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Investigating the Relationship between TyG, TyG-BMI Index and Laboratory Indicators and COVID-19 Severity

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Abstract

Objective: The objective of this study was to investigate the relationship between the triglyceride-glucose (TyG) index, triglyceride-glucose-BMI (TyG-BMI) index, laboratory indices, and disease severity in patients with COVID-19. **Methods:** A retrospective analysis of COVID-19 patients treated at a tertiary hospital in Mianyang City, Sichuan Province, China, from 1 May to 31 May 2023 was performed. The patients were divided into two groups: 66 cases in the moderate group and 61 cases in the severe group. Additionally, 69 uninfected individuals from the medical examination center during the same period were selected as the control group. Spearman rank correlation was used to determine the correlation between the indices and COVID-19 severity. Multiple logistic regression analysis was performed to identify the factors affecting COVID-19 severity. ROC curves were constructed to assess the predictive value of the TyG and TyG-BMI indices for severe COVID-19. **Results:** There were significant differences in smoking and diabetes between the three groups ($P < 0.05$). The levels of ALT, AST, TyG index, and TyG-BMI index were higher in the severe group compared to the moderate and control groups, while the levels of ALB were lower in the severe group ($P < 0.05$). Correlation analysis showed that ALT, AST, TC, TG, HbA1c, TyG index, and TyG-BMI index were positively correlated with COVID-19 severity, while ALB was negatively correlated ($P < 0.05$). The multivariate logistic regression analysis revealed that AST, ALB, TyG index and TyG-BMI index were risk factors for moderate COVID-19, and smoking, AST, ALB, TyG index, and TyG-BMI index were risk factors for severe COVID-19. ROC curves demonstrated that the TyG index predicted an area under the curve (AUC) of 0.642, while the

TyG-BMI index predicted an AUC of 0.718 in severe patients. **Conclusion:** Smoking, AST, ALB, TyG index, and TyG-BMI index are valuable in assessing the severity of COVID-19, with the TyG-BMI index having a higher predictive value than the TyG index.

Keywords

COVID-19, TyG Index, TyG-BMI Index, Severity, Liver Function

1. Introduction

The SARS-CoV-2 is primarily transmitted through respiratory droplets and close contact. The virus enters the human body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of cells, facilitated by surface-spiking proteins [1]. This binding can be hydrolysed and infected by bronchial epithelial transmembrane serine protease 2 (TMPRSS2) [2]. Specifically, TMPRSS2-mediated hydrolysis in bronchial epithelial cells is responsible for viral infection.

In COVID-19 patients, metabolomic analysis of sera has shown significant changes in fatty acid metabolism, as well as unexpected alterations in glucose and amino acid metabolism [3]. The liver, as the primary organ for glycogen storage and lipid synthesis, is crucial for glucose and lipid metabolism. Some studies have indicated a correlation between liver function abnormalities and the severity of COVID-19 [4]. He *et al.* [5] discovered that COVID-19 patients without pre-existing metabolic disorders often exhibit elevated blood sugar levels, which may lead to new-onset insulin resistance (IR) following SARS-CoV-2 infection. Furthermore, IR plays a role in mediating metabolic and inflammatory processes that can contribute to the severity of COVID-19 [6]. In the assessment of COVID-19 disease, IR-related clinical biochemical markers can be used as indicators to assess patient prognosis [6].

The triglyceride-glucose (TyG) index, which is the logarithm of the product of triglycerides (TG) and fasting blood glucose (FBG), is increasingly recognised as a reliable surrogate marker of IR because of its association with lipotoxicity and glucotoxicity [7]. Additionally, some researchers have suggested that the triglyceride-glucose-BMI (TyG-BMI) index, a derivative index of TyG, can also be utilized as an alternative marker for IR [8]. Therefore, the objective of this study was to investigate the association between the TyG and TyG-BMI indices and the severity of COVID-19 in patients. The findings aim to provide clinical insights for the early detection of serious adverse outcomes in patients.

2. Methods

2.1. Materials

A total of 127 patients diagnosed with COVID-19 in May 2023 at a tertiary hos-

pital in Mianyang, China, all of whom had not been previously diagnosed with COVID-19, were enrolled in this study. Among them, 61 were classified as belonging to the moderate group, while the remaining 66 were classified as belonging to the severe group.

