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# BMJ Open

## The TyG index on admission was associated with a better long-term mortality of critically ill patients

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4 1 **The TyG index on admission was associated with a better long-term mortality of**  
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6 2 **critically ill patients**  
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11 4 Lingli Dai<sup>1</sup>, Yun Yu<sup>1</sup>, Kunlin Wang<sup>1</sup>, Cuining Hu<sup>1</sup>, Dan Wu<sup>1</sup>, Shan Shan<sup>1\*</sup>  
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4 28 **Abstract**

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6 29 **Aim:** To evaluate the association of triglycerides glucose (TyG) index on admission with outcomes  
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9 30 of critically ill patients.

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11 31 **Methods:** We conducted a retrospective study that included all intensive care unit (ICU) admissions  
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14 32 extracted from the Medical Information Mart for Intensive Care III database (MIMIC III). The TyG  
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17 33 index was calculated as  $\ln$  [triglycerides (mg/dL) \*glucose (mg/dL)/2]. The primary endpoint was  
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20 34 360-day mortality. Multivariable Cox regression analysis was used to explore the prognostic effect  
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22 35 of TyG index.

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25 36 **Results:** A total of 3902 patients with an average age of  $63.1 \pm 15.9$  years old were enrolled,  
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27 37 including 1623 (41.6%) females. The 360-day mortality were lower in a higher TyG group.  
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30 38 Compared with the lowest TyG group, the hazards ratio of 360-day mortality was 0.79 (95%  
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32 39 confidence interval [0.66, 0.95];  $p=0.011$ ) in the fully adjusted Cox model and 0.71 ([0.59, 0.85];  
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35 40  $p<0.001$ ) in the stepwise Cox model. In the subgroup analysis, an interaction effect was detected  
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38 41 between TyG index and gender.

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40 42 **Conclusions:** The TyG index was negatively associated with the risk of 360-day mortality in  
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43 43 critically ill patients.

44 44 **Keywords:** TyG index; mortality; ICU; critically illness; cohort study

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## 50 **Introduction**

51 The triglyceride glucose (TyG) index is calculated using fasting triglyceride and fasting glucose  
52 measurements. It has been suggested as a surrogate marker of insulin resistance (IR)<sup>1, 2</sup>. Critical  
53 illness is characterized by a hypermetabolic state associated with increased mortality due to  
54 enhanced IR<sup>3,4</sup>.

55 Several studies have examined the associations between IR and mortality in critically ill patients.  
56 Nathan found that IR was a predictor for mortality in traumatic brain injury<sup>5</sup> and increased the  
57 mortality of surgical care population<sup>6</sup>. Recently, a study concluded that the TyG index was a  
58 potential predictor for hospital and ICU mortality in critically ill stroke patients<sup>7</sup>. To the best of our  
59 knowledge, there is no research to evaluate the association of TyG index on intensive care unit  
60 (ICU) admission with long-term outcome of critically ill patients.

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

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## 72 **Materials and methods**

### 73 **Participants**

74 This was a retrospective cohort study using data from the MIMIC database, which is a large publicly  
75 available database consisting of patients in the ICU of Beth Israel Deaconess Medical Center  
76 between 2001 and 2012. The database was approved from the institutional review boards of both  
77 Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates.

78 Adult patients of first hospital and ICU admission with complete triglycerides and glucose records  
79 were included, but patients staying at ICU for < 24 hours were excluded. The selection process was  
80 shown in **Figure 1**. Our study was approved by the Review Boards of Jiangsu Province Official  
81 Hospital (201921A011).

### 82 **Variables**

83 We used PostgreSQL 13 to extract data from the database. The baseline characteristics within the  
84 first 24 hours after ICU admission included the following: age, gender, ethnicity, weight, severity  
85 measured by Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology  
86 Score II (SAPS II) score, laboratory examination including white blood cell (WBC), platelet,  
87 potassium, sodium, triglycerides, and glucose, treatment including albumin infusion, mechanical  
88 ventilation, administration of vasopressors, and dialysis, comorbidities including coronary artery  
89 disease (CAD), hypertension (HBP), diabetes (DM) and chronic obstructive pulmonary disease  
90 (COPD), as well as the length of stay (LOS) in hospital and in ICU.

### 91 **Outcomes**

92 The primary exposure was the triglycerides and glucose (TyG) index, defined as  $\ln$   
93  $(\text{triglycerides} \times \text{glucose} / 2)$ . The outcomes of the present study were in-hospital mortality, 30-day

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4 94 mortality and 360-day mortality.  
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7 95 **Statistical analysis**  
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9 96 Continuous variables are expressed as the mean  $\pm$  standard deviation or median (interquartile range),  
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11 97 as appropriate, and categorical variables are shown as number (proportions). One way analysis of  
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14 98 variance and the  $\chi^2$  tests were used to compare the difference among groups. The Kaplan-Meier  
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17 99 analysis was used to explore the association between TyG quartile and 30-day mortality and 360-  
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19 100 day mortality. Multivariate modeling of the association between TyG index (as continuous and  
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22 101 categorical variables) and 360-day mortality was performed with Cox regression. Baseline variables  
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25 102 that were considered clinically relevant or associated with the TyG index ( $P < 0.05$ ) were entered  
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27 103 into a multivariate Cox regression model, while all baseline variables were entered into a stepwise  
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30 104 model. Subgroup analyses according to gender, age and mechanical ventilation were performed. All  
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33 105 statistical analysis was performed by R software version 3.6.

