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Association between TyG index and long-term mortality of critically ill patients: a retrospective study based on the MIMIC Database

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ABSTRACT

Objective To evaluate the association of triglyceride–glucose (TyG) index on admission with outcomes of critically ill patients.

Design A retrospective study.

Setting A population-based cohort study of Medical Information Mart for Intensive Care III Database (MIMIC III).

Participants All intensive care unit admissions were extracted from MIMIC III.

Main outcome measures The TyG index was calculated as ln [triglycerides (mg/dL)×glucose (mg/dL)/2]. The primary endpoint was 360-day mortality.

Results A total of 3902 patients with an average age of 63.1±15.9 years old were enrolled, including 1623 (41.6%) women. The 360-day mortality was lower in a higher TyG group. Compared with the lowest TyG group, the HR of 360-day mortality was 0.79 (95% CI (0.66, 0.95); p=0.011) in the fully adjusted Cox model and 0.71 (95% CI (0.59, 0.85); p<0.001) in the stepwise Cox model. In the subgroup analysis, an interaction effect was detected between TyG index and gender.

Conclusions A lower TyG index was associated with the risk of 360-day mortality in critically ill patients, which could be a predictor of long-term survival of critically ill patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To the best of our knowledge, this is the first study assessing the association between triglyceride–glucose index and long-term mortality of critically ill patients.
⇒ This was a retrospective analysis, which could not definitively establish causality.
⇒ We only included the baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic and lipid-lowering drugs.

INTRODUCTION

The triglyceride–glucose (TyG) index is calculated using fasting triglyceride and fasting glucose measurements. It has been suggested as a surrogate marker of insulin resistance (IR)[1 2] and has been found associated with bladder cancer that is widespread among men.[3] Critical illness is characterised by a hypermetabolic state associated with increased mortality due to enhanced IR.[4 5]

Several studies have examined the associations between IR and mortality in critically ill patients. Mowery *et al* found that IR was a predictor for mortality in traumatic brain injury[6] and increased the mortality of surgical care population.[7] Recently, a study concluded that the TyG index was a potential predictor for hospital and intensive care unit (ICU) mortality in critically ill patients who had a stroke.[8] To the best of our knowledge, there is no research to evaluate the association of TyG index on ICU admission with long-term outcomes of critically ill patients.

Thus, we performed a retrospective cohort study to clarify whether there is an association between TyG index and long-term outcomes in critically ill patients.

MATERIALS AND METHODS

Participants

This was a retrospective cohort study using data from the Medical Information Mart for Intensive Care Database, which is a large, publicly available database consisting of patients in the ICU of Beth Israel Deaconess Medical Center between 2001 and 2012.

Adult patients of first hospital and ICU admission with complete triglyceride and glucose records were included, but patients staying at ICU for <24 hours were excluded. The selection process was shown in figure 1.

Variables

We used PostgreSQL 13 to extract data from the database. The baseline characteristics within the first 24 hours after ICU admission included the following: age; gender; ethnicity; weight; severity measured by Sequential Organ Failure Assessment score; Simplified Acute Physiology Score II; laboratory