To be eligible for inclusion in the study, patients needed to adhere to the protocol for diagnosis and treatment of novel coronavirus infection (Trial 10th edition) [9]. We excluded individuals with a history of radiotherapy for malignant tumors, patients with active secondary tuberculosis, those who were pregnant or lactating, individuals with pulmonary embolism or lower limb venous thrombosis, patients with a history of organ failure (such as significantly impaired cardiac, pulmonary, or renal function), and those with incomplete data.

The control group consisted of 69 uninfected individuals selected from medical examination centres during the same study period who denied ever having been diagnosed with COVID-19. The control group was matched to the moderate and severe groups for age, sex and other relevant demographic variables. Ethical approval for the study was obtained from the hospital ethics committee.

2.2. Data Collection

Details of the participants' demographic information and health conditions were recorded, including their sex, age, smoking and alcohol history, height and weight. In addition, their medical history regarding chronic illnesses such as diabetes mellitus (DM), hypertension (HTN), coronary heart disease (CHD), and chronic obstructive pulmonary disease (COPD) was documented, and whether they take statins, hypoglycemic drugs, insulin and hypertensive drug. To assess the participants' overall health status, various laboratory tests were conducted. These tests included measurements of alanine transferase (ALT), aspartate transferase (AST), albumin (ALB), triglyceride (TC), TG, and FBG. To further evaluate the participants' metabolic health, the TyG index was calculated. The TyG index is a composite measure derived from the equation:

$$\text{TyG?} \quad = \left(\frac{\text{TG}\left(\text{mg/dl}\right) \times \text{FBG}\left(\text{mg/dl}\right)}{2} \right)$$

Additionally, another composite index, known as the TyG-BMI index, was calculated by multiplying the TyG index with the anthropometric indicator known as body mass index (BMI).

2.3. Statistical Analyses

Statistical analyses were performed using SPSS 26.0 software and GraphPad Prism 8.0 software for graphing. Normally distributed measurements were presented as mean ± standard deviation ($\overline{x} \pm s$) and analyzed using independent samples t-test or one-way ANOVA. Nonnormally distributed measurements were presented using the quartile method [M (P25, P75)] and analyzed using nonparametric tests. Count data were presented as percentages. The Spearman rank correlation test was used to analyze the correlation between laboratory in-

dicators and the severity of COVID-19. Multiple logistic regression was employed to analyze the factors influencing the severity of COVID-19. ROC curves were constructed to assess the predictive value of TyG and TyG-BMI indices for COVID-19 severity. Statistical significance was defined as a p-value of less than 0.05.

3. Results

3.1. General Information

The comparison of sex, age, height, weight and BMI between the three groups is shown in Table 1, and the three groups were comparable ($P > 0.05$). Furthermore, the most commonly reported comorbid chronic diseases were HTN (40.9%), DM (33.9%), COPD (14.2%), and CHD (13.4%). Among these, only DM showed a statistically significant difference among the three groups ($P < 0.05$).

Moreover, the prevalence of smoking was found to be higher in the severe group when compared to the moderate and control groups ($P < 0.05$). Conversely, there was no statistically significant difference in the prevalence of alcohol consumption across the three groups ($P > 0.05$).

Table 1. Comparison of the general conditions of the three groups.

Values	Control Group (n = 69)	Moderate Group (n = 61)	Severe Group (n = 66)	*P*
Socio-economic factors				
Age, years	67 (63.74 - 68.06)	70 (61.36 - 69.72)	73 (66.14 - 72.77)	0.171
Male, n (%)	45 (65.2%)	33 (54.1%)	35 (53.0%)	0.285
Weight (Kg)	59.00 (57.46 - 60.99)	60.00 (56.98 - 62.11)	60.00 (58.18 - 64.57)	0.997
Height (cm)	164.00 (161.82 - 165.68)	163.00 (159.76 - 164.17)	160.00 (159.49 - 163.48)	0.995
BMI (Kg/m^2)	22.23 (22.12 - 23.77)	22.68 (22.11 - 23.76)	24.16 (22.80 - 24.58)	0.246
Smoking, n (%)	20 (30.0%)	31 (50.8%)	25 (37.9%)	0.038
Alcohol, n (%)	28 (40.6%)	30 (49.2%)	32 (48.5%)	0.541
Comorbid conditions				
HNT, n (%)	28 (40.6%)	25 (41.0%)	27 (40.9%)	0.999
DM, n (%)	11 (15.9%)	23 (37.7%)	32 (48.5%)	<0.001
COPD, n (%)	9 (13.0%)	7 (11.5%)	11 (16.7%)	0.681
CHD, n (%)	8 (11.6%)	8 (13.1%)	10 (15.2%)	0.830
Medication				
Statin, n (%)	8 (11.6%)	7 (11.5%)	7 (10.6%)	0.981
Hypoglycemic drug, n (%)	9 (13.0%)	16 (26.2%)	19 (28.8%)	0.063
Insulin, n (%)	2 (2.9%)	6 (9.8%)	8 (12.1%)	0.125
Hypotensive drug, n (%)	27 (39.1%)	23 (37.7%)	24 (36.4%)	0.946