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35 106 **Patient and Public Involvement**  
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37 107 No patient involved.  
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116 **Results**

117 The present study included 3902 patients admitted into ICU. The baseline characteristics of the  
 118 study population according to TyG quartile were shown in the **Table 1**. Participants with a higher  
 119 TyG index tended to have a higher weight, WBC, platelet and more percentage of DM and  
 120 mechanical ventilation, as well as longer LOS in hospital and LOS in hospital (**Figure 2A&B**). In  
 121 addition (**Figure 3A**), there was less 360-day mortality (P=0.002) in a higher TyG group while no  
 122 difference was observed in in-hospital mortality (P=0.866), and 30-day mortality (P=0.244).

124 **Table 1. Baseline characteristics across the quartile of TyG index.**

Variables	Q1 (n=963)	Q2 (n=987)	Q3 (n=969)	Q4 (n=983)	P
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
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 <sup>9</sup> /L	10.94 (6.14)	11.76 (5.59)	11.86 (6.54)	12.72 (9.96)	<0.001
Platelet, 10 <sup>9</sup> /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

125 Q1: TyG<8.51, Q2: 8.51≤TyG<8.95, Q3: 8.95≤TyG<9.44, Q4: TyG≥9.44. CAD, coronary artery diseases; HBP,  
 126 hypertension; DM, diabetes mellites; COPD, chronic obstructive pulmonary diseases; SOFA, Sequential Organ  
 127 Failure Assessment; SAPS II, Simplified Acute Physiology Score II; WBC, white blood cell; LOS, length of stay.

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

132 As shown in **Table 2**, we constructed three models for analyzing the prognostic role of TyG index  
 133 in 360-day mortality. When compared with the lowest quartile, the highest quartile of TyG  
 134 decreased the risk of mortality (HR 0.79, 95% CI [0.66, 0.95]; P=0.011) in the multivariable-  
 135 adjusted model. The stepwise model also showed the same trend (HR 0.71, 95%CI [0.59, 0.85];  
 136 P<0.001). Per 1-unit increasement of TyG was associated with 0.85-fold lower risk of mortality  
 137 (HR 0.85, 95% CI [0.79, 0.92]; P<0.001).

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139 **Table 2. Multivariable Cox regression analyzing TyG index and 360-day mortality.**

	Cases	N	Unadjusted		Adjusted <sup>#</sup>		Stepwise*	
			HR	P	HR	P	HR	P
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

140 <sup>#</sup> Adjusted for age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPSII score, WBC, platelet,  
 141 creatine, ventilation, vasopressors, and dialysis.

142 \*All variables except for outcomes were entered.

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144 Subgroup analysis (**Table 3**) showed that an interaction was observed between TyG index and  
 145 gender (P=0.03). In male patients, TyG was negative associated with 360-day mortality (HR 0.86,  
 146 95% CI [0.78,0.95]; P=0.004) while the association was reversed in female subgroup (HR 1.03, 95%  
 147 CI [0.91,1.16]; P=0.681).

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

	HR	P for trend	P for interaction
<b>Gender</b>			0.03
female	1.03 [0.91, 1.16]	0.681	
male	0.86 [0.78, 0.95]	0.004	
<b>Age</b>			0.13
≤65	0.83 [0.73, 0.94]	0.003	
>65	0.96 [0.87, 1.07]	0.472	
<b>Ventilation</b>			0.357
No	1.01 [0.87, 1.17]	0.868	
Yes	0.91 [0.83, 1.00]	0.057	

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151 **Discussion**

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

155 The TyG index has been well-recognized as a simple and reliable surrogate of IR<sup>8</sup>. It does not  
 156 require levels of insulin and may be applicable to all of the patients and healthy population. Several  
 157 studies reported that TyG index predicted outcomes in patients with acute coronary syndrome<sup>9</sup> and  
 158 ischemic stroke<sup>10</sup>. Only one study found that TyG index was linearly associated with short-term  
 159 mortality in ICU stroke after adjusting for confounding factors<sup>7</sup>. However, we did not find a positive

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4 160 correlation between TyG index and in-hospital and 30-day mortality. Contrary, we demonstrated  
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7 161 that TyG could be a protective predictor in long-term mortality in critically ill patients. The  
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9 162 difference could be that we included more diseases in ICU and followed a longer time.

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11 163 The mechanism underlying the relationship between the TyG index and critically illness is not fully  
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14 164 elucidated. Insulin resistance is an adaptive mechanism that prioritizes utilization of energy for  
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17 165 immune response in the presence of infection or injury<sup>11</sup>. However, the underlying molecular  
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19 166 mechanisms involved in this association should be further investigated in the future study.

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22 167 Our study still has some limitations. First, this was a retrospective analysis derived from an  
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25 168 observational study, which could not definitively establish causality. Second, we did not measure  
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28 169 HOMA-IR because the examination of insulin levels is not included. Third, we only included the  
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31 170 baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic  
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34 171 and lipid-lowering drugs. Therefore, it is unknown whether the change in the TyG index could have  
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37 172 predicted the mortality.

### 38 173 **Conclusions**

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40 174 We found that TyG index was negatively associated with 360-day mortality, which could be a  
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43 175 protective predictor in the long-term outcome in critically ill patients.

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### 47 48 177 **Declarations**

### 49 50 51 178 **Ethics approval and consent to participate**

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53 179 The protocol was approved by the Institutional Review Board of both Beth Israel Deaconess  
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56 180 Medical Center and Massachusetts Institute of Technology Affiliates and no new data was added.

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58 181 All methods were carried out in accordance with Helsinki regulations. The need for informed  
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4 182 consent was waived off by the Institutional Review Board of both Beth Israel Deaconess Medical  
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6 183 Center and Massachusetts Institute of Technology Affiliates. Our study was approved by the Review  
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9 184 Boards of Jiangsu Province Official Hospital (201921A011).

