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Association between the Triglyceride Glucose Index and All-Cause Mortality in Critically Ill Patients with Acute Kidney Injury

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Keywords
Triglyceride glucose index · Insulin resistance · Acute kidney injury · All-cause mortality · MIMIC-IV database

Abstract
Introduction: The triglyceride glucose (TyG) index is a reliable alternative biomarker of insulin resistance, but the association between the TyG index and acute kidney injury (AKI) in critically ill patients remains unclear. ***Methods:*** The data for the study were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Cox regression and restricted cubic spline (RCS) analysis were performed to analyze the association between the TyG index and all-cause mortality. Besides, Cox regression was carried out in subgroups of age, gender, BMI, diabetes history, and dialysis status. ***Results:*** A total of 7,508 critically ill participants with AKI from the MIMIC-IV database were included in this study, with 3,688 (49.12%) participants failed to survive. In Cox regression, after confounder adjustment, patients with a higher TyG index had a higher risk of all-cause mortality (HR = 1.845, 95% CI = 1.49–2.285, $p < 0.001$). In RCS, after confounder adjustment, the risk of death was positively correlated with the increased value of the TyG index when TyG index surpassed 10.014. This relationship was validated in age, gender, BMI, diabetes subgroups but not in the dialysis subgroup. Interestingly, RCS analysis demonstrated that, in patients undertaking dialysis, there is a "U"-shaped curve for the value of TyG index and risk of all-cause mortality. When TyG index is less than 10.460, the risk of all-cause mortality would decrease with the increased value of TyG index, while when TyG index is higher than 11.180, the risk of all-cause mortality would increase firmly with the increased value of TyG index. ***Conclusion:*** Overall, a higher TyG index is associated with a higher risk of all-cause mortality in critically ill AKI. Interestingly, the relationship in the dialysis subgroup follows a "U"-shaped curve, indicating the importance of proper clinical blood glucose and lipid management in this particular population.

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Introduction

Acute kidney injury (AKI) is a severe public health issue, posing high incidence and mortality rates [1]. The clinical manifestations of AKI include a sustained decline in urine output and/or significant elevation in serum creatinine (SCr) level extending for a minimum of 7 days [2]. Among hospitalized patients, the incidence rate of AKI ranges from 10 to 15%, while those admitted to intensive care units (ICUs) have a markedly high incidence rate of up to 50%, with 10–20% of them requiring

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renal replacement therapy (RRT) [3]. The average pooled mortality rate of AKI stands at 23% and even surges to 49.4% in patients requiring RRT [2].

Insulin resistance (IR) is a pathophysiologic condition characterized by reduced sensitivity of peripheral tissues to the hormone insulin and is closely correlated with renal disease [4]. Insulin plays a unique role in the kidney by regulating metabolic and growth pathways, as well as influencing the kidney micro-circulation [5]. The presence of IR often leads to detrimental effects on renal blood flow and glomerular filtration, resulting in various injuries such as inflammation and even fibrosis [4, 5]. IR can occur in patients with impaired renal function, with or without diabetes mellitus (DM) [6, 7], and is positively correlated with proteinuria and renal function decline [8, 9]. Importantly, IR serves as a significant and independent risk factor for kidney disease [9–11].

The gold standard technique for IR testing is the glucose clamping technique, which assesses glucose metabolic rate by intravenous perfusion. However, its invasive procedure and relatively high cost limit its widespread clinical use. As an alternative, the triglyceride glucose (TyG) index, calculated by fasting blood glucose and triglyceride (TG) levels, can serve as a reliable proxy for assessing IR [12, 13]. The TyG index has emerged as a vital predictor of diabetes and atherosclerosis. Previous cross-sectional studies have shown that a high TyG index is strongly associated with proteinuria and decreased kidney function [14]. Cohort studies have also revealed that TyG index can effectively predict the occurrence and development of chronic kidney diseases including diabetic nephropathy [9] and aging nephropathy [15]. However, the role of TyG index in AKI remains poorly understood. Given that critically ill patients with AKI often present with metabolic disorders, this study aimed to explore the association between TyG index and all-cause mortality in this population.