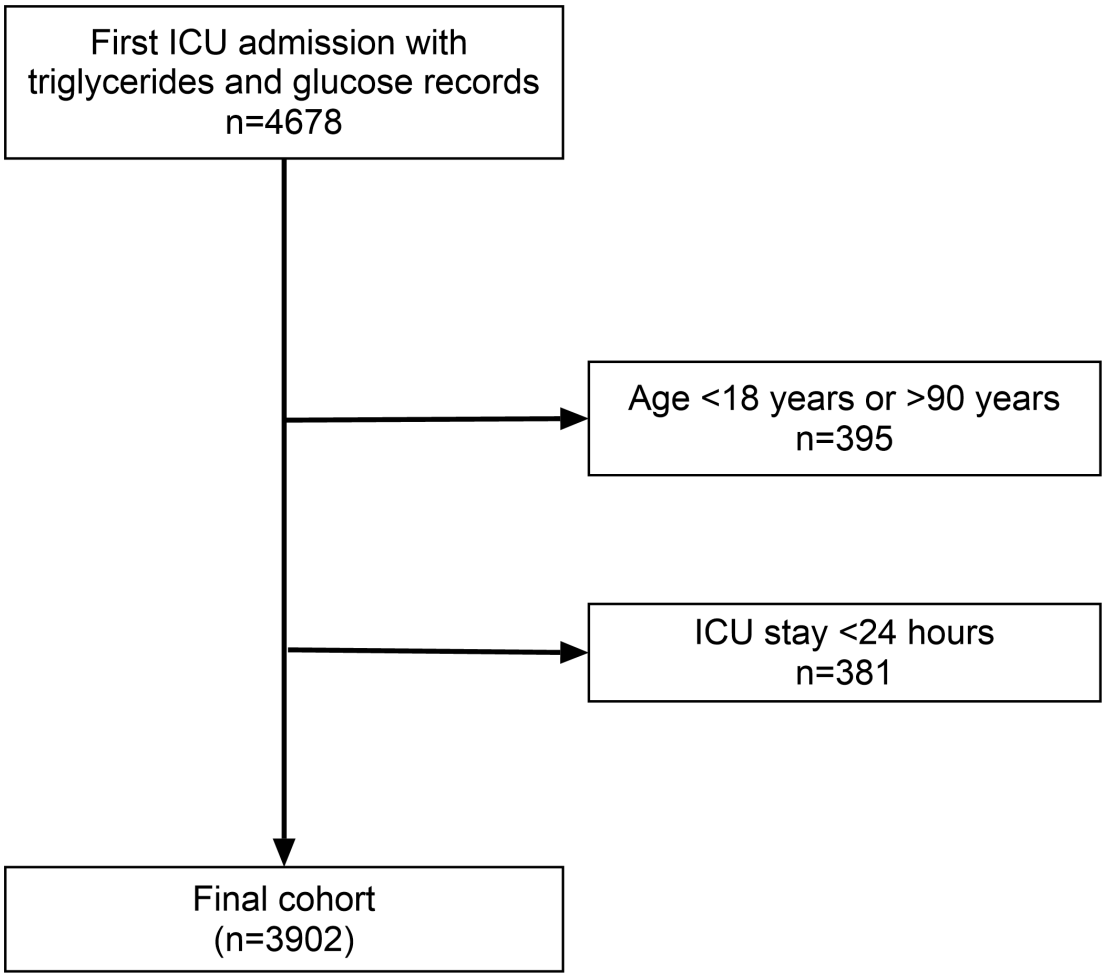

Figure 1 The flow diagram of study population. ICU, intensive care unit.

examination including white blood cell (WBC), platelet, potassium, sodium, triglycerides and glucose; treatment including albumin infusion, mechanical ventilation, administration of vasopressors and dialysis; comorbidities including coronary artery disease, hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease and chronic kidney disease; as well as the length of stay (LOS) in hospital and in ICU.

Outcomes

The primary exposure was the TyG index, defined as ln (triglycerides×glucose/2). The outcomes of the present study were in-hospital mortality, 30-day mortality and 360-day mortality.

Statistical analysis

Continuous variables are expressed as the mean±SD or median (IQR), as appropriate, and categorical variables are shown as number (proportions). One way analysis of variance and $\chi 2$ tests were used to compare the difference among groups. The Kaplan-Meier analysis was used to explore the association between TyG quartile and 30-day mortality and 360-day mortality. Multivariate modelling of the association between TyG index (as continuous and categorical variables) and 360-day mortality was performed with Cox regression. Baseline variables that were considered clinically relevant or associated with the TyG index ($p<0.05$) were entered into a multivariate Cox regression model, while all baseline variables were entered into a stepwise model. Subgroup analyses according to gender, age and mechanical ventilation were performed. All statistical analyses were performed by R software V.3.6.