#### 11 185 **Consent for publication**

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14 186 Yes

#### 15 187 **Availability of data and materials**

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18 188 The datasets used during the current study available from the corresponding author on reasonable  
19  
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21  
22 189 request.

#### 23 190 **Competing interests**

24  
25  
26 191 The authors have nothing to disclose regarding conflict of interest with respect to this manuscript.

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28  
29  
30 193 None.

#### 31 194 **Authors' contributions**

32  
33  
34 195 D LL and Y Y made the statistical analysis; W KL and H CN wrote the original manuscript; S S  
35  
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37 196 and W D designed the study. All authors approved it.

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#### 45 200 **References**

- 46  
47  
48 201 1. Guerrero-Romero F, Villalobos-Molina R, Jimenez-Flores JR, et al. Fasting Triglycerides and  
49 202 Glucose Index as a Diagnostic Test for Insulin Resistance in Young Adults. *Arch Med Res.*  
50 203 2016;47(5):382-387. doi: 10.1016/j.arcmed.2016.08.012  
51 204 2. Vasques AC, Novaes FS, de Oliveira Mda S, et al. TyG index performs better than HOMA in a  
52 205 Brazilian population: a hyperglycemic clamp validated study. *Diabetes Res Clin Pract.* 2011;93(3):e98-  
53 206 e100. doi: 10.1016/j.diabres.2011.05.030

- 1  
2  
3 207 3. Zauner A, Nimmerrichter P, Anderwald C, et al. Severity of insulin resistance in critically ill  
4 208 medical patients. *Metabolism*. 2007;56(1):1-5. doi: 10.1016/j.metabol.2006.08.014  
5  
6 209 4. Saberi F, Heyland D, Lam M, et al. Prevalence, incidence, and clinical resolution of insulin  
7 210 resistance in critically ill patients: an observational study. *JPEN J Parenter Enteral Nutr*.  
8 211 2008;32(3):227-35. doi: 10.1177/0148607108316195  
9  
10 212 5. Mowery NT, Gunter OL, Guillaumondegui O, et al. Stress insulin resistance is a marker for mortality  
11 213 in traumatic brain injury. *J Trauma*. 2009;66(1):145-51; discussion 151-3. doi:  
12 214 10.1097/TA.0b013e3181938c5e  
13  
14 215 6. Mowery NT, May AK, Collier BC, et al. Glucose metabolism, not obesity, predicts mortality in  
15 216 critically ill surgical patients. *Am Surg*. 2010;76(12):1377-83.  
16  
17 217 7. Zhang B, Liu L, Ruan H, et al. Triglyceride-Glucose Index Linked to Hospital Mortality in  
18 218 Critically Ill Stroke: An Observational Multicentre Study on eICU Database. *Front Med (Lausanne)*.  
19 219 2020;7:591036. doi: 10.3389/fmed.2020.591036  
20  
21 220 8. Du T, Yuan G, Zhang M, et al. Clinical usefulness of lipid ratios, visceral adiposity indicators, and  
22 221 the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol*.  
23 222 2014;13:146. doi: 10.1186/s12933-014-0146-3  
24  
25 223 9. Ma X, Dong L, Shao Q, et al. Triglyceride glucose index for predicting cardiovascular outcomes  
26 224 after percutaneous coronary intervention in patients with type 2 diabetes mellitus and acute coronary  
27 225 syndrome. *Cardiovasc Diabetol*. 2020;19(1):31. doi: 10.1186/s12933-020-01006-7  
28  
29 226 10. Shi W, Xing L, Jing L, et al. Value of triglyceride-glucose index for the estimation of ischemic  
30 227 stroke risk: Insights from a general population. *Nutr Metab Cardiovasc Dis*. 2020;30(2):245-253. doi:  
31 228 10.1016/j.numecd.2019.09.015  
32  
33 229 11. Dhar A, Castillo L. Insulin resistance in critical illness. *Curr Opin Pediatr*. 2011;23(3):269-74. doi:  
34 230 10.1097/MOP.0b013e3283464b3e  
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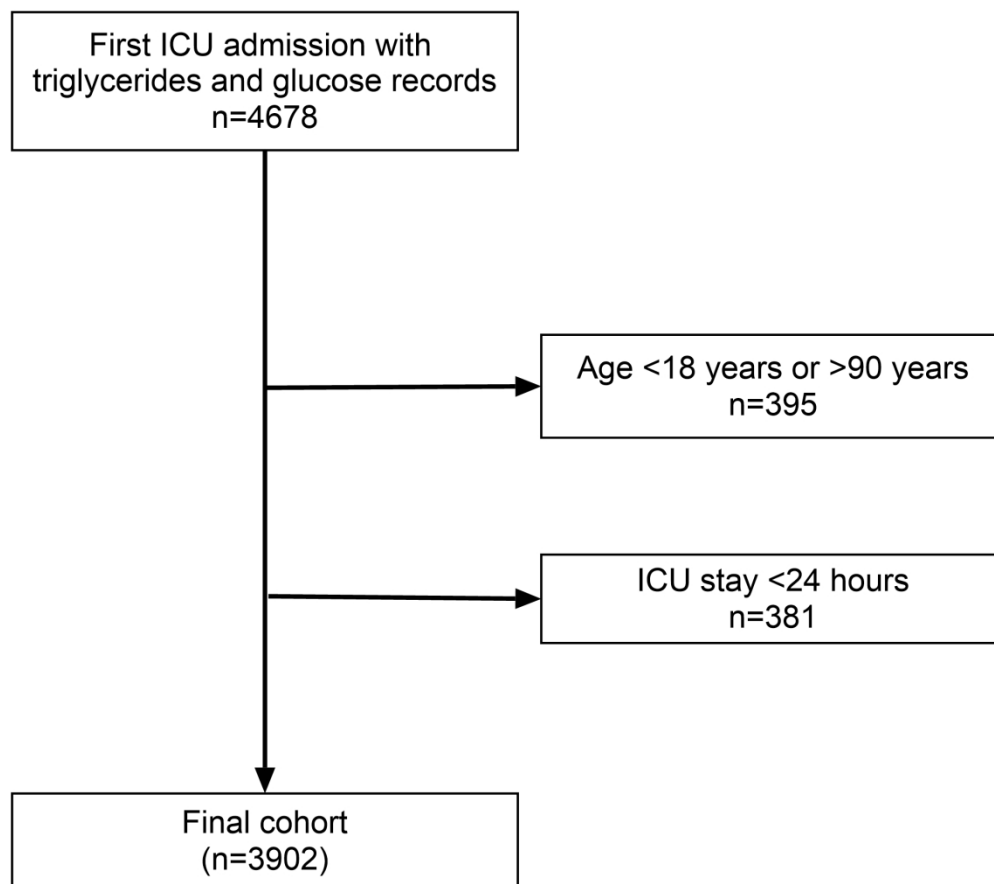
242 **Figure legends**