Method

Source of Data

The data for this study were obtained from the MIMIC-IV 2.1 database [16], a comprehensive critical care database that is publicly available and accessible free of charge [https://www.physionet.org/content/mimiciv/2.1/]. Briefly, the MIMIC database contains data on ICU patients admitted to the Beth Israel Deaconess Medical Center between 2001 and 2012. The database is approved by the Institutional Review Board (IRB) at the Massachusetts Institute of Technology (MIT). With the successful completion of the National Institutes of Health's (NIH) online training course and the Protecting Human Research Participants exam (Record ID: 52839555), we were authorized to use the data.

Study Population

This study included patients who were admitted to the ICU, diagnosed with AKI, and aged 18 years or older. Exclusion criteria are comprised of patients without AKI or missing AKI data, ICU stays less than 48 h, patients with ICU readmissions, and those with end-stage renal disease or kidney transplantation at the time of admission (Fig. 1).

Data Collection

Postgres Structured Query Language (PostgreSQL version 14.6-1) was used to extract data from MIMIC-IV 2.1 database, and Navicat Premium (version 15.0.12) was utilized to screen characteristics, such as age, sex, body mass index (BMI), laboratory variables within the first 24 h after ICU admission, and comorbidities of patients enrolled in this study. The follow-up started from the date of admission and ended at death. Severity at admission was measured by the sequential organ failure assessment score, systemic inflammatory response syndrome score, acute physiology score III, and simplified acute physiological score II. Comorbidities such as myocardial infarction, peripheral vascular disease, cerebrovascular disease, and diabetes were defined with ICD-10 codes. The TyG index was calculated as ln (fasting TG [mg/dL] × fasting glucose [mg/dL])/2 [17].

Outcome and Clinical Definition

The primary outcome of this study was all-cause mortality. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as an increase in the SCr level by ≥0.3 mg/dL above baseline within 48 h or a decrease of urine output by <0.5 mL/kg/h over a period >6 h [18, 19].

Statistical Analysis

The descriptive statistics were grouped by endpoint. Continuous variables with a normal distribution are represented by mean ± standard deviation. Continuous variables with non-normal distribution are represented as medians (interquartile ranges). Continuous variable between-group comparisons were conducted using either the *t* test or the Mann-Whitney U test. Categorical variables are expressed as frequency or percentages, and χ^2 tests are used for between-group comparisons. To measure the relationship between TyG tertiles and all-cause mortality in critically ill patients with AKI, binary logistic regression and Cox regression were performed where TyG index is categorized into three tertiles or as continuous variable. Also, restricted cubic spline (RCS) analysis was performed where TyG index is a continuous variable. Subgroup analysis, including Cox regression and/or RCS analysis, was performed based on age, sex, BMI, diabetes history, and dialysis status. Statistical analysis was performed using SPSS 26.0 (IBM, Armonk, NY, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). p value <0.05 was considered statistically significant for all analyses.

Results

Baseline Characteristics

A total of 7,508 patients were finally enrolled in the present study. The clinical characteristics of participants grouped by survivors and non-survivors are shown in

