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Elevated Triglyceride-Glucose (TyG) Index Predicts Poor Clinical Outcomes in Critically Ill AECOPD Patients: A Retrospective Study

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Purpose: The triglyceride-glucose (TyG) index is a surrogate biomarker of insulin resistance which has been widely used in intensive care unit (ICU) to predict prognosis. However, its role in critically ill acute exacerbation of COPD (AECOPD) patients remains largely unknown.

Material and methods: A total of 645 AECOPD patients were induced in this retrospective cohort study, which extracted data from the eICU Collaborative Research Database (eICU-CRD). The TyG index was calculated as Ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2). The primary endpoint includes in-hospital mortality and ICU mortality. The secondary endpoint was sepsis, acute kidney injury (AKI), and acute respiratory failure (ARF).

Results: Multivariable Cox regression analysis revealed that the TyG index was independently associated with an increased risk of in-hospital mortality (hazard ratio, HR: 1.45, 95% CI: 1.04–2.01, $P = 0.028$) and ICU mortality (HR: 2.13, 95% CI: 1.28–3.54, $P = 0.004$). Moreover, the TyG index was independently associated with an increased risk of sepsis (odds ratio, OR: 1.54, 95% CI: 1.24–1.93, $P < 0.001$), AKI (OR: 1.57, 95% CI: 1.26–2.02, $P < 0.001$) and ARF (OR: 1.50, 95% CI: 1.20–1.87, $P < 0.001$). Kaplan–Meier survival analysis revealed that higher TyG indexes were also related to increased in-hospital mortality and ICU mortality. In addition, the restricted cubic splines regression model demonstrated that the in-hospital mortality and ICU mortality increased linearly with increasing TyG index (P for non-linearity = 0.897, P for non-linearity = 0.897, respectively).

Conclusion: Elevated TyG index was independently associated with an increased risk of poor clinical outcomes in critically ill AECOPD patients. A prospective study to define TyG as a biomarker for prognosis prediction in critically ill AECOPD patients is warranted.

Keywords: triglyceride-glucose index, AECOPD, mortality, eICU-CRD database

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by expiratory airflow limitation that is not fully reversible, deregulated chronic inflammation, and emphysematous destruction of the lungs, which has a high mortality worldwide and is the fifth leading cause, COPD is caused by exposure to inhaled noxious particles, notably tobacco smoke and pollutants. Its incidence rate is about 12%, and 3 million deaths annually due to COPD.[1,2] The important causes of exacerbations include airway bacteria, viruses, and pollution; frequent acute exacerbation of COPD (AECOPD) is strongly associated with higher mortality, accelerates the deterioration in lung function, and lowers the quality of life of the patient. AECOPD is a major health issue that leads to hospitalization of patients, as it affects disease outcomes and household expenses. It was reported that the 1-year mortality rate of AECOPD patients is about 25%.[3,4] Under certain conditions, AECOPD can lead to acute respiratory failure, leading to rapid deterioration of the condition, requiring

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tracheal intubation and invasive mechanical ventilation, which consume large ICU resources. Due to these reasons, severe AECOPD causing acute or acute chronic respiratory failure typically requires ICU admission, where the clinical course may be complicated by concurrent multiple organ dysfunction, which has a high mortality.[5,6] The mortality in AECOPD patients admitted to the ICU was extremely high, particularly those who require invasive mechanical ventilation.One study found mortality rates AECOPD patients admitted to the ICU at 6-months, 1-year, and 5-years from hospitalization of 39.0%, 42.7% and 75.9%, respectively.[7] The mortality rate for critically ill AECOPD patients remains high despite numerous attempts. Therefore, it is critical to determine the possible risk factors for critically ill AECOPD patients in order to potentially improve the prognosis of those high-risk patients.

Numerous studies are being conducted in a variety of illness settings to determine the prediction of the triglyceride glucose (TyG) index as a biomarker for the diagnosis of insulin resistance (IR). Recently, the TyG index was found to be a useful predictor to identify those at high risk in patients admitted to the ICU. Zheng et al intended to check the link between the TyG index and the risk of in-hospital mortality in critically ill patients with sepsis and concluded that a high TyG index is associated with increased in-hospital mortality in critically ill sepsis patients.[8] Another study tried to examine the role of the TyG index in predicting acute kidney injury (AKI) in ICU patients and found that the TyG index could predict AKI in ICU patients.[9] Moreover, TyG was also found to be a good predictor of one-year mortality and in-hospital mortality in ICU patients with cardiovascular diseases and chronic kidney disease (CKD).[10] In addition, Zaigham et al tried to evaluate TyG index as a potential risk marker for future incident COPD events in the general population, and the results indicated that after an average of 31 years of follow-up, TyG index was a strong predictor of future COPD events in women even after adjusting for potential confounders.[11] A recent study aimed to check the correlation between TyG index and all-cause mortality in critically ill patients with COPD and asthma and found that the TyG index is a potential predictor of all-cause mortality in critically ill patients with COPD and asthma, and in patients with a TyG index exceeding 4.8, there was a heightened risk of mortality.[12] However, the role of TyG index in predicting clinical outcomes in AECOPD patients admitted to ICU remains largely unknown.

In the present study, we aimed to undertake a retrospective cohort study based on the eICU Collaborative Research Database (eICU-CRD) to check the prognostic role of the TyG index in predicting clinical outcomes in AECOPD patients admitted to the ICU.

Methods

Study Population

This retrospective study utilized information from the eICU Collaborative Research Database (eICU-CRD).[13] The multi-center telehealth database known as the eICU-CRD has information on over 200,000 admissions to 335 ICUs at 208 hospitals across the United States between 2014 and 2015. One author (Tianyang Hu) complied with the requirements for access to the database and was responsible for the data extraction. Patients diagnosed with AECOPD were enrolled. AECOPD was defined according to the International Classification of Diseases (ICD) code. Patients with one of the following conditions were excluded: 1) less than 18 years old; 2) less than 24 hours of hospital stay; 3) patients with missing values of fasting blood glucose or triglyceride; 4) patients with repeated ICU admissions. The detailed flowchart was depicted in Figure 1. Finally, a total of 645 patients were enrolled in this study and grouped into four groups based on the quartiles of the TyG index. The multi-center telehealth database known as the eICU-CRD has information on over 200,000 admissions to 335 ICUs at 208 hospitals across the United States between 2014 and 2015. The study was carried out in accordance with the Helsinki Declaration, and this study was approved by the Ethics Committee of Second Affiliated Hospital of Chongqing Medical University without the need for informed consent from the participants.