243 **Figure 1.** The flow diagram of study population.

244 **Figure 2.** The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

245 **Figure 3.** The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day  
246 mortality (B), and 360-day mortality (C).

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35 Figure 1. The flow diagram of study population.

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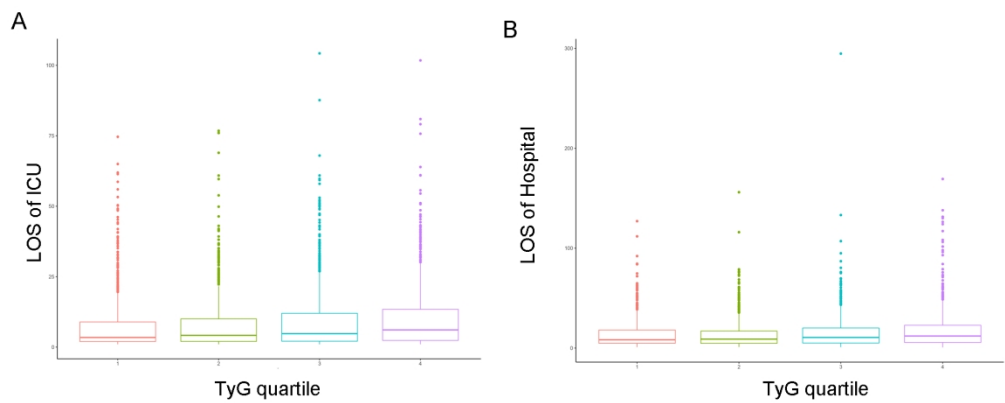


Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

180x76mm (300 x 300 DPI)

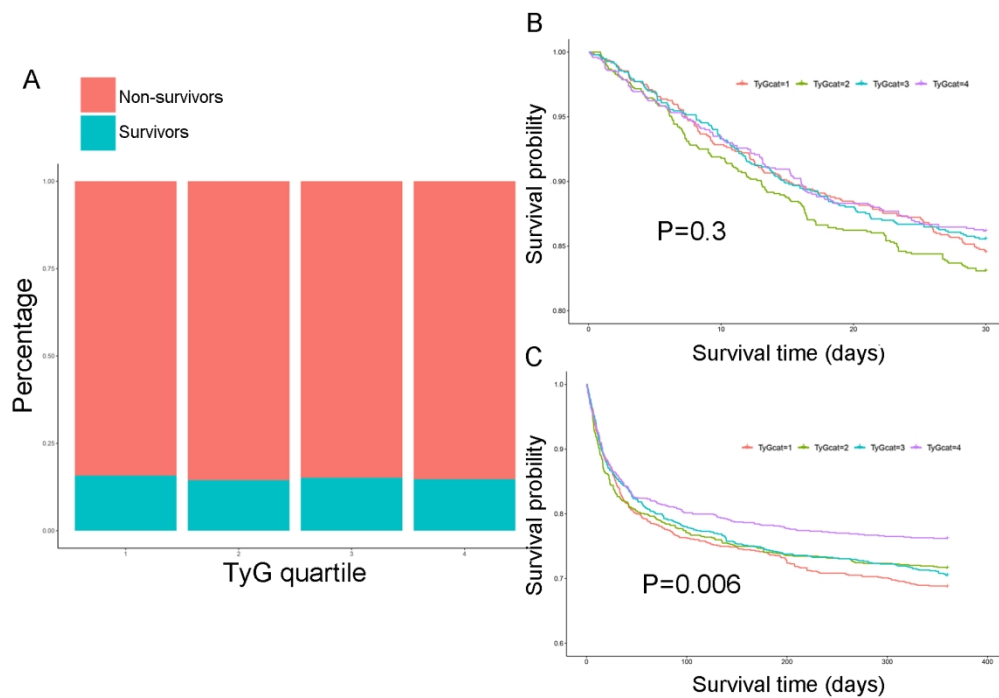


Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B),  $P < 0.05$ : Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C),  $P < 0.05$ : Q1 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4.

160x115mm (300 x 300 DPI)

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
	5	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	5
		(e) Describe any sensitivity analyses	5

Continued on next page

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	6
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

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

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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Epidemiology
Keywords:	DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

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4 1 **Association between TyG index and long-term mortality of critically ill patients:**  
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6 2 **a retrospective study based on the MIMIC database**  
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10 4 Lingli Dai<sup>1</sup>, Yun Yu<sup>1</sup>, Kunlin Wang<sup>1</sup>, Cuining Hu<sup>1</sup>, Dan Wu<sup>1</sup>, Shan Shan<sup>1\*</sup>  
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4 28 **Abstract**

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6 29 **Objective** To evaluate the association of triglycerides glucose (TyG) index on admission with  
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9 30 outcomes of critically ill patients.