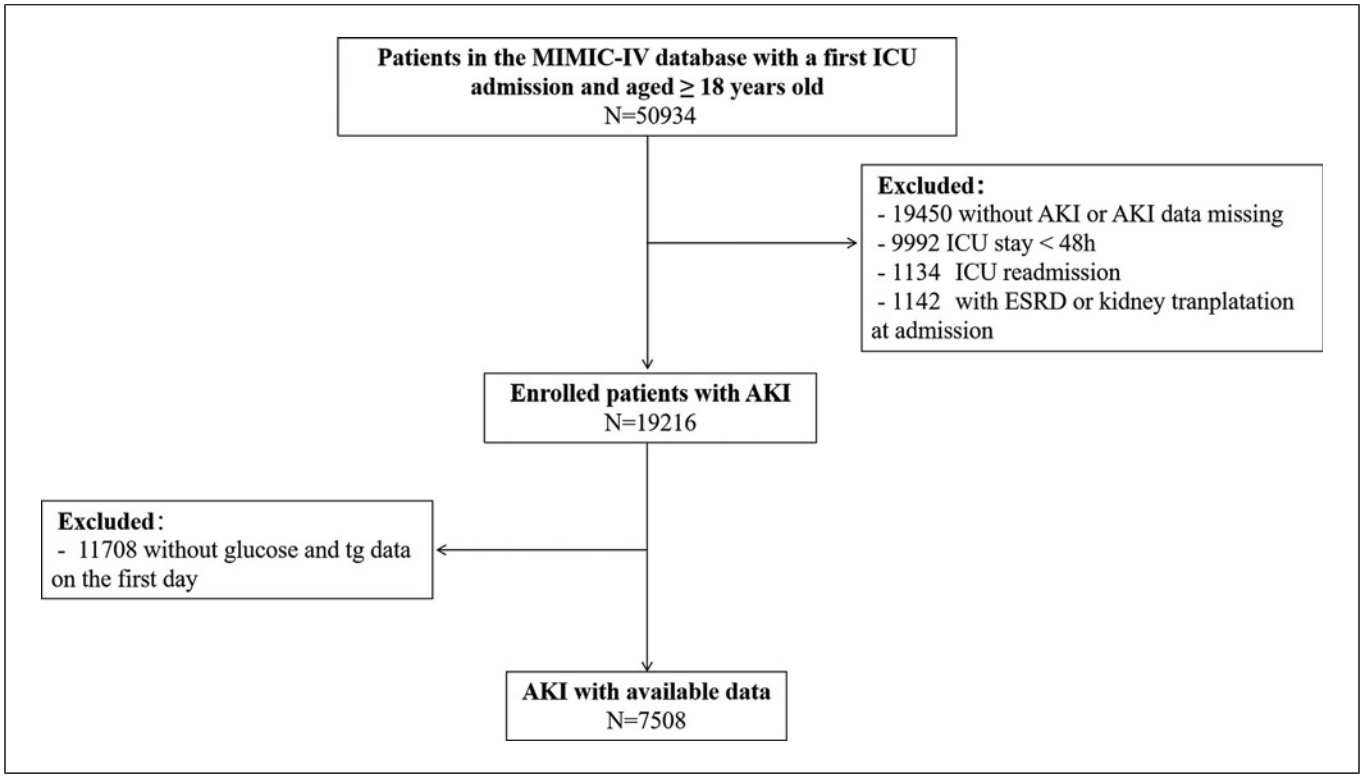

Fig. 1. Flowchart of the study population.

Table 1. The mean age of participants was 69 (range: 58–79) years, and 56.2% were men. Patients in the non-survivor group showed a higher prevalence of heart failure, peripheral vascular disease, and need of dialysis ($p < 0.05$). In terms of laboratory indicators, participants with an endpoint event had higher levels of SCr and blood urine nitrogen ($p < 0.05$). Besides, the clinical characteristics of participants grouped by three TyG tertiles can be found in online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000535891).

Correlation between the TyG Index and Risk Factors of AKI

The TyG index was associated with traditional or commonly used risk factors for AKI such as age, BMI, and myocardial infarction ($p < 0.05$). Positive correlations were found between the TyG index and BMI, diabetes, and dialysis ($r^2 > 0$, $p < 0.05$, online suppl. Table S2).

Relationship between the TyG Index and All-Cause Mortality in Critically Ill Patients with AKI

To investigate the cross-sectional correlation between TyG index and all-cause mortality in critically ill patients with AKI, we split TyG index into three tertiles (shown in online suppl. Table S1) and conducted binary logistics regression analysis. In model 1, with the low tertile of the TyG index set as the reference, the TyG index in the top tertile was associated with a higher OR for all-cause mortality (OR = 1.647, 95% confidence interval [CI] = 1.473–1.841, $p < 0.001$) (online suppl. Table S3). After adjustment for age, gender, BMI (model 2), myocardial infarction, heart failure, peripheral vascular disease, and cerebrovascular disease (model 3), this trend was retained (online suppl. Table S3).