Data Collection and Definitions

Baseline characteristics including demographics, ethnicity, vital signs, laboratory values, scoring systems, complications, comorbidities, drugs usage, length of hospital stay, and length of ICU stay were collected. All baseline characteristics were obtained within 24 hours after ICU admission. The detailed variables were exhibited in Table 1.

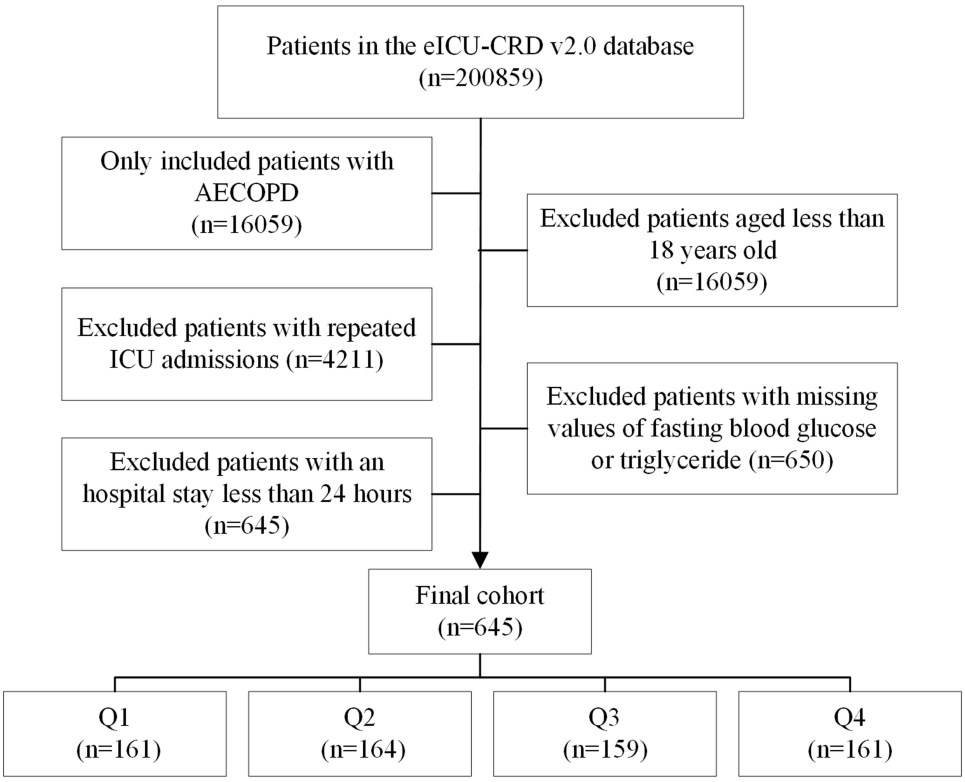

Figure 1 The flow chart of this study.

The TyG index was calculated according to previously reported Ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2).[14] Acute kidney injury (AKI) was diagnosed according to KDIGO-AKI criteria based on serum creatinine in the first 48 hours of their ICU admission.[15] The sepsis was defined according to Sepsis 3.0 including a patient with a suspected infection and a Sequential Organ Failure Assessment score (SOFA) score ≥2.[16] Acute respiratory failure (ARF) was defined as the decrease in oxygen saturation (<92%) in room air with severe respiratory distress or hypoxemia (partial oxygen pressure <60 mm Hg) and/or requirement of invasive/noninvasive mechanical ventilation.[17]

Table 1 Comparisons of Baseline Characteristics for All Patients

Characteristics	Overall	Q1 (7.10–8.49)	Q2 (8.50–8.94)	Q3 (8.95–9.47)	Q4 (9.48–11.2)	P value
N	645	161	164	159	161	
Age, years old	67.4 ± 10.9	69.1 ± 10.7	68.4 ± 11.2	66.9 ± 10.1	65.2 ± 11.3	0.006
Gender, male, n (%)	313 (48.5)	92 (57.1)	79 (48.2)	71 (44.7)	71 (44.1)	0.072
Body mass index, kg/m^2	29.8 ± 9.8	27.8 ± 9.6	28.3 ± 9.4	31.3 ± 10.0	31.9 ± 9.8	<0.001
Ethnicity, n (%)						0.188
White	485 (75.2)	109 (67.7)	131 (79.9)	125 (78.6)	120 (74.5)	
Black	121 (18.8)	41 (25.5)	25 (15.2)	26 (16.4)	29 (18.0)	
Others	39 (6.1)	11 (6.8)	8 (4.9)	8 (5.0)	12 (7.5)	
Comorbidity, n (%)						
Myocardial infarction	65 (10.1)	14 (8.7)	16 (9.8)	17 (10.7)	18 (11.2)	0.887
Congestive heart failure	176 (27.3)	47 (29.2)	38 (23.2)	47 (29.6)	44 (27.3)	0.550
Hypertension	117 (18.1)	29 (18.0)	27 (16.5)	33 (20.8)	28 (17.4)	0.776
Diabetes	183 (28.4)	47 (29.2)	46 (28.1)	40 (25.2)	50 (31.1)	0.696
Chronic kidney disease	71 (11.0)	18 (11.2)	20 (12.2)	18 (11.3)	15 (9.3)	0.867

(*Continued*)

Table 1 (Continued).