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11 31 **Design** A retrospective study.

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14 32 **Setting** A population-based cohort study of Medical Information Mart for Intensive Care III  
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17 33 database (MIMIC III).

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19 34 **Participants:** All intensive care unit (ICU) admissions were extracted from MIMIC III.

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22 35 **Main outcome measures** The TyG index was calculated as  $\ln$  [triglycerides (mg/dL) \*glucose  
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25 36 (mg/dL)/2]. The primary endpoint was 360-day mortality.

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27 37 **Results** A total of 3902 patients with an average age of  $63.1 \pm 15.9$  years old were enrolled, including  
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30 38 1623 (41.6%) females. The 360-day mortality was lower in a higher TyG group. Compared with the  
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33 39 lowest TyG group, the hazards ratio of 360-day mortality was 0.79 (95% confidence interval [0.66,  
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35 40 0.95];  $p=0.011$ ) in the fully adjusted Cox model and 0.71 ([0.59, 0.85];  $p<0.001$ ) in the stepwise  
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38 41 Cox model. In the subgroup analysis, an interaction effect was detected between TyG index and  
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41 42 gender.

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43 43 **Conclusions** A lower TyG index was associated with the risk of 360-day mortality in critically ill  
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46 44 patients, which could be a predictor of long-term survival of critically ill patients.

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48 45 **Keywords:** TyG index; mortality; ICU; critically illness; cohort study  
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53 47 **Strengths and limitations of this study**

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56 48 To the best of our knowledge, this is the first study assessing the association between TyG index  
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59 49 and long-term mortality of critically ill patients.  
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## 72 **Introduction**

73 The triglyceride glucose (TyG) index is calculated using fasting triglyceride and fasting glucose  
74 measurements. It has been suggested as a surrogate marker of insulin resistance (IR)<sup>1,2</sup> and has been  
75 found associated to bladder cancer that is widespread among men<sup>3</sup>. Critical illness is characterized  
76 by a hypermetabolic state associated with increased mortality due to enhanced IR<sup>4,5</sup>.

77 Several studies have examined the associations between IR and mortality in critically ill patients.  
78 Nathan found that IR was a predictor for mortality in traumatic brain injury<sup>6</sup> and increased the  
79 mortality of surgical care population<sup>7</sup>. Recently, a study concluded that the TyG index was a  
80 potential predictor for hospital and ICU mortality in critically ill stroke patients<sup>8</sup>. To the best of our  
81 knowledge, there is no research to evaluate the association of TyG index on intensive care unit  
82 (ICU) admission with long-term outcomes of critically ill patients.

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

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## 94 **Materials and methods**

### 95 **Participants**

96 This was a retrospective cohort study using data from the MIMIC database, which is a large publicly  
97 available database consisting of patients in the ICU of Beth Israel Deaconess Medical Center  
98 between 2001 and 2012. The database was approved from the institutional review boards of both  
99 Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates.  
100 Adult patients of first hospital and ICU admission with complete triglycerides and glucose records  
101 were included, but patients staying at ICU for < 24 hours were excluded. The selection process was  
102 shown in **Figure 1**. Our study was approved by the Review Boards of Jiangsu Province Official  
103 Hospital (201921A011).

### 104 **Variables**

105 We used PostgreSQL 13 to extract data from the database. The baseline characteristics within the  
106 first 24 hours after ICU admission included the following: age, gender, ethnicity, weight, severity  
107 measured by Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology  
108 Score II (SAPS II) score, laboratory examination including white blood cell (WBC), platelet,  
109 potassium, sodium, triglycerides, and glucose, treatment including albumin infusion, mechanical  
110 ventilation, administration of vasopressors, and dialysis, comorbidities including coronary artery  
111 disease (CAD), hypertension (HBP), diabetes (DM), chronic obstructive pulmonary disease  
112 (COPD), and chronic kidney disease (CKD) as well as the length of stay (LOS) in hospital and in  
113 ICU.

### 114 **Outcomes**

115 The primary exposure was the triglycerides and glucose (TyG) index, defined as In

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4 116 (triglycerides\*glucose/2). The outcomes of the present study were in-hospital mortality, 30-day  
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6 117 mortality and 360-day mortality.  
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### 9 118 **Statistical analysis**

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11 119 Continuous variables are expressed as the mean  $\pm$  standard deviation or median (interquartile range),  
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14 120 as appropriate, and categorical variables are shown as number (proportions). One way analysis of  
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17 121 variance and the  $\chi^2$  tests were used to compare the difference among groups. The Kaplan-Meier  
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19 122 analysis was used to explore the association between TyG quartile and 30-day mortality and 360-  
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22 123 day mortality. Multivariate modeling of the association between TyG index (as continuous and  
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25 124 categorical variables) and 360-day mortality was performed with Cox regression. Baseline variables  
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27 125 that were considered clinically relevant or associated with the TyG index ( $P < 0.05$ ) were entered  
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30 126 into a multivariate Cox regression model, while all baseline variables were entered into a stepwise  
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33 127 model. Subgroup analyses according to gender, age and mechanical ventilation were performed. All  
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35 128 statistical analysis was performed by R software version 3.6.