To investigate the longitudinal correlation between TyG index and all-cause mortality in critically ill patients with AKI, we undertook Cox regression analysis. In model 1, compared with patients in low tertile of the TyG index, participants in the high tertile had a significantly higher risk of all-cause mortality (hazard ratio [HR] = 1.205, 95% CI = 1.111–1.308, $p < 0.001$). In model 2, we adjusted for age, gender coupled with BMI, and found that incident all-cause mortality in the high tertile of the TyG index was also increased. After adjusting plus myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease (model 3), participants in the high tertile of the TyG index continued to have a higher risk of all-cause mortality compared with those in

Table 1. Baseline characteristics of the survivor and non-survivor groups

	All (7,508)	Survivors (*n* = 3,820)	Non-survivors (*n* = 3,688)	*p* value
Age, years	69 (58, 79)	63.6 (62.96, 64.24)	70.13 (69.58, 70.68)	<0.001
Male, *n* (%)	4,218 (56.2)	2,198 (58)	2,020 (55)	0.016
BMI, kg/m^2	28.37 (24.12, 33.92)	30.91 (22.32, 39.5)	28.97 (19.98, 37.96)	0.956
Laboratory results				
WBC, K/μL	6.2 (4.6, 8.3)	7.0716 (6.8855, 7.2577)	7.2383 (7.0503, 7.4262)	0.053
Serum potassium, mEq/L	140 (137, 141)	4.21 (3.64, 4.78)	4.21 (3.62, 4.8)	0.803
Serum sodium, mEq/L	4.2 (3.8, 4.5)	139.09 (135.12, 143.06)	139.08 (135.04, 143.12)	0.954
Serum calcium, Eq/L	9 (8.4, 9.5)	8.93 (8.14, 9.72)	8.91 (8.04, 9.78)	0.436
Glucose, mg/dL	257 (195, 337)	276.26 (107.2, 445.32)	304.94 (141.31, 468.57)	<0.001
Albumin, g/dL	4.1 (3.4, 4.4)	3.87 (3.13, 4.61)	3.85 (3.09, 4.61)	0.465
SCr, mg/dL	0.9 (0.7, 1.2)	1.228 (1.179, 1.278)	1.321 (1.27, 1.372)	<0.001
BUN, mg/dL	17 (13, 25)	21.48 (20.83, 22.14)	22.73 (22.08, 23.39)	<0.001
TC, mg/dL	165 (110, 254)	182.51 (131.63, 233.39)	181.31 (133.22, 229.4)	0.347
TG, mg/dL	180 (150, 211)	230.82 (217.18, 244.46)	233.68 (224.24, 243.11)	0.354
LDL, mg/dL	107 (84, 137)	112.54 (74.05, 151.03)	112.06 (70.1, 154.02)	0.889
HDL, mg/dL	55 (44, 69)	57.34 (37.69, 76.99)	57.82 (37.76, 77.88)	0.352
Comorbidities, *n* (%)				
Myocardial infarction	867 (11.5)	440 (12)	427 (12)	0.935
Heart failure	1,776 (23.7)	779 (20)	997 (27)	<0.001
Peripheral vascular disease	636 (8.5)	293 (8)	343 (9)	0.011
Cerebrovascular disease	809 (10.8)	399 (10)	410 (11)	0.348
Diabetes	2,272 (30.3)	1,133 (30)	1,139 (31)	0.248
Dialysis	1,539 (20.5)	566 (15)	973 (26)	<0.001
SOFA score	49 (36, 71)	3.67 (3.59, 3.76)	3.81 (3.72, 3.9)	0.01
SIRS score	3 (2, 5)	2.51 (2.47, 2.55)	2.5 (2.46, 2.54)	0.887
APSIII	3 (2, 3)	51.08 (50.08, 52.09)	63.56 (62.41, 64.71)	<0.001
SAPSII	37 (29, 47)	36.21 (35.65, 36.77)	42.05 (41.47, 42.63)	<0.001
TyG index	9.96 (9.4, 10.57)	9.92 (9.05, 10.79)	10.11 (9.25, 10.97)	<0.001

BMI, body mass index; WBC, white blood cell; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; SCr, serum creatinine; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II; TyG, triglyceride glucose.

the low tertile (HR = 1.845, 95% CI = 1.49–2.285, $p < 0.001$) (Table 2).