Characteristics	Overall	Q1 (7.10–8.49)	Q2 (8.50–8.94)	Q3 (8.95–9.47)	Q4 (9.48–11.2)	P value
Drugs usage, n (%)						
ACEI/ARB	166 (25.7)	42 (26.1)	47 (28.7)	39 (24.5)	38 (23.6)	0.690
β blockers	294 (45.6)	77 (47.8)	79 (48.2)	73 (45.9)	65 (40.4)	0.418
Statin	151 (23.4)	41 (25.5)	46 (28.0)	32 (20.1)	32 (19.9)	0.177
NSAID	285 (44.2)	81 (50.3)	79 (48.2)	61 (38.4)	64 (39.8)	0.041
PPI	229 (35.5)	54 (33.5)	58 (35.4)	54 (34.0)	63 (39.1)	0.701
Severity scores, points						
APACHE IV	59.1 ± 22.7	55.2 ± 20.9	56.1 ± 21.5	61.7 ± 23.0	63.6 ± 24.5	<0.001
SOFA	3.1 ± 1.7	2.6 ± 1.5	2.9 ± 1.9	3.4 ± 1.6	3.9 ± 1.7	0.002
OASIS	27.7 ± 10.0	19.8 ± 9.7	24.5 ± 10.6	28.0 ± 9.7	33.2 ± 10.0	0.008
APS III	45.7 ± 20.9	35.9 ± 19.7	43.8 ± 22.4	49.9 ± 20.1	57.9 ± 21.0	<0.001
Vital signs						
MAP, mmHg	94.0 ± 21.0	94.0 ± 20.2	93.0 ± 21.3	92.6 ± 19.6	96.3 ± 22.6	0.388
Heart rate, bpm	108.1 ± 20.5	108.7 ± 21.6	107.2 ± 21.2	108.3 ± 18.9	108.0 ± 20.4	0.931
SpO2, %	98.8 ± 1.6	98.8 ± 1.6	98.9 ± 1.5	98.7 ± 1.9	98.9 ± 1.4	0.854
Laboratory values						
WBC, × 10^9/L	11.6 ± 4.5	12.2 ± 5.2	11.2 ± 4.9	11.5 ± 4.2	11.5 ± 4.8	0.445
Hemoglobin, g/dL	11.7 ± 2.3	11.5 ± 2.3	11.9 ± 2.3	11.6 ± 2.3	11.9 ± 2.2	0.409
Platelet, × 10^9/L	229.9 ± 91.1	228.7 ± 92.2	222.6 ± 87.4	236.5 ± 91.6	232.1 ± 92.5	0.562
Albumin, g/dL	3.3 ± 0.5	3.3 ± 0.6	3.5 ± 0.5	3.3 ± 0.6	3.3 ± 0.5	0.715
Bilirubin, mmol/L	0.9 ± 0.4	0.9 ± 0.4	1.1 ± 0.5	0.7 ± 0.3	0.8 ± 0.3	0.222
Anion gap, mEq/L	11.8 ± 4.8	11.8 ± 5.0	11.6 ± 4.0	11.8 ± 4.9	11.7 ± 4.4	0.976
Bicarbonate, mEq/L	28.8 ± 6.7	28.5 ± 5.6	29.3 ± 6.6	29.7 ± 7.0	27.9 ± 7.2	0.027
Triglyceride, mg/dL	126.6 ± 46.4	65.9 ± 25.6	100.8 ± 42.1	127.0 ± 39.1	213.8 ± 68.2	<0.001
Glucose, mg/dL	165.2 ± 50.8	119.9 ± 36.4	140.6 ± 38.1	166.2 ± 50.0	234.8 ± 85.9	<0.001
TyG index	9.0 ± 0.7	8.1 ± 0.2	8.7 ± 0.1	9.2 ± 0.1	10.0 ± 0.4	<0.001
BUN, mg/dL	27.4 ± 8.3	28.9 ± 9.2	27.4 ± 9.3	25.5 ± 9.5	28.2 ± 10.5	0.386
Creatinine, mg/dL	1.1 ± 0.4	1.2 ± 0.5	1.2 ± 0.5	1.0 ± 0.4	1.1 ± 0.5	0.306
Potassium, mmol/L	4.4 ± 0.7	4.3 ± 0.7	4.3 ± 0.6	4.4 ± 0.6	4.5 ± 0.7	0.028
Sodium, mmol/L	137.3 ± 5.4	137.5 ± 5.6	136.8 ± 6.3	137.9 ± 4.4	137.8 ± 5.0	0.311
Primary outcomes						
Hospital LOS, days	8.2 (4.8, 13.7)	6.9 (4.1, 11.1)	8.3 (4.5, 14.9)	9.5 (5.5, 16.7)	8.8 (5.4, 13.1)	0.007
ICU LOS, days	3.5 (1.7, 7.6)	2.7 (1.3, 5.6)	3.0 (1.4, 7.6)	4.0 (1.9, 7.0)	5.0 (2.8, 8.7)	<0.001
In-hospital death, n (%)	69 (10.7)	11 (6.8)	14 (8.5)	17 (10.7)	27 (16.8)	0.023
ICU death, n (%)	27 (4.2)	4 (2.5)	1 (0.6)	6 (3.8)	16 (9.9)	<0.001
Other clinical outcomes						
Sepsis	246 (38.1)	53 (32.9)	50 (30.5)	61 (38.4)	82 (50.9)	<0.001
AKI, n (%)	258 (40.0)	52 (32.3)	56 (34.2)	67 (42.1)	83 (51.6)	0.001
ARF, n (%)	367 (56.9)	77 (47.8)	84 (51.2)	94 (59.1)	112 (69.6)	<0.001

Abbreviations:: ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker, NSAID, non-steroidal anti-inflammatory drugs, PPI, proton pump inhibitors, APACHE IV, acute physiology and chronic health evaluation IV, SOFA, sequential organ failure assessment, OASIS, oxford acute severity of illness score, APSIII, acute physiology score III, MAP, mean arterial pressure, WBC, white blood cell, TyG, index, triglyceride-glucose index, BUN, blood urea nitrogen, LOS, length of stay, ICU, intensive care unit, AKI, acute kidney injury, ARF, acute respiratory failure.

Endpoints

The primary endpoint includes in-hospital mortality and ICU mortality. The secondary endpoint was sepsis, AKI, and ARF. All of the endpoints occurred after admitting to the ICU.

Statistical Analysis

Based on the quartiles (Q1-Q4) of the TyG index, study participants were divided into four groups. Whereas frequency and percentage were used to represent categorical variables, mean and standard deviation (SD) were used to summarize

continuous variables. For continuous factors, one-way ANOVA was used, and for categorical data, the Pearson chi-square test was employed to compare baseline characteristics between TyG quartile groups.