3.2. Analysis of Laboratory Indices

The laboratory indices were carefully analyzed to gain insights into the severity of the infection. Notably, the levels of ALT, AST, TyG index, and TyG-BMI index were found to be significantly higher in the severe group compared to the moderate and control groups (Figure 1). Conversely, the levels of ALB were remarkably lower in the severe group compared to the other two groups ($P < 0.05$). Moreover, the control group exhibited lower levels of TC, TG, HbA1c, and FBG compared to the moderate and severe groups ($P < 0.05$). However, the difference in these levels between the severe and moderate groups was not statistically significant ($P > 0.05$).

3.3. Laboratory Indicators and COVID-19 Severity

A comprehensive examination of the laboratory indicators was conducted to investigate their correlation with the severity of COVID-19 in the participants. The

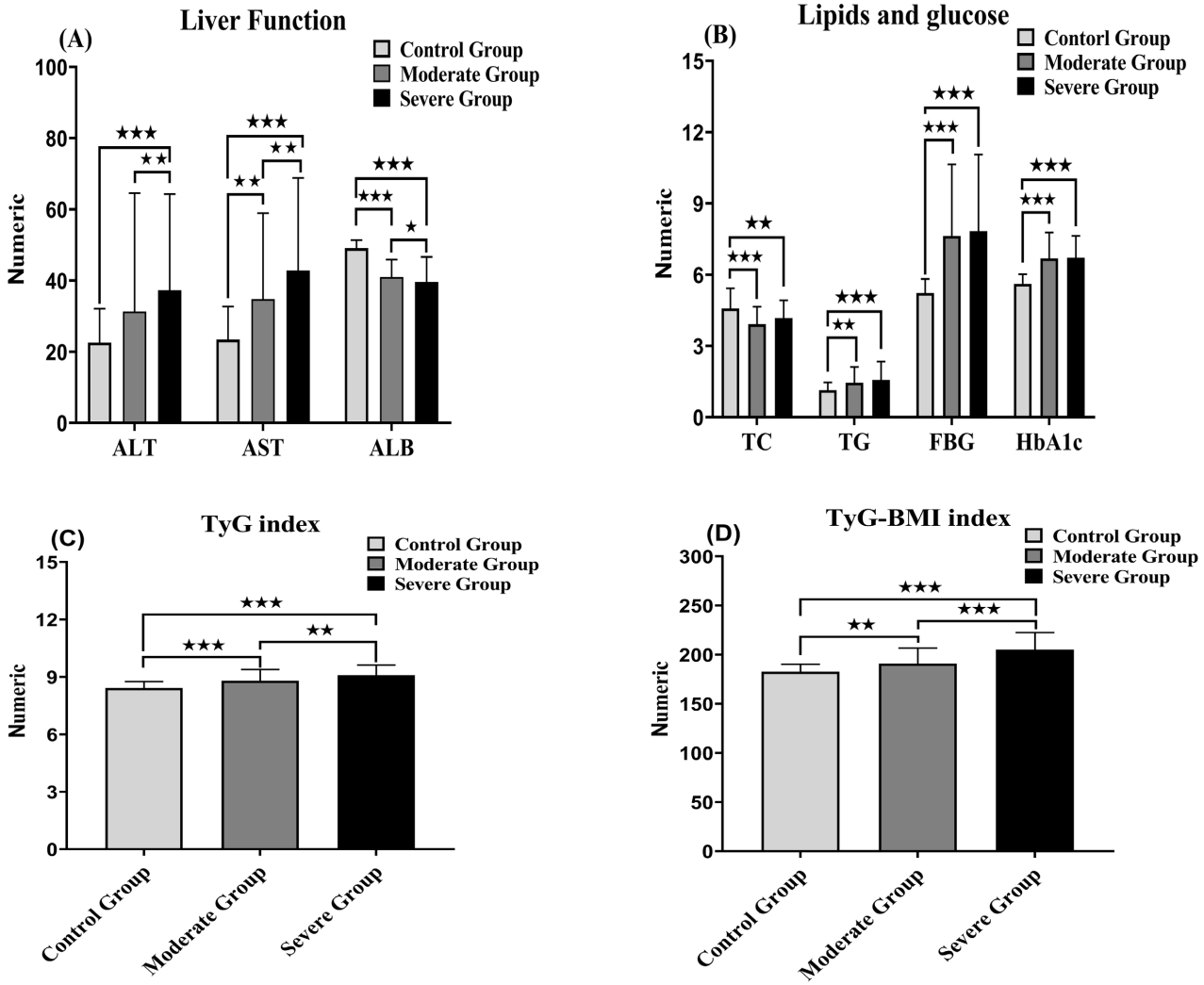

Figure 1. Comparison of laboratory indicators among the three cohorts. Note: Among the two groups, *indicates $P < 0.05$, **indicates $P < 0.01$, ***indicates $P < 0.001$.

results from the correlation analysis revealed that ALT, AST, TC, TG, HbA1c, TyG, and TyG-BMI index exhibited a positive correlation with COVID-19 severity, as illustrated in Table 2. Conversely, ALB and COVID-19 were found to have a negative correlation with disease severity ($P < 0.05$).

3.4. Factors Influencing Severity