### 36 37 38 129 **Patient and public involvement**

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40 130 Patients and the public were not directly involved in the design or implementation of this study,  
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43 131 since we used previously collected data.  
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## 138 Results

139 The present study included 3902 patients admitted into ICU. The baseline characteristics of the  
140 study population according to TyG quartile were shown in the **Table 1**. Participants with a higher  
141 TyG index tended to have a higher weight, WBC, platelet and more percentage of DM and  
142 mechanical ventilation, as well as longer LOS in ICU and LOS in hospital (**Figure 2A&B**). In  
143 addition (**Figure 3A**), there was less 360-day mortality ( $P=0.002$ ) in a higher TyG group while no  
144 difference was observed in in-hospital mortality ( $P=0.866$ ), and 30-day mortality ( $P=0.244$ ).

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

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

154 Subgroup analysis (**Table 3**) showed that an interaction was observed between TyG index and  
155 gender ( $P=0.03$ ). In male patients, TyG was negative associated with 360-day mortality (HR 0.86,  
156 95% CI [0.78,0.95];  $P=0.004$ ) while the association was reversed in female subgroup (HR 1.03, 95%  
157 CI [0.91,1.16];  $P=0.681$ ).

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4 160 **Discussion**

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6 161 This is the first study to evaluate the association of the TyG index with long-term mortality in  
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9 162 critically ill patients. We found that TyG index was negatively associated with 360-day mortality,  
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12 163 not in-hospital or 30-day mortality of critically ill patients.

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14 164 The TyG index has been well-recognized as a simple and reliable surrogate of IR<sup>9</sup>. It does not  
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17 165 require levels of insulin and may be applicable to all of the patients and healthy population. Several  
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20 166 studies reported that TyG index predicted outcomes in patients with acute coronary syndrome<sup>10</sup> and  
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23 167 ischemic stroke<sup>11</sup>. Only one study found that TyG index was linearly associated with short-term  
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26 168 mortality in ICU stroke after adjusting for confounding factors<sup>8</sup>. However, we did not find a positive  
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29 169 correlation between TyG index and in-hospital and 30-day mortality. Contrary, we demonstrated  
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32 170 that TyG could be a protective predictor in long-term mortality in critically ill patients. The  
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35 171 difference could be that we included more diseases in ICU and followed a longer time. Besides, a  
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38 172 higher TyG index may be related to a good nutrition status and be compensatory for the development  
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41 173 of various diseases.

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43 174 The mechanism underlying the relationship between the TyG index and critically illness is not fully  
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46 175 elucidated. Insulin resistance is an adaptive mechanism that prioritizes utilization of energy for  
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49 176 immune response in the presence of infection or injury<sup>12</sup>. However, the underlying molecular  
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52 177 mechanisms involved in this association should be further investigated in the future study.

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54 178 Our study still has some limitations. First, this was a retrospective analysis derived from an  
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57 179 observational study, which could not definitively establish causality. Secondly, we only included  
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60 180 the baseline levels of plasma glucose and triglyceride, which could be affected by the use of  
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183 181 antidiabetic and lipid-lowering drugs. Therefore, it is unknown whether the change of the TyG index

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4 182 could predict the mortality.  
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6 183 **Conclusions**  
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9 184 We found that TyG index predicted a better long-term prognosis of critically ill patients, regardless  
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11 185 of other risk factors. However, no association was observed in respect to in-hospital or 30-day  
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13 186 mortality.  
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19 188 **Declarations**  
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21  
22 189 **Ethics approval and consent to participate**  
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24 190 The protocol was approved by the Institutional Review Board of both Beth Israel Deaconess  
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26 191 Medical Center and Massachusetts Institute of Technology Affiliates and no new data was added.  
27

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29 192 All methods were carried out in accordance with Helsinki regulations. The need for informed  
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31 193 consent was waived off by the Institutional Review Board of both Beth Israel Deaconess Medical  
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33 194 Center and Massachusetts Institute of Technology Affiliates. Our study was approved by the Review  
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35 195 Boards of Jiangsu Province Official Hospital (201921A011).  
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39 196 **Consent for publication**  
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41 197 Yes.  
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44 198 **Availability of data and materials**  
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47 199 The datasets used during the current study available from the corresponding author on reasonable  
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49 200 request.  
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51  
52 201 **Competing interests**  
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54  
55 202 The authors have nothing to disclose regarding conflict of interest with respect to this manuscript.  
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58 203 **Funding**  
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4 204 None.

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6 205 **Authors' contributions**

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9 206 D LL and Y Y made the statistical analysis; W KL and H CN wrote the original manuscript; S S  
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12 207 and W D designed the study. All authors approved it.