Kaplan–Meier survival analysis was used to assess the incidence rate of endpoints among groups based on different levels of the TyG index and compared using the Log rank test. A restricted cubic spline regression analysis was also used to examine the nonlinear relationship between baseline TyG index and ICU and in-hospital mortality. Multivariate Cox regression analyses were carried out to assess the relationship between the TyG index and the risk of primary endpoints. To assess the impact of the TyG index on the primary endpoint, the hazard ratio (HR) and the 95% confidence intervals (CIs) were calculated to quantify. Multivariate logistic regression analyses were performed to assess the relationship between TyG index and the risk of secondary endpoint. To assess the impact of the TyG index on the secondary endpoint, odds ratios (ORs) and the 95% confidence intervals (CIs) were calculated to quantify. Subgroup analysis was exhibited by the forest plot. And clinically relevant and prognosis-associated variables were also enrolled in the multivariate model: model 1: unadjusted; model 2: adjusted for age, gender, and ethnicity; model 3: adjusted for age, gender, and ethnicity, comorbidity, and severity scores.

The predictive abilities for clinical outcomes with several severity scores were then analyzed by receiver operating characteristic (ROC) curves. The significance of TyG index in endpoint prediction was assessed by the use of the likelihood ratio test of nested models.

All analyses were performed in R software (version 4.1.0). $P < 0.05$ was used to indicate a statistically significant difference on either side.

Results

Baseline Characteristics

Finally, a total of 645 AECOPD patients were induced in this retrospective cohort study. Table 1 exhibited the baseline characteristics. Finally, included AECOPD patients were grouped into four groups stratified by quartiles of the TyG index (Q1: 7.10–8.49; Q2: 8.50–8.94; Q3: 8.95–9.47; Q4: 9.48–11.2). Compared to the lowest quartile of TyG index, patients in the highest quartile of TyG index were younger, had higher body mass index, and had higher severity scores including acute physiology and chronic health evaluation IV (APACHE IV), sequential organ failure assessment (SOFA), oxford acute severity of illness score (OASIS), acute physiology score III (APSIII), higher bicarbonate, triglyceride, glucose, triglyceride, TyG index, potassium and length of ICU stay (all $P < 0.05$, Table 1). Moreover, compared to the lowest quartile of TyG index, patients in the highest quartile of TyG index had a higher proportion of in-hospital mortality, ICU mortality, sepsis, AKI and ARF (all $P < 0.05$, Table 1).

TyG Index and in-Hospital Mortality and ICU Mortality

Multivariable Cox regression analysis revealed that TyG index was independently associated with an increased risk of in-hospital mortality (HR: 1.45, 95% CI: 1.04–2.01, $P = 0.028$, Table 2) and ICU mortality (HR: 2.13, 95% CI: 1.28–3.54, $P = 0.004$, Table 2). The results were further verified in the fully adjusted model 3, compared to the lowest tertile, patients in the highest TyG index tertile were significantly associated with increased risk of in-hospital mortality (HR: 3.08, 95% CI: 1.27–7.44, $P = 0.013$, Table 2) and ICU mortality (HR: 3.51, 95% CI: 1.23–16.78, $P = 0.026$, Table 2). Moreover, the risk of in-hospital mortality and ICU mortality indicated a consistent upward trend with increasing TyG index tertiles, with all trend p-values below 0.05 (Table 2). In addition, data were divided into two groups according to 75th percentile of TyG index (9.47) including high-TyG index group (>9.47) and low-TyG index group (≤9.47). And we found the high-TyG index group (>9.47) was significantly associated with increased risk of in-hospital mortality and ICU mortality compared to low-TyG index group (≤9.47) (Table 2). Kaplan–Meier survival analysis curves were applied to analyze the association between in-hospital mortality and ICU mortality among different TyG index groups, and the results demonstrated that patients in the highest TyG index tertiles exhibited the highest risk of in-hospital mortality and ICU mortality (Figure 2A and B). In addition, data were divided into two groups according to 75th percentile of TyG index (9.47) including high-TyG index group (>9.47) and low-TyG index group (≤9.47). And we found the high-TyG

Table 2 The Association Between TyG Index and In-Hospital and ICU Mortality

Exposure	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
In-hospital mortality						
TyG as continuous	1.45 (1.04–2.01)	0.028	1.69 (1.21–2.36)	0.002	1.48 (1.04–2.12)	0.031
Q1	Ref.		Ref.		Ref.	
Q2	1.60 (0.65–3.92)	0.308	1.69 (0.69–4.16)	0.253	1.66 (0.67–4.19)	0.282
Q3	1.76 (0.7404.20)	0.200	2.35 (0.98–5.63)	0.056	2.33 (0.96–5.69)	0.062
Q4	2.83 (1.83–6.51)	<0.001	4.03 (1.72–9.44)	0.001	3.44 (1.42–8.33)	0.006
P for trend	0.001		0.004		0.033	
High TyG index[1]	1.87 (1.15–3.03)	0.012	2.30 (1.39–3.80)	0.001	1.94 (1.13–3.32)	0.016
ICU mortality						
TyG as continuous	2.13 (1.28–3.54)	0.004	2.10 (1.54–2.97)	<0.001	1.84 (1.41–3.02)	<0.001
Q1	Ref.		Ref.		Ref.	
Q2	0.76 (0.11–5.41)	0.786	0.82 (0.12–5.80)	0.838	0.74 (0.19–5.59)	0.768
Q3	2.33 (0.48–8.24)	0.292	1.32 (0.68–9.27)	0.138	1.91 (0.67–13.97)	0.094
Q4	4.08 (1.53–9.58)	0.006	3.54 (1.69–10.79)	0.008	3.27 (1.76–11.35)	0.009
P for trend	0.001		0.002		0.004	
High TyG index[1]	3.10 (1.44–6.70)	0.004	4.37 (1.97–9.71)	<0.001	4.15 (1.78–9.68)	0.001

Notes: TyG, triglyceride-glucose index, ICU, intensive care unit, HR, hazard ratio, 95% CI, 95% confidence index, Model 1 was unadjusted, model 2 adjusted for age, gender, body mass index, ethnicity. Model 3 adjusted for model 2 plus comorbidity, drug usage, and severity scores. [1]High TyG index means that the cut-off value for TyG was 9.47, the 75th of TyG index.

index group (>9.47) was significantly associated with increased risk of in-hospital mortality (Supplemental Figure 1A) and ICU mortality (Supplemental Figure 1B) compared to low-TyG index group (≤9.47).

In addition, the restricted cubic splines regression model was used to demonstrate the risk of in-hospital mortality and ICU mortality increased linearly with increasing TyG index (P for non-linearity = 0.897, P for non-linearity = 0.897, respectively, Figure 3A and B).