Patient and public involvement

Patients and the public were not directly involved in the design or implementation of this study, since we used previously collected data.

RESULTS

The present study included 3902 patients admitted to ICU. The baseline characteristics of the study population according to TyG quartile were shown in table 1. Participants with a higher TyG index tended to have a higher weight, WBC, platelet and more percentage of DM and mechanical ventilation, as well as longer LOS in ICU and LOS in hospital (figure 2A,B). In addition (figure 3A), there was less 360-day mortality (p=0.002) in a higher TyG

Table 1 Baseline characteristics across the quartile (Q) of TyG index

Variables	Q1 (n=963)	Q2 (n=987)	Q3 (n=969)	Q4 (n=983)	P value
Age, years	66.84 (15.61)	64.63 (15.04)	62.82 (15.96)	58.22 (15.77)	<0.001
Female, %	400 (41.5)	441 (44.7)	395 (40.8)	387 (39.4)	0.105
Ethnicity, %					0.073
White	738 (76.6)	737 (74.7)	700 (72.2)	722 (73.4)	
Asian	30 (3.1)	18 (1.8)	19 (2.0)	17 (1.7)	
Black	6 (0.6)	5 (0.5)	3 (0.3)	2 (0.2)	
Hispanic	25 (2.6)	31 (3.1)	28 (2.9)	37 (3.8)	
Other	164 (17.0)	196 (19.9)	219 (22.6)	205 (20.9)	
Weight, kg	76.8 (21.6)	80.9 (23.1)	84.2 (24.5)	90.9 (29.3)	<0.001
CAD, %	321 (33.3)	334 (33.8)	324 (33.4)	299 (30.4)	0.345
HBP, %	402 (41.7)	455 (46.1)	429 (44.3)	431 (43.8)	0.285
DM, %	206 (21.4)	242 (24.5)	297 (30.7)	418 (42.5)	<0.001
COPD, %	16 (1.7)	15 (1.5)	16 (1.7)	15 (1.5)	0.99
CKD, %	36 (3.7)	35 (3.5)	40 (4.1)	45 (4.6)	0.689
SOFA score	3 (2–6)	3 (1–6)	4 (2–6)	4 (2–7)	<0.001
SAPS II score	35 (27–45)	34 (25–45.5)	34 (26–44)	34 (25–46)	0.7
WBC, 10^9/L	10.94 (6.14)	11.76 (5.59)	11.86 (6.54)	12.72 (9.96)	<0.001
Platelet, 10^9/L	219.4 (117.0)	238.0 (128.8)	240.9 (134.5)	245.3 (157.8)	<0.001
Potassium, mmol/L	4.02 (0.70)	4.03 (0.53)	4.04 (0.56)	4.04 (0.54)	0.937
Sodium, mmol/L	138.8 (4.90)	139.18 (4.52)	139.41 (4.70)	139.16 (5.05)	0.075
Triglycerides, mg/dL	68.0 (22.2)	107.6 (28.7)	152.5 (49.6)	337.1 (330.9)	<0.001
Glucose, mg/dL	106.8 (26.2)	122.8 (30.5)	138.2 (43.7)	176.8 (87.3)	<0.001
Albumin, g	38.2 (26.5)	39.5 (24.3)	43.9 (32.9)	42.1 (23.5)	0.750
Mechanical ventilation, %	381 (39.6)	439 (44.5)	500 (51.6)	582 (59.2)	<0.001
Vasopressors, %	28 (2.9)	28 (2.8)	32 (3.3)	28 (2.8)	0.92
Dialysis, %	87 (9.0)	85 (8.6)	74 (7.6)	111 (11.3)	0.037
LOS in hospital, day	8.2 (4.8–18.1)	9.0 (4.7–17.0)	10.6 (5.0–20.1)	12.0 (5.6–22.8)	<0.001
LOS in ICU, day	3.4 (2.0–8.9)	4.2 (2.0–10.0)	4.8 (2.1–12.0)	6.1 (2.4–13.4)	<0.001
In-hospital mortality, %	152 (15.8)	143 (14.5)	147 (15.2)	145 (14.8)	0.866
30-day mortality, %	149 (15.5)	167 (16.9)	140 (14.4)	136 (13.8)	0.244
360-day mortality, %	301 (31.3)	280 (28.4)	286 (29.5)	234 (23.8)	0.002