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14 208 **Acknowledgements**

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22 211 **References**

- 23  
24 212 1. Guerrero-Romero F, Villalobos-Molina R, Jimenez-Flores JR, et al. Fasting Triglycerides and  
25 213 Glucose Index as a Diagnostic Test for Insulin Resistance in Young Adults. *Arch Med Res.*  
26 214 2016;47(5):382-387. doi: 10.1016/j.arcmed.2016.08.012  
27  
28 215 2. Vasques AC, Novaes FS, de Oliveira Mda S, et al. TyG index performs better than HOMA in a  
29 216 Brazilian population: a hyperglycemic clamp validated study. *Diabetes Res Clin Pract.* 2011;93(3):e98-  
30 217 e100. doi: 10.1016/j.diabres.2011.05.030  
31  
32 218 3. Tarantino G, Crocetto F, Di Vito C, et al. Association of NAFLD and Insulin Resistance with Non  
33 219 Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. *J Clin Med.* 2021;10(2)doi:  
34 220 10.3390/jcm10020346  
35  
36 221 4. Zauner A, Nimmerrichter P, Anderwald C, et al. Severity of insulin resistance in critically ill  
37 222 medical patients. *Metabolism.* 2007;56(1):1-5. doi: 10.1016/j.metabol.2006.08.014  
38  
39 223 5. Saberi F, Heyland D, Lam M, et al. Prevalence, incidence, and clinical resolution of insulin  
40 224 resistance in critically ill patients: an observational study. *JPEN J Parenter Enteral Nutr.*  
41 225 2008;32(3):227-35. doi: 10.1177/0148607108316195  
42  
43 226 6. Mowery NT, Gunter OL, Guillaumondegui O, et al. Stress insulin resistance is a marker for mortality  
44 227 in traumatic brain injury. *J Trauma.* 2009;66(1):145-51; discussion 151-3. doi:  
45 228 10.1097/TA.0b013e3181938c5e  
46  
47 229 7. Mowery NT, May AK, Collier BC, et al. Glucose metabolism, not obesity, predicts mortality in  
48 230 critically ill surgical patients. *Am Surg.* 2010;76(12):1377-83.  
49  
50 231 8. Zhang B, Liu L, Ruan H, et al. Triglyceride-Glucose Index Linked to Hospital Mortality in  
51 232 Critically Ill Stroke: An Observational Multicentre Study on eICU Database. *Front Med (Lausanne).*  
52 233 2020;7:591036. doi: 10.3389/fmed.2020.591036  
53  
54 234 9. Du T, Yuan G, Zhang M, et al. Clinical usefulness of lipid ratios, visceral adiposity indicators, and  
55 235 the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol.*  
56 236 2014;13:146. doi: 10.1186/s12933-014-0146-3  
57  
58 237 10. Ma X, Dong L, Shao Q, et al. Triglyceride glucose index for predicting cardiovascular outcomes  
59 238 after percutaneous coronary intervention in patients with type 2 diabetes mellitus and acute coronary  
60 239 syndrome. *Cardiovasc Diabetol.* 2020;19(1):31. doi: 10.1186/s12933-020-01006-7



- 1  
2  
3 240 11. Shi W, Xing L, Jing L, et al. Value of triglyceride-glucose index for the estimation of ischemic  
4 241 stroke risk: Insights from a general population. *Nutr Metab Cardiovasc Dis.* 2020;30(2):245-253. doi:  
5 242 10.1016/j.numecd.2019.09.015  
6  
7 243 12. Dhar A, Castillo L. Insulin resistance in critical illness. *Curr Opin Pediatr.* 2011;23(3):269-74. doi:  
8 244 10.1097/MOP.0b013e3283464b3e  
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284 **Table 1. Baseline characteristics across the quartile of TyG index.**

Variables	Q1 (n=963)	Q2 (n=987)	Q3 (n=969)	Q4 (n=983)	P
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 <sup>9</sup> /L	10.94 (6.14)	11.76 (5.59)	11.86 (6.54)	12.72 (9.96)	<0.001
Platelet, 10 <sup>9</sup> /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

285 Q1: TyG<8.51, Q2: 8.51≤TyG<8.95, Q3: 8.95≤TyG<9.44, Q4: TyG≥9.44. CAD, coronary artery diseases; HBP,  
 286 hypertension; DM, diabetes mellites; COPD, chronic obstructive pulmonary diseases; CKD, chronic kidney disease;  
 287 SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; WBC, white blood  
 288 cell; LOS, length of stay.

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291 **Table 2. Multivariable Cox regression analyzing TyG index and 360-day mortality.**

	Cases	N	Unadjusted		Adjusted <sup>#</sup>		Stepwise*	
			HR	P	HR	P	HR	P
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

292 <sup>#</sup> Adjusted for age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPSII score, WBC, platelet,  
 293 creatine, ventilation, vasopressors, and dialysis.

294 <sup>\*</sup>All variables except for outcomes were entered.

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

	HR	P for trend	P for interaction
<b>Gender</b>			0.03
female	1.03 [0.91, 1.16]	0.681	
male	0.86 [0.78, 0.95]	0.004	
<b>Age</b>			0.13
≤65	0.83 [0.73, 0.94]	0.003	
>65	0.96 [0.87, 1.07]	0.472	
<b>Ventilation</b>			0.357
No	1.01 [0.87, 1.17]	0.868	
Yes	0.91 [0.83, 1.00]	0.057	