The severity scores including APACHE IV, SOFA, OASIS and APSIII scores were commonly used in the ICU condition to predict clinical outcomes. These severity scores exhibited predictive abilities of in-hospital mortality and ICU mortality (Table 3). And adding TyG index to these severity scores improved the predictive ability of in-hospital mortality and ICU mortality, as reflected by increased AUC (Table 3).

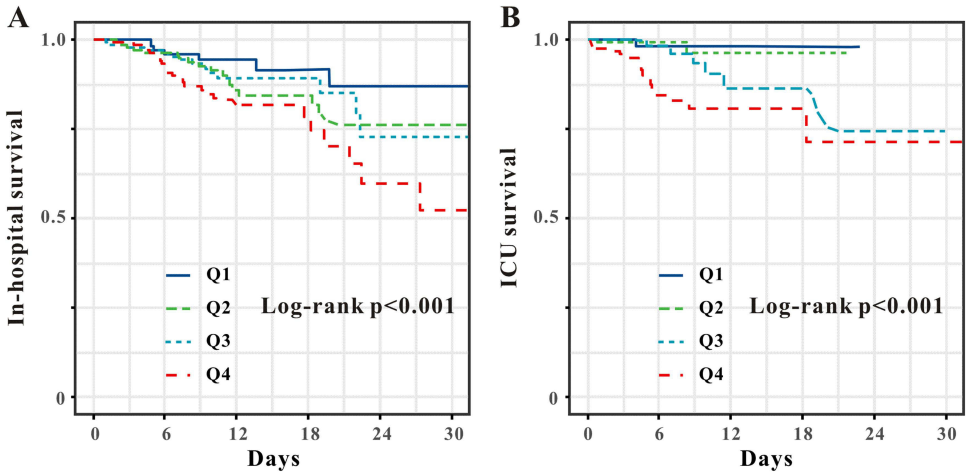

Figure 2 Kaplan-Meier survival analysis curves of the quartile of TyG index for in-hospital mortality (**A**) and ICU mortality (**B**). TyG index, triglyceride-glucose index, ICU, intensive care unit.

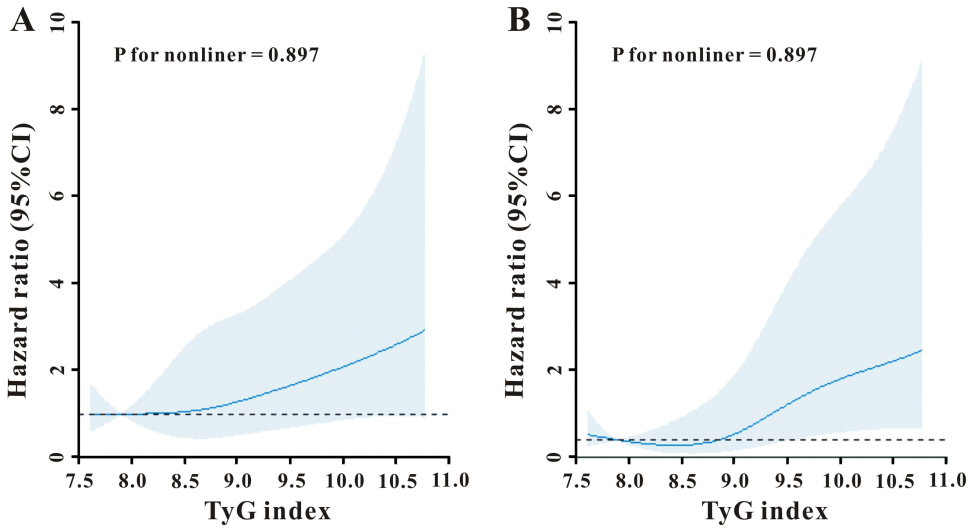

Figure 3 Restricted cubic spline curve for (**A**) in-hospital mortality and (**B**) ICU mortality. CI, confidence interval; TyG index, triglyceride-glucose index, ICU, intensive care unit.

TyG Index and Sepsis, AKI and ARF

Except for the primary outcomes, we then tried to evaluate the predictive ability of the TyG index for the prediction of secondary endpoints including sepsis, AKI and ARF. Multivariable logistic regression analysis demonstrated that TyG index was independently associated with an increased risk of sepsis (OR: 1.54, 95% CI: 1.24–1.93, $P < 0.001$, Table 4), AKI (OR: 1.57, 95% CI: 1.26–2.02, $P < 0.001$, Table 4) and ARF (OR: 1.50, 95% CI: 1.20–1.87, $P < 0.001$, Table 4). The results were further verified in the fully adjusted model 3, and compared to the lowest tertile, patients in the highest TyG index tertile were significantly associated with increased risk of sepsis (OR: 2.18, 95% CI: 1.34–3.55, $P < 0.001$, Table 4), AKI (OR: 1.93, 95% CI: 1.19–3.13, $P = 0.008$, Table 4) and ARF (OR: 2.48, 95% CI: 1.53–4.03, $P < 0.001$, Table 4). Moreover, the risk of sepsis, AKI and ARF indicated a consistent upward trend with increasing TyG index tertiles, with all trend p-values below 0.05 (Table 4). In addition, data were divided into two groups according to 75th percentile of TyG index (9.47) including high-TyG index group (>9.47) and low-TyG index group (≤9.47). And we found the high-TyG index group (>9.47) was significantly associated with increased risk of sepsis, AKI and ARF compared to low-TyG index group (≤9.47) (Table 4).

Subgroup Analysis

Moreover, to verify the association between TyG index and primary outcomes and secondary outcomes, subgroup analyses were conducted based on age, gender, ethnicity, myocardial infarction, CHF, hypertension, diabetes mellitus and CKD. The TyG index was significantly associated with higher risk of in-hospital mortality in subgroups of male (HR: 1.79, 95% CI: 1.13–2.81, Figure 4A), those age >65 years (HR: 1.73, 95% CI: 1.21–2.47, Figure 4A), those white people (HR: 1.61, 95% CI: 1.11–2.35, Figure 4A), those without myocardial infarction (HR: 1.50, 95% CI: 1.07–2.12, Figure 4A), those with CHF (HR: 1.69, 95% CI: 1.05–2.74, Figure 4A), those without hypertension (HR: 1.62, 95% CI: 1.13–2.32, Figure 4A), those without diabetes mellitus (HR: 1.49, 95% CI: 1.01–2.18, Figure 4A) and those with CKD (HR: 4.28, 95% CI: 1.56–11.73, Figure 4). Similar results were obtained in subgroup analyses of the TyG index and ICU mortality (Figure 4B), secondary endpoints including sepsis, AKI and ARF (Figure 5A–C).