Q1: TyG <8.51, Q2: 8.51≤TyG<8.95, Q3: 8.95≤TyG<9.44, Q4: TyG ≥9.44.
CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HBP, hypertension; ICU, intensive care unit; LOS, length of stay; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; TyG, triglyceride–glucose; WBC, white blood cell.

group, while no difference was observed in in-hospital mortality (p=0.866) and 30-day mortality (p=0.244).

The Kaplan-Meier analysis was performed to explore the prognostic effect of TyG index on 30-day or 360-day mortality (figure 3B,C). As shown, a higher TyG index was associated with a lower risk of 360-day mortality (p for log-rank=0.006).

As shown in table 2, we constructed three models for analysing the prognostic role of TyG index in 360-day mortality. When compared with the lowest quartile, the highest quartile of TyG decreased the risk of mortality (HR 0.79, 95% CI (0.66, 0.95); p=0.011) in the multivariable-adjusted model. The stepwise model also showed the same trend (HR 0.71, 95% CI (0.59, 0.85); p<0.001). Per one-unit increasement of TyG was associated with 0.85-fold lower risk of mortality (HR 0.85, 95% CI (0.79, 0.92); p<0.001).

Subgroup analysis (table 3) showed that an interaction was observed between TyG index and gender (p=0.03). In male patients, TyG was negatively associated with 360-day mortality (HR 0.86, 95% CI (0.78,0.95); p=0.004), while the association was reversed in the female subgroup (HR 1.03, 95% CI (0.91,1.16); p=0.681).

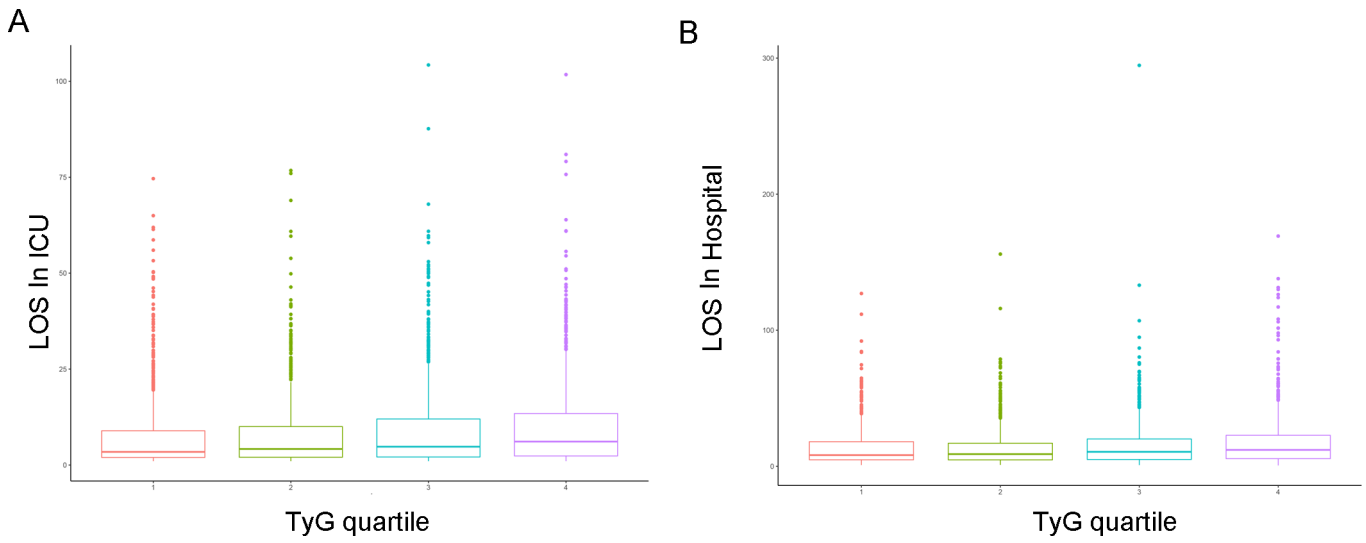

Figure 2 The LOS in ICU (A) and LOS in hospital (B) across TyG quartiles. ICU, intensive care unit; LOS, length of stay; TyG, triglyceride–glucose.