Further, to evaluate and visualize the longitudinal correlation between TyG index and all-cause mortality in critically ill patients with AKI, we drew the RCS curve, which considered TyG index as a continuous variable. When the TyG index was higher than 10.014, the risk of death was positively correlated with the value of the TyG index, while the correlation became negative when the TyG index was less than 10.014 (Fig. 2).

Subgroup Analysis of Correlation between the TyG Index and All-Cause Mortality in Critically Ill Patients with AKI

To confirm the relationship between the TyG index and all-cause mortality stratified by age, sex, BMI, diabetes history, and dialysis status, subgroup analyses were carried out. These results validated the relationship between the TyG index and all-cause mortality in age, gender, BMI, and diabetes subgroups. Surprisingly, dialysis status was found to interact with the relationship between the TyG index and all-cause mortality (Table 3). Higher TyG index tertile was associated with a higher risk of all-cause mortality in the non-dialysis subgroup (HR = 1.393, 95% CI = 1.167–1.662, $p < 0.001$), while the correlation disappeared in the dialysis subgroup (HR = 0.970, 95% CI = 0.739–1.274, $p = 0.829$).

Thus, RCS analysis was conducted in dialysis status subgroups. Interestingly, RCS curve of TyG index and all-cause mortality in the dialysis subgroup was presented as a "U" shape. When TyG index is less than 10.460, the risk of all-cause mortality would decrease, while when TyG index is higher than 11.18, the risk of all-cause mortality would increase firmly with the increase of value of TyG

Table 2. Cox regression for all-cause mortality in critically ill patients with AKI

TyG tertiles	Model 1		Model 2		Model 3	
	HR	*p* value for 1sd	HR	*p* value for 1sd	HR	*p* value for 1sd
Low	Ref		Ref		Ref	
Medium	1.205 (1.111–1.308)	<0.001	1.154 (0.984–1.353)	0.032	1.158 (0.987–1.358)	0.031
High	1.405 (1.297–1.522)	<0.001	1.473 (1.268–1.711)	<0.001	1.473 (1.268–1.712)	<0.001

Model 1, crude model; model 2, model 1 plus age, gender, BMI; model 3, model 2 plus myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease.