Discussion

To the best of our knowledge, this is the first study to explore the association between the TyG index and the clinical outcomes of AECOPD admitted to ICU. In the present study, we provided evidence that the TyG index was independently associated with in-hospital mortality and ICU mortality, meanwhile, elevated TyG index was linked to increased risk of sepsis, AKI and ARF. This correlation remained robust, even after adjusting for several clinical and laboratory characteristics.

Table 3 Discrimination of Each Predictive Model for the Outcomes Using AUC

Models	AUC (95% CI)	P value	Models	AUC (95% CI)	P value
In-hospital mortality					
APACHE IV score	0.715 (0.650–0.781)	<0.001	+ TyG index	0.748 (0.690–0.803)	<0.001
SOFA score	0.524 (0.454–0.594)	0.516	+ TyG index	0.649 (0.574–0.715)	<0.001
OASIS score	0.513 (0.430–0.582)	0.718	+ TyG index	0.646 (0.568–0.713)	<0.001
APSIII score	0.500 (0.430–0.570)	0.999	+ TyG index	0.647 (0.568–0.715)	<0.001
ICU mortality					
APACHE IV score	0.755 (0.671–0.839)	<0.001	+ TyG index	0.809 (0.737–0.881)	<0.001
SOFA score	0.526 (0.390–0.576)	0.652	+ TyG index	0.717 (0.621–0.813)	<0.001
OASIS score	0.517 (0.424–0.610)	0.763	+ TyG index	0.730 (0.646–0.813)	<0.001
APSIII score	0.581 (0.467–0.695)	0.155	+ TyG index	0.748 (0.664–0.833)	<0.001

Notes: AUC, area under curve, 95% CI, 95% confidence index, APACHE IV, acute physiology and chronic health evaluation IV, SOFA, sequential organ failure assessment, OASIS, oxford acute severity of illness score, APSIII, acute physiology score III, TyG, index triglyceride-glucose index.

Table 4 The Association Between TyG Index and Other Clinical Outcomes

Exposure	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sepsis						
TyG as continuous	1.54 (1.24–1.93)	<0.001	1.65 (1.31–2.07)	<0.001	1.51 (1.19–1.93)	0.001
Q1	Ref.		Ref.		Ref.	
Q2	0.96 (0.60–1.54)	0.879	1.02 (0.63–1.64)	0.952	0.95 (0.58–1.55)	0.834
Q3	1.31 (0.83–2.08)	0.246	1.44 (0.90–2.30)	0.132	1.25 (0.77–2.04)	0.370
Q4	2.20 (1.40–3.46)	<0.001	2.50 (1.56–4.00)	<0.001	2.17 (1.33–3.55)	0.002
P for trend	0.001		<0.001		0.003	
High TyG index[1]	2.03 (1.41–2.91)	<0.001	2.18 (1.50–3.16)	<0.001	2.03 (1.38–2.99)	<0.001
Acute kidney injury						
TyG as continuous	1.57 (1.26–2.02)	<0.001	1.56 (1.24–1.96)	<0.001	1.45 (1.14–1.84)	0.003
Q1	Ref.		Ref.		Ref.	
Q2	1.11 (0.70–1.76)	0.664	1.13 (0.70–1.80)	0.619	1.08 (0.66–1.75)	0.765
Q3	1.53 (0.97–2.42)	0.067	1.49 (0.93–2.38)	0.094	1.32 (0.81–2.15)	0.264
Q4	2.25 (1.43–3.55)	<0.001	2.24 (1.40–3.58)	0.001	1.99 (1.22–3.24)	0.006
P for trend	0.002		0.003		0.024	
High TyG index[1]	1.88 (1.31–2.69)	0.001	1.86 (1.29–2.69)	0.001	1.75 (1.19–2.57)	0.004
ARF						
TyG as continuous	1.50 (1.20–1.87)	<0.001	1.60 (1.27–2.02)	<0.001	1.51 (1.19–1.92)	0.001
Q1	Ref.		Ref.		Ref.	
Q2	1.11 (0.71–1.71)	0.655	1.15 (0.74–1.79)	0.533	1.12 (0.70–1.74)	0.658
Q3	1.51 (0.97–2.35)	0.067	1.67 (1.06–2.62)	0.026	1.53 (0.96–2.44)	0.075
Q4	2.43 (1.54–3.85)	<0.001	2.78 (1.73–4.46)	<0.001	2.55 (1.56–4.15)	<0.001
P for trend	0.001		<0.001		0.001	
High TyG index[1]	2.05 (1.40–3.01)	<0.001	2.21 (1.50–3.26)	<0.001	2.10 (1.41–3.14)	<0.001

Notes: TyG, triglyceride-glucose index, ARF, acute respiratory failure, OR, odds ratio, 95% CI, 95% confidence index, Model 1 was unadjusted, model 2 adjusted for age, gender, ethnicity. Model 3 adjusted for model 2 plus comorbidity, drug usage, and severity scores. [1]High TyG index means that the cut-off value for TyG was 9.47, the 75th of TyG index.

Recently, several prior studies have assessed the association between TyG index and clinical outcomes in different lung diseases. Wu et al tried to explore the relationship between TyG and respiratory symptoms, chronic lung disease, and lung function and the results indicated that a one-unit increase in TyG was associated with higher odds of cough, phlegm production, wheeze, exertional dyspnea, and a diagnosis of chronic bronchitis; moreover, TyG index was associated with