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4 328 **Figure legends**  
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6 329 **Figure 1.** The flow diagram of study population.  
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9 330 **Figure 2.** The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.  
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11 331 **Figure 3.** The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day  
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14 332 mortality (B), P <0.05: Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C), P<0.05: Q1  
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17 333 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4.  
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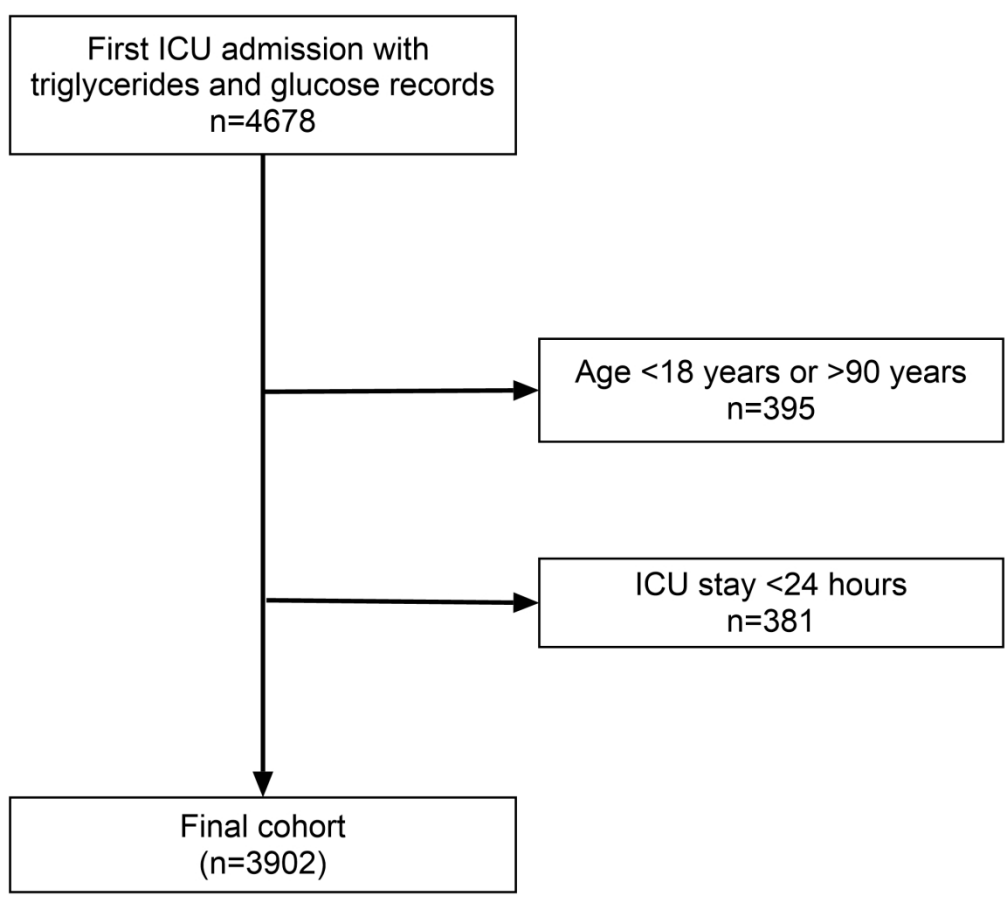


Figure 1. The flow diagram of study population.

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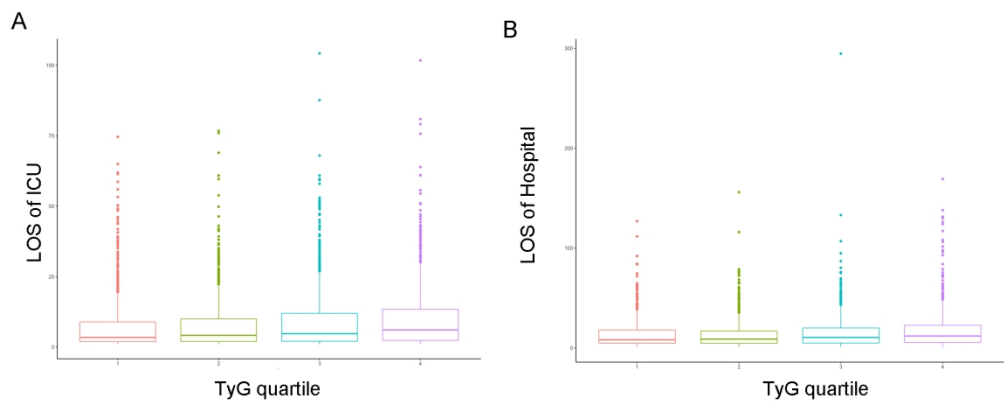


Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

180x76mm (300 x 300 DPI)

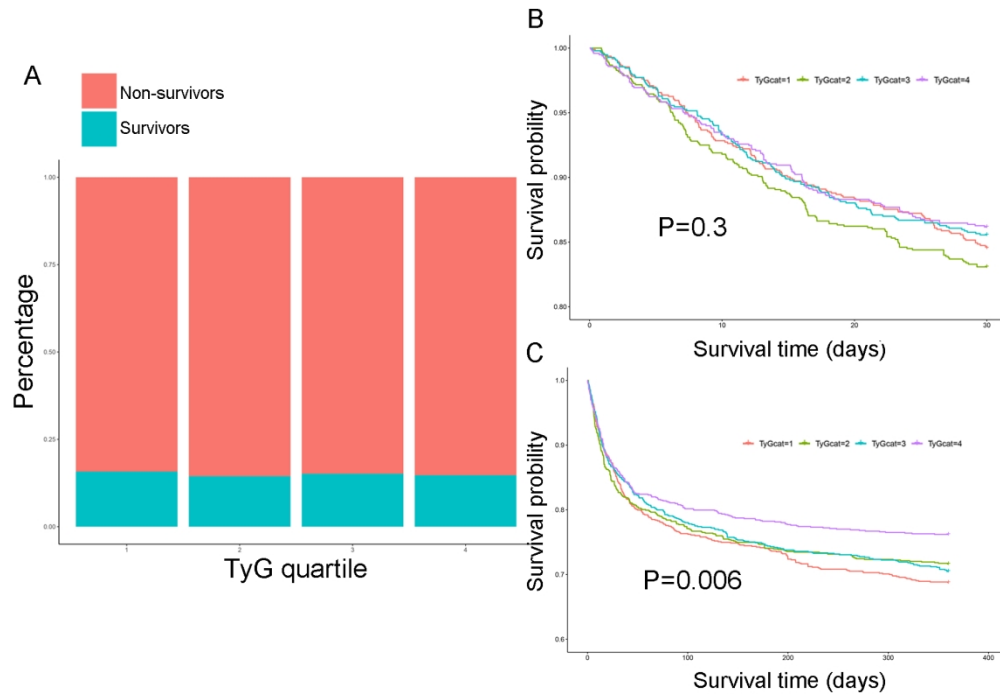


Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B),  $P < 0.05$ : Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C),  $P < 0.05$ : Q1 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4.

160x115mm (300 x 300 DPI)



## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
	5	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	5
		(e) Describe any sensitivity analyses	5

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<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	6
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).