DISCUSSION

This is the first study to evaluate the association of the TyG index with long-term mortality in critically ill patients. We found that TyG index was negatively associated with 360-day mortality, not in-hospital or 30-day mortality of critically ill patients.

The TyG index has been well recognised as a simple and reliable surrogate of IR.[9] It does not require levels of insulin and may be applicable to all of the patients and healthy population. Several studies reported that TyG index predicted outcomes in patients with acute coronary syndrome[10] and ischaemic stroke.[11] Only one study found that TyG index was linearly associated with short-term mortality in ICU stroke after adjusting for confounding factors.[8] However, we did not find a positive correlation between TyG index and

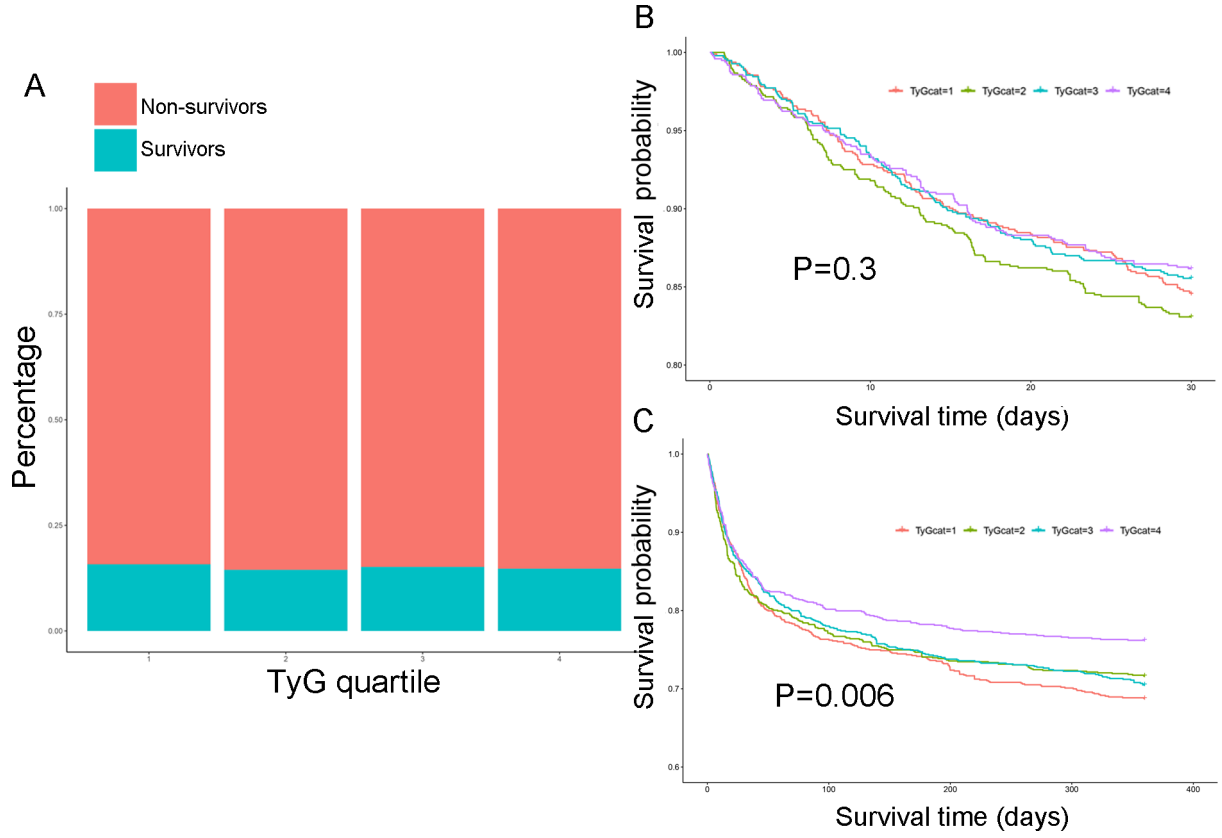

Figure 3 The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B), p<0.05: Q2 vs Q1, Q2 vs Q3, Q2 vs Q4; and 360-day mortality (C), p<0.05: Q1 vs Q2, Q1 vs Q3, Q1 vs Q4, Q2 vs Q4, Q3 vs Q4. TyG, triglyceride–glucose.

Table 2 Multivariable Cox regression analysing TyG index and 360-day mortality

			Unadjusted		Adjusted*		Stepwise†	
	Cases	N	HR	P value	HR	P value	HR	P value
Q1	301	963	Ref	–				
Q2	280	987	0.91 (0.77, 1.07)	0.259	0.97 (0.82, 1.14)	0.717	0.95 (0.81, 1.12)	0.548
Q3	286	969	0.93 (0.79, 1.10)	0.412	1.04 (0.88, 1.23)	0.633	0.98 (0.83, 1.16)	0.857
Q4	234	983	0.74 (0.63, 0.88)	0.001	0.79 (0.66, 0.95)	0.011	0.71 (0.59, 0.85)	<0.001
Continuous	1101	3902	0.89 (0.82, 0.96)	0.003	0.93 (0.86, 1.00)	0.063	0.85 (0.79, 0.92)	<0.001

*Adjusted for age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPS II, WBC, platelet, creatine, ventilation, vasopressors and dialysis.
†All variables except for outcomes were entered.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HBP, hypertension; Q, quartile; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; TyG, triglyceride–glucose; WBC, white blood cell.

Table 3 Subgroup analysis of TyG index and 360-day mortality

	HR	P for trend	P for interaction
Gender			0.03
Female	1.03 (0.91, 1.16)	0.681	
Male	0.86 (0.78, 0.95)	0.004	
Age			0.13