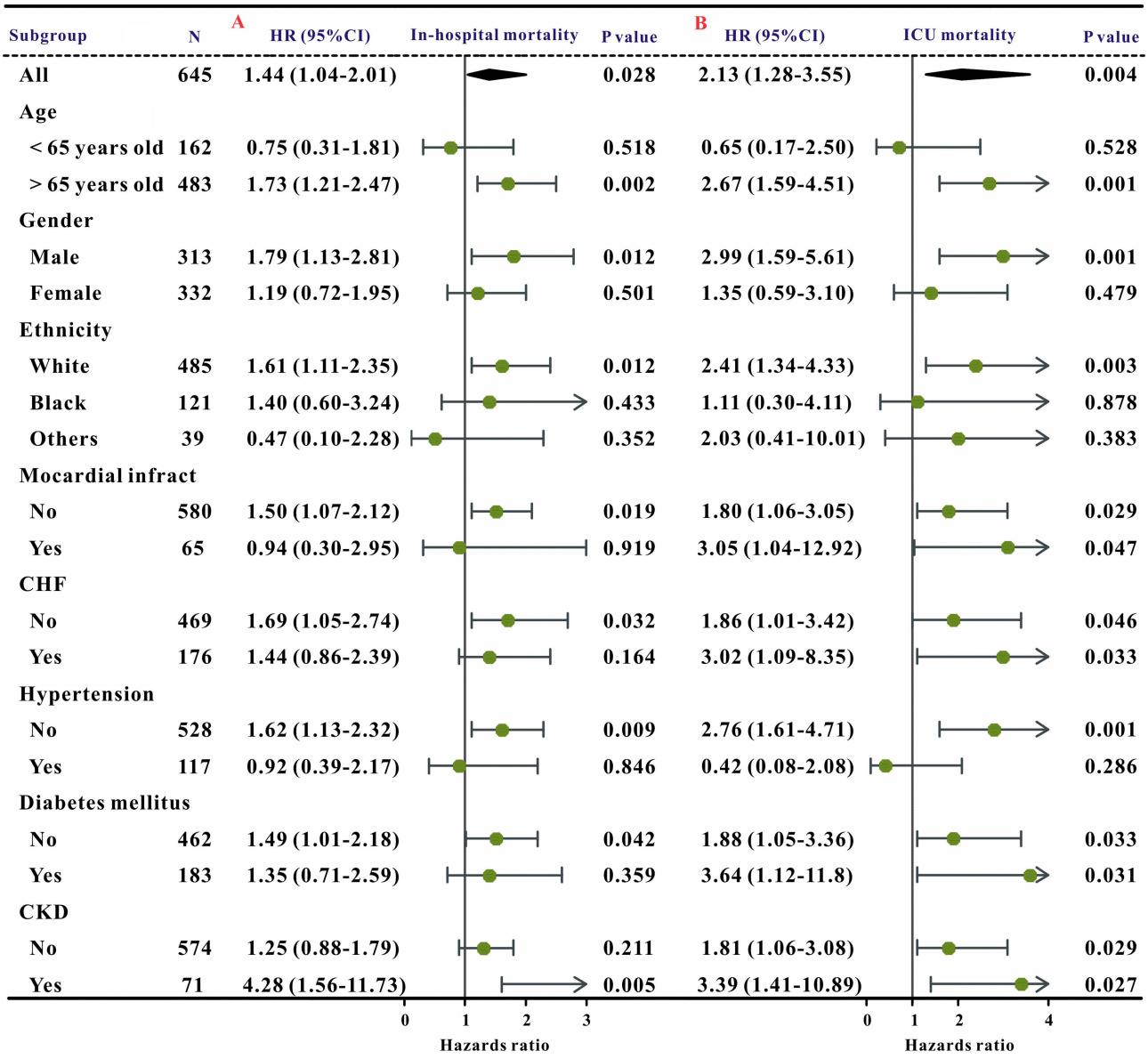

Figure 4 The forest plot revealed the results of subgroup analysis for in-hospital mortality and ICU mortality, respectively, based on the TyG index.

the higher relative risk of a restrictive spirometry pattern.[18] Yan et al aimed to explore the association of TyG index with the risk of non-small cell lung cancer (NSCLC) and concluded that TyG index is significantly correlated with NSCLC risk.[19] A meta-analysis aimed to assess the association between obstructive sleep apnea (OSA) and the TyG index and the results concluded that TyG index is an easy-to-measure marker of insulin resistance for diagnostic ability for OSA and predicting adverse outcomes in OSA patients.[20] However, the role of TyG index in predicting clinical outcomes of AECOPD patients admitted to the ICU remains largely unknown. In line with previous reported,[12] the present study indicated that TyG index was independently associated with in-hospital mortality and ICU mortality in critically ill AECOPD patients. In addition, an elevated TyG index was associated with an increased risk of sepsis, AKI and ARF. These findings indicate that the TyG index is expected to be a novel risk factor that is related to poor clinical outcomes in critically ill AECOPD patients and still needs to be prospectively verified in the general population.

However, the exact mechanisms underlying the association between elevated TyG index and increased risk of poor prognosis in critically ill AECOPD patients. TyG index is a reliable proxy for insulin resistance (IR) and IR may be the potential mechanism. Zuberi et al tried to determine the impact of IR using Homeostatic Model Assessment of Insulin