Factors influencing the severity of COVID-19 were examined using multiple logistic regression analysis. Disease typing served as the dependent variable, while the TyG and TyG-BMI indices were considered independent variables. Smoking history and DM were corrected for in the analysis. The results revealed that increased levels of AST and the TyG index, as well as decreased levels of ALB, were identified as risk factors for moderate COVID-19 ($P < 0.05$) (Table 3 Model 1). Furthermore, after correction for DM, the smoking history, decreased ALB levels, and increased levels of AST and the TyG index were found to be risk factors for severe COVID-19 ($P < 0.05$) (Table 3 Model 2).

With the TyG-BMI index as the independent variable, multiple logistic regression analysis showed that increased AST and TyG-BMI index, along with decreased ALB levels, were risk factors for moderate COVID-19 ($P < 0.05$) (Table 3 Model 3). After adjusting for DM, the analysis indicated that smoking history, reduced ALB levels, and increased levels of AST and the TyG-BMI index were risk factors for severe COVID-19 ($P < 0.05$) (Table 3 Model 4).

3.5. Predictive Value of TyG and TyG-BMI Indices

The results of the ROC curve analysis demonstrate the potential of the TyG index in predicting severe COVID-19. As shown in Figure 2, the area under the curve (AUC) was 0.642 (95% CI 0.546 - 0.738, $P = 0.006$) when choosing a cut-off value of 8.73. This indicates a moderate predictive value. The sensitivity

Table 2. Spearman's correlation analysis between laboratory indicators and COVID-19 severity.