≤65	0.83 (0.73, 0.94)	0.003	
>65	0.96 (0.87, 1.07)	0.472	
Ventilation			0.357
No	1.01 (0.87, 1.17)	0.868	
Yes	0.91 (0.83, 1.00)	0.057	

TyG, triglyceride–glucose.

in-hospital and 30-day mortality. On the contrary, we demonstrated that TyG could be a protective predictor in long-term mortality in critically ill patients. The difference could be that we included more diseases in ICU and followed for a longer time. Besides, a higher TyG index may be related to a good nutrition status and be compensatory for the development of various diseases.

The mechanism underlying the relationship between the TyG index and critical illness is not fully elucidated. IR is an adaptive mechanism that prioritises utilisation of energy for immune response in the presence of infection or injury.[12] However, the underlying molecular mechanisms involved in this association should be further investigated in the future study.

Our study still has some limitations. First, this was a retrospective analysis derived from an observational study, which could not definitively establish causality. Second, we only included the baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic and lipid-lowering drugs. Therefore, it is unknown whether the change of the TyG index could predict mortality.

CONCLUSIONS

We found that TyG index predicted a better long-term prognosis of critically ill patients, regardless of other risk factors. However, no association was observed in respect of in-hospital or 30-day mortality.

Contributors LD and YY made the statistical analysis. KW and CH wrote the original manuscript. SS and DW designed the study. SS was responsible for the overall content as the guarantor. All authors approved it.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants. The MIMIC Database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates. Our study was approved by the review boards of Jiangsu Province Official Hospital (201921A011). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used during the current study are available from the corresponding author on reasonable request.

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