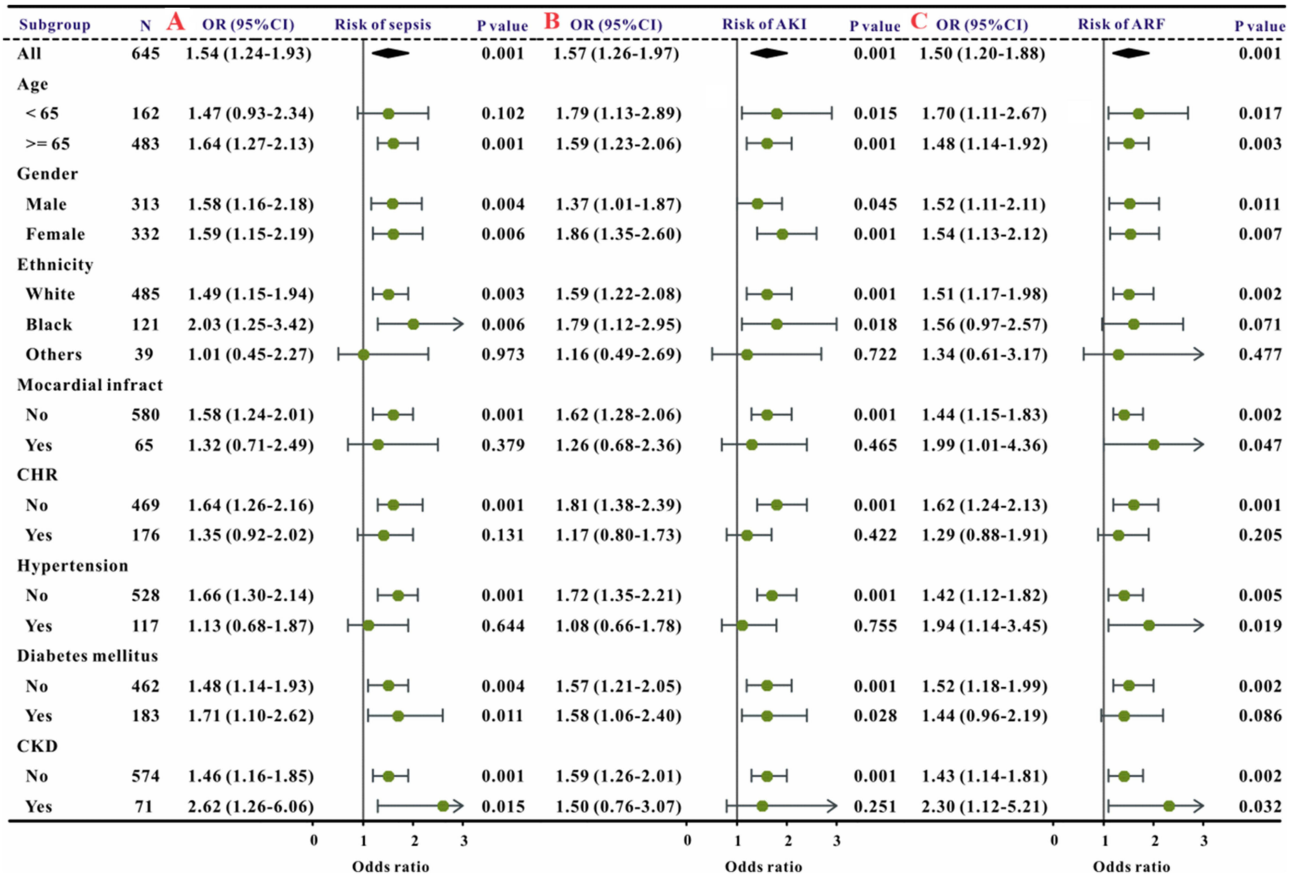

Figure 5 The forest plot revealed the results of subgroup analysis for sepsis, acute kidney injury, and acute respiratory failure, respectively, based on the TyG index.

Resistance (HOMA-IR) score in non-hypoxemic out-patients with COPD on FEV_1, and they found significant increase in HOMA-IR was seen from GOLD-2 to 3 and from GOLD-3 to 4 classes and the impact of HOMA-IR on FEV1 was 49.9%, the results revealed that there is a high prevalence of IR in non-hypoxemic COPD.[21] TyG index is a measure of metabolic dysfunction and is associated with metabolic syndrome. There are reports indicating that between 21% and 58% of COPD patients have metabolic syndrome.[22] COPD patients with metabolic syndrome exhibit a more severe disease course, increased dyspnea, decreased FEV1, and a greater need for inhalational glucocorticoids to manage their condition.[23]

An ongoing systemic inflammatory response is linked to COPD. Oxidative stress and inflammation are key players in IR progression and may be a link between IR and COPD, increased oxidative stress can worsen inflammation, which in turn further exacerbates oxidative stress.[24] Low-grade inflammation is the main mechanism via which the risk factors for metabolic syndrome and COPD are mediated. It has been suggested that low-grade inflammation is the shared link between COPD comorbidities and metabolic syndrome. In individuals with COPD, systemic inflammation fosters IR, which in turn promotes the development of metabolic syndrome.[25] In comparison to individuals without metabolic syndrome, Watz et al discovered that patients with COPD who had metabolic syndrome also had considerably higher levels of interleukin (IL)-6 and high-sensitivity C-reactive protein.[26] Furthermore, IR was linked to IL-6 and tumor necrosis factor (TNF)-α in COPD patients, according to Bolton et al.[27] A number of biomarkers linked to neutrophilic inflammation (elastase, calprotectin, and bronchoalveolar lavage neutrophils) and pro-inflammatory cytokines (IL-6, IL-1β, CRP and TNF-α) are elevated in peripheral blood as a result of lung inflammation during COPD. These inflammatory factors would promote IR, which is the key component of metabolic syndrome.[28] Taken together, IR, increased oxidative stress and inflammation may contribute to initiation and development of AECOPD, which lead to poor clinical outcomes ultimately.

Moreover, numerous ICU severity scores, such as the APACHE IV, SOFA, OASIS and APSIII scores, have been shown to be effective risk stratification tools for critically ill patients.[29] However, its clinical application is limited due to

most severity scores requiring the collection of multiple physiological parameters and the specificity of the predictive value of severity scores for certain ICU populations. Under these conditions, we tried to evaluate whether adding TyG index could improve the predictive abilities of these severity scores, and our results indicated that adding TyG index to these severity scores improved the predictive ability of in-hospital mortality and ICU mortality. In summary, our findings expand and enhance the clinical application of the TyG index in the clinical outcome prediction of critically ill AECOPD. Further studies are needed to examine the relationship between the TyG index and clinical outcomes in critically ill AECOPD patients in large, randomized controlled trials (RCTs).

Several limitations should be noted in this manuscript. First, since this was a retrospective study, prospective trials are needed to confirm if the elevated TyG index in this certain population is linked to an increased risk of in-hospital mortality, ICU mortality, sepsis, AKI and ARF. Secondly, the statistical power of the investigation was diminished due to the small sample size. Moreover, all baseline characteristics were obtained within 24-hours after ICU admission, and data on dynamic changes of TyG index during the hospital stay are lacking, and more thorough investigations with a bigger sample size and dynamic changes of TyG index to offer more evidence to support our conclusions.

Conclusion

An increased TyG index is independently associated with a greater risk of in-hospital mortality, ICU mortality, sepsis, AKI and ARF in critically ill AECOPD patients. In summary, the TyG index is helpful for prognosis prediction and risk stratification in critically ill AECOPD patients. Further prospective, multicenter, large multicenter prospective cohort study is required to evaluate the ideal cut-off value for the TyG index and to ascertain the impact of the TyG index on long-term clinical outcomes in critically ill AECOPD patients.

Data Sharing Statement

The datasets used are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board (IRB) of the Massachusetts Institute of Technology (MIT), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for Publication

All authors consent for publication.

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Disclosure

The authors declare that they have no conflict of interest.

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