The relatively short timeframe of the mortality examination led to

the decision to treat all-cause mortality as a single category, without delving into the nuances of cardiovascular versus non-cardiovascular death. This approach, while simplifying the analysis, may overlook important distinctions in the types of mortality affecting the patient population.

Moreover, the absence of data regarding the implementation of stabilisation procedures during the initial phase may have exerted an influence on the levels of the TyG index and the probability of survival. It is important to note that the potential for bias resulting from the implementation of interventions may lead to an underestimation of the association between the TyG index and mortality.

It's important to note that the study participants were emergency department patients with varied medical issues, limiting the generalizability of the findings to other populations. This highlights the need for further research to better understand the mechanisms behind the observed associations and to evaluate the TyG index's applicability in different clinical settings. Future studies should explore whether this index is useful across a variety of healthcare environments, which could improve clinical decision-making and patient outcomes beyond the emergency department context.

Conclusions

This large multicentre retrospective cohort study, including 14,414 critically ill patients from the eICU-CRD database, demonstrated that revealed an elevated TyG index is associated with an increased risk of mortality in this patient population. Furthermore, this association appears to be partially mediated by BUN levels. The findings of this cohort study provides important insights into the mediating effect of BUN on the TyG index in critically ill patients, contributing to a deeper understanding of the underlying mechanisms at play.

Data availability

Data were fully available at https://eicu-crd.mit.edu/.

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Author contributions

XL.C. performed statistical analysis. JH. L. cleaned the data. JH. L., LM.W., and HL.X. conceived and designed the research. JH. L. and XL.C. drafted the manuscript. SF.S., C.Y., XL.C., JR.Y., YL.C., and HL.X.made critical revision of the manuscript for key intellectual content. JH. L., and LM.W. contributed equally to this work. All authors reviewed the manuscript.

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Declarations

Ethics approval and consent to participate

Data was extracted from the eICU Collaborative Research Database (eICU-CRD)[16] in accordance with the data usage agreement (our record ID: 40859994) by the PhysioNet review committee. The utilized database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. This was a retrospective analysis based on an anonymous database for researchers and did not require ethical approval from the local ethics committee.

Competing interests

The authors declare no competing interests.

Additional information

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