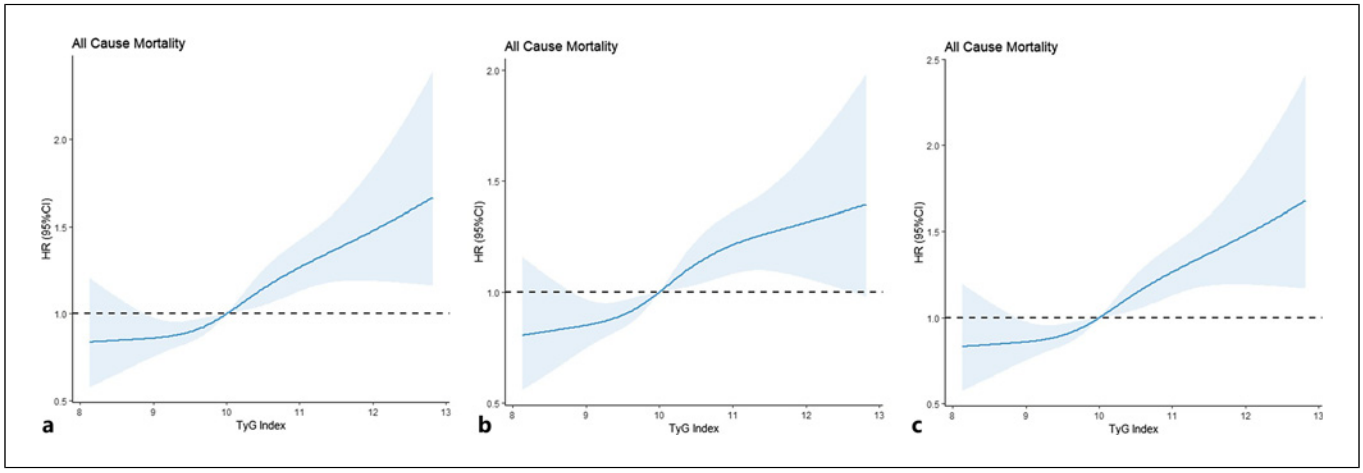

Fig. 2. RCS curve for the TyG index HR. **a** RCS for all-cause mortality in model 1. **b** RCS for all-cause mortality in model 2. **c** RCS for all-cause mortality in model 3. HR, hazard ratio; CI, confidence interval; TyG, triglyceride glucose.

index (Fig. 3a). But in the non-dialysis group, the risk of all-cause mortality steadily increased when TyG index exceeded 9.950 (Fig. 3b).

Discussion

In the present study utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, we aimed to assess the association of the TyG index on all-cause mortality in critically ill patients with AKI. Overall, we found that patients with high TyG index are at higher risk of all-cause mortality (HR = 1.205, 95% CI = 1.111–1.308, $p < 0.001$). This relationship between TyG index and all-cause mortality was validated in subgroup analysis. Interestingly, RCS analysis of subgroups of patients undertaking dialysis drew our attention. There is a "U"-shaped curve for the value of TyG index and risk of all-cause mortality, which means when TyG index is less than 10.460 the risk of all-cause mortality would decrease while when TyG index is higher than 11.18, the risk of all-cause mortality would increase firmly.

Insulin is not only a hormone that regulates glucose levels, but also a signaling molecule for many tissues and cells [5]. The kidney, as one of the insulin effector organs, contains a variety of insulin-sensitive cells, such as podocytes that express insulin receptors like GLUT4 and GLUT1 [20, 21]. Insulin plays a unique role in the kidneys such as regulating glomerular filtration, maintaining tubular sodium homeostasis, and modulating gluconeogenesis [4, 5]. If IR occurs, insulin signaling is impaired, resulting in renal damage such as increased glomerular hyperfiltration [21], decreased podocyte viability, and tubular dysfunction. Besides, cytoskeletal rearrangement [22], mitochondrial dysfunction [23], inflammation [4], and lipid toxicity [5]

Table 3. The subgroup Cox regression analysis of the association between the TyG index and all-cause mortality in critically ill patients with AKI

	Adjusted HR (95% CI)			*p* value	*p* for interaction
	Q1	Q2	Q3		
Age, years					
<65	Ref	1.250 (0.944, 1.655)	1.488 (1.145, 1.933)	0.003	0.357
>65	Ref	1.137 (0.937, 1.380)	1.477 (1.230, 1.775)	<0.001	
Sex					
Female	Ref	1.209 (0.955, 1.531)	1.504 (1.197, 1.889)	<0.001	0.846
Male	Ref	1.126 (0.906, 1.399)	1.446 (1.185, 1.765)	<0.001	
BMI, kg/m^2					
<30	Ref	1.082 (0.89, 1.315)	1.521 (1.267, 1.825)	<0.001	0.831
>30	Ref	1.292 (0.978, 1.706)	1.402 (1.075, 1.828)	0.013	
Diabetes					
Yes	Ref	1.167 (0.881–1.546)	1.340 (1.027–1.748)	0.031	0.926
No	Ref	1.117 (0.920–1.356)	1.528 (1.273–1.835)	<0.001	
Dialysis					
Yes	Ref	0.842 (0.630–1.125)	0.970 (0.739–1.274)	0.829	<0.001
No	Ref	1.024 (0.848–1.237)	1.393 (1.167–1.662)	<0.001	

TyG, triglyceride glucose; BMI, body mass index; HR, hazard ratio.

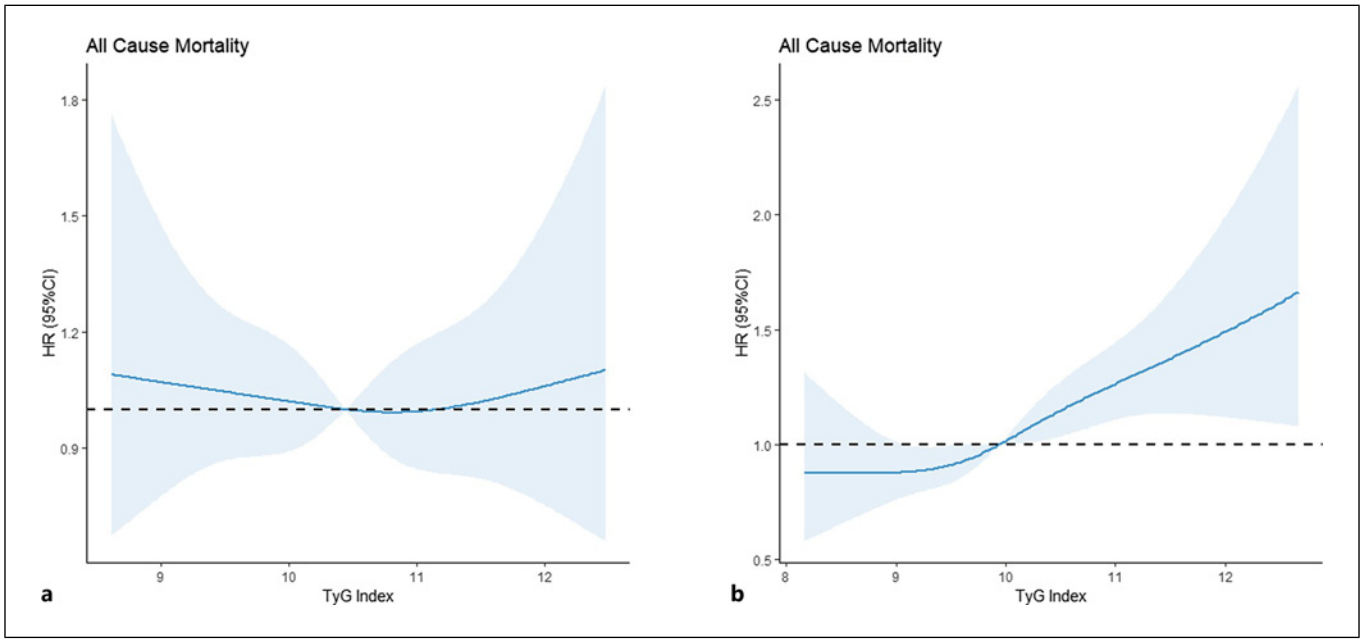

Fig. 3. RCS curve for the TyG index HR. **a** RCS for all-cause mortality in dialysis subgroup. **b** RCS for all-cause mortality in non-dialysis subgroup. HR, hazard ratio; CI, confidence interval; TyG, triglyceride glucose.

are considered to be possible mechanisms of IR-related renal damage. Clinically, studies have validated the presence of IR in renal dysfunction patients. IR is associated with proteinuria levels [8] and decreased renal function, which is independent of diabetes status [6, 7].

The TyG index serves as a surrogate marker for IR, and previous studies have demonstrated its application in predicting the incidence and progression of various kidney diseases including diabetic nephropathy [9], aging nephropathy [15], and so on. Nonetheless, there is limited

evidence regarding the role of TyG index in AKI. A previous study, enrolling 928 patients with DM who had undergone coronary angiology or percutaneous coronary intervention, investigated the relationship between TyG index and contrast-induced AKI (CI-AKI) in DM. They identified that the incidence of CI-AKI is correlated with an elevation in TyG index levels, and patients who developed CI-AKI displayed significantly higher TyG levels compared to the control (OR: 2.370, 95% CI: [1.887–3.368], $p < 0.001$) [24]. Another study, enrolling 1,108 patients with non-ST segment elevation acute coronary syndrome who underwent percutaneous coronary intervention, reported that higher TyG index significantly correlated with an increased risk of contrast-induced nephropathy regardless of diabetes status. Notably, there was a "J-shaped" nonlinear correlation between TyG index and contrast-induced nephropathy risk after adjusting for confounding factors in RCS analysis [25]. Both of the studies highlighted the predictive value of TyG index in CI-AKI. However, evidence on the relationship between TyG index and the prognosis of critically ill patients with AKI is poor.