Values	Control Group (n = 69)	Moderate group (n = 61)	Severe Group (n = 66)	r_s	*P*
ALT (U/L)	22.60 (20.27 - 24.86)[b]	22.77 (21.00 - 39.84)[c]	30.55 (30.47 - 42.50)	0.259	0.001
AST (U/L)	23.06 (21.15 - 25.64)[ab]	29.00 (28.25 - 39.20)[c]	36.95 (36.16 - 47.78)	0.445	<0.001
ALB (g/L)	48.54 (48.54 - 49.64)[ab]	42.30 (39.75 - 42.26)[c]	38.95 (27.86 - 41.33)	−0.753	<0.001
FBG (mmol/L)	5.11 (5.08 - 5.37)[ab]	6.88 (6.60 - 8.62)	7.03 (6.81 - 8.60)	0.558	<0.001
TC (mmol/L)	3.57 (3.37 - 3.78)[ab]	3.95 (3.72 - 4.10)	4.18 (3.99 - 4.35)	0.206	<0.001
TG (mmol/L)	1.13 (1.06 - 1.22)[ab]	1.31 (1.28 - 1.62)	1.38 (1.39 - 1.76)	0.263	0.001
HbA1c (%)	5.60 (5.51 - 5.71)[ab]	6.50 (6.39 - 6.94)	6.50 (6.49 - 6.95)	0.552	<0.001
TyG	8.47 (8.34 - 8.50)[ab]	8.83 (8.65 - 8.95)[c]	9.04 (8.97 - 9.23)	0.526	<0.001
TyG-BMI	182.68 (180.70 - 184.36)[ab]	188.60 (186.82 - 194.92)[c]	206.76 (200.74 - 209.30)	0.528	<0.001

Note: 1) Comparison of patients in the control group with those in the moderate group, [a]$P < 0.05$; 2) Comparison of patients in the control group with those in the severe group, [b]$P < 0.05$; and 3) Comparison of patients in the moderate group with those in the severe group, [c]$P < 0.05$.

Table 3. Multivariate logistic regression analysis of factors influencing COVID-19 severity.

Projects	Values	β	SE	Wald	P	*OR*	95% CI
Model 1	AST	0.061	0.027	5.051	0.025	1.062	1.008 - 1.120
	ALB	−0.369	0.069	29.001	<0.001	0.691	0.605 - 0.791
	TyG	2.143	0.879	5.939	0.015	8.525	1.521 - 47.781
Model 2	Smoking	2.957	0.773	14.642	<0.001	19.237	4.231 - 87.474
	AST	0.085	0.028	9.329	0.002	1.089	1.031 - 1.150
	ALB	−0.366	0.073	25.196	<0.001	0.693	0.601 - 0.800
	TyG	5.028	1.016	24.473	<0.001	152.654	20.823 - 1119.121
Model 3	AST	0.049	0.025	3.884	0.049	1.050	1.003 - 1.102
	ALB	−0.387	0.069	31.107	<0.001	0.679	0.593 - 0.778
	TyG-BMI	0.054	0.026	4.292	0.038	1.056	1.003 - 1.111
Model 4	Smoking	2.722	0.771	12.471	<0.001	15.204	3.357 - 68.857
	AST	0.069	0.026	7.316	0.007	1.072	1.019 - 1.127
	ALB	−0.391	0.077	26.090	<0.001	0.676	0.582 - 0.786
	TyG-BMI	0.160	0.031	26.199	<0.001	1.174	1.104 - 1.248

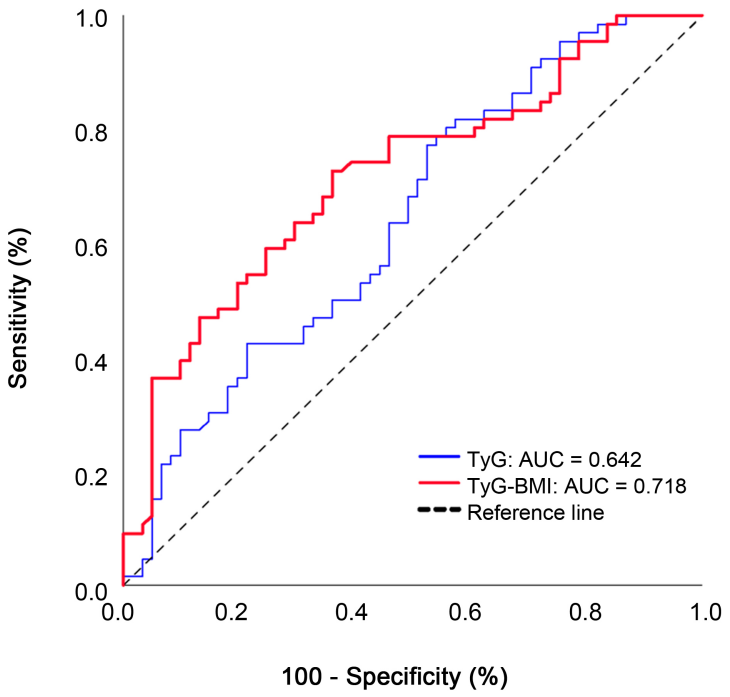

Figure 2. ROC curve of predictive value of TyG and TyG-BMI indices for COVID-19 severity.

and specificity for predicting severe COVID-19 was found to be 77.3% and 47.0%, respectively.

In addition, the TyG-BMI index also displayed promising results in predicting severe COVID-19. The ROC curve analysis revealed an AUC of 0.718 (95% CI

0.630 - 0.807, P < 0.001), which indicated a relatively strong predictive value. By setting the optimal cut-off value at 192.90, both sensitivity and specificity for predicting severe COVID-19 were observed at 72.7% and 63.9%, respectively.

These findings suggest that both the TyG index and the TyG-BMI index hold potential as predictive markers for severe COVID-19. Further research is warranted to validate and explore their clinical utility in larger population studies.

4. Discussion

The current study conducted a retrospective analysis of a population comprising 196 cases, and no significant differences in age and sex were observed among the three groups. Previous research has indicated that advanced age is a risk factor for severe and critical COVID-19. This may be attributed to the reduced pathogenicity of the omicron variant, as well as the decline in immune competence in the elderly population. Additionally, of the three groups, the number of people with a history of diabetes was higher in the severe group than in the other two groups. Moreover, the prevalence of smoking was found to be higher in the severe group compared to the moderate and control groups. Further, multiple regression analysis revealed a positive association between smoking history and the occurrence of severe COVID-19. This may be attributed to the ability of cigarette smoke to induce overexpression of ACE2 and TMPRSS2 in airway epithelial cells, thereby increasing the susceptibility to SARS-CoV-2 infection [1].

The liver, a vital organ responsible for regeneration, detoxification, and metabolism in the human body, plays a crucial role in maintaining environmental homeostasis. In COVID-19 patients, liver function abnormalities have been observed, potentially linked to various factors such as direct viral injury, inflammation, hypoxia-reperfusion disorder, and drug-induced liver injury [6]. Among these factors, the severe group exhibited elevated levels of ALT and AST, which were positively correlated with the severity of COVID-19 according to correlation and multiple regression analyses. Notably, elevated AST levels were identified as risk factors for severe COVID-19. Recent studies have hypothesized that both cholangiocytes and hepatocytes express ACE2 and TMPRSS2, with cholangiocytes demonstrating the highest ACE2 expression. This suggests that SARS-CoV-2 may directly affect these cell types, leading to impaired liver function in patients [10]. Moreover, this study found a close association between low ALB levels and the severity of COVID-19. It is important to note that the enrolled population had no history of heart, liver, or kidney failure, implying that the decline in ALB levels may be attributed to an increased basal metabolic rate, malnutrition, and reduced synthetic function of the damaged liver after viral infection. In addition, reduced levels of ALB, as a negative acute phase reactant, are a threat to long-term survival in clinical Settings and a strong biomarker for poor prognosis in most diseases [11].

Previous studies have revealed that when the body is infected, lipid metabol-

ism and glucose metabolism are altered. Sun *et al*. [12] proposed that elevated levels of TG in COVID-19 patients signify persistent exacerbation of the infection and an elevated risk of poor prognosis. In our study, we observed significantly higher levels of TC and TG in the severe and moderate groups compared to the control group. This may be attributed to the inhibition of lipoprotein lipase activity by the inflammatory factor storm, resulting in an increase in free fatty acids and TG synthesis [12]. Furthermore, when the body is in a state of IR, various metabolic disorders such as glucose metabolism and lipid metabolism can be induced, thereby increasing the likelihood of an inflammatory factor storm. Consequently, the incidence of severe COVID-19 cases is higher [13]. Santos *et al*. [14] have suggested that SARS-Cov-2 can activate inflammatory factors, impair insulin signaling, and subsequently reduce insulin sensitivity in insulin-activated target organs. This leads to abnormal glucose metabolism and IR. Therefore, IR may be linked to the severity and poor prognosis of COVID-19.

The TyG and TyG-BMI indices are reliable surrogate markers of IR and have been consistently linked to various diseases such as coronary atherosclerotic heart disease [7], hyperuricemia [15], and nonalcoholic fatty liver disease [16]. In this study, we discovered that these indices also demonstrate a correlation with the severity of COVID