The association between obesity and IR is well established, and both are key clinical features of metabolic syndrome. Previously, an observational study, enrolling 5,232 patients with AKI requiring RRT from 53 Austrian ICUs, demonstrated that the relationship between obesity, defined by BMI, and hospital mortality rates followed a "U-shaped" pattern [26]. Interestingly, in the present study, we found a similar "U-shaped" pattern in the RCS curve depicting the relationship between TyG index and the risk of all-cause mortality in subgroups of patients requiring dialysis (Fig. 3a). When TyG index exceeded 11.18, the risk of death increased with increasing TyG. Considering that TyG index is a substitute indicator for IR, which is also one of the triggers of inflammatory signaling [27], it appears that in these patients, the more severe the IR is, the higher the risk of death is. When the TyG index was less than 10.46, the risk of death decreased with increasing TyG. Since immune cells are regulated by insulin signaling [28, 29], appropriate insulin levels in critically ill patients with AKI may enhance the immunity of T cells and bring positive immune modulation. Besides, given that the TyG index is calculated by fasting blood glucose and TG levels, which are the raw materials for glucose and lipid metabolism, in addition that glucose and lipid metabolism are vital life processes for material and energy supply, a lower TyG index in these patients may indicate for insufficient energy and materials, leading to poor nutrition and increased risk of mortality. Therefore, management of blood glucose and lipid control for critically ill patients with AKI requiring dialysis should not simply focus on reducing glucose or lipid levels, but also consider the nutritional status of patients, which ought to be paid extra attention.

Indeed, the present study has important strengths and limitations that should be taken into consideration. The advantages of the study include being the first to investigate the effect of the TyG index on all-cause mortality in critically ill patients with AKI. This novel approach provides valuable insights into the relationship between metabolic parameters and renal function in a clinical setting. Additionally, the study population was obtained from the MIMIC-IV cohort, representing a large sample size and a high reliability of the results. Nevertheless, there are limitations to acknowledge. First, the study population is critically ill, which does not reflect the continuous spectrum of metabolic state. Nonetheless, studying critically ill patients is of great importance due to their high mortality rates and the need for reliable risk predictors in this vulnerable population. Besides, the study population was mainly white, indicating that the relationship between TyG index and all-cause mortality of AKI in other races, such as the Asian population, requires further validation. Second, these findings are based on observational results, and further researches are necessary to investigate and explicate the underlying causes and mechanisms of kidney injury induced by IR to establish a clearer understanding of the observed associations.

Conclusion

Our findings suggest that high TyG index is associated with a higher risk of all-cause mortality in critically ill patients with AKI. This relationship is validated in subgroups. Interestingly, in patients undertaking dialysis, the relationship is more complex and can be described as a "U"-shaped curve. When TyG index is less than 10.460, the risk of all-cause mortality would decrease with the increased value of TyG index, while when TyG index is higher than 11.18, the risk of all-cause mortality would increase firmly with the increased value of TyG index, indicating the importance of a proper blood glucose and lipid management of this population.

Acknowledgments

This work utilized the MIMIC-IV resource. We thank all participants in the MIMIC-IV research team for survey design and data collection.

Statement of Ethics

The study was performed according to the guidelines of the Helsinki Declaration. The use of the MIMIC-III database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The data are available in the MIMIC-III database; therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Conflict of Interest Statement

All authors declare that they have no relevant conflict of interest.

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Author Contributions

Liangjing Lv: performing the research, data analysis, and writing the original draft; Jiachuan Xiong, Yinghui Huang, and Ting He: interpreting the results, and writing review and editing; Jinghong Zhao: designing and approving this work.

Data Availability Statement

Data generated and analyzed in this study are not publicly available due to ethical reasons. Further inquiries can be directed to corresponding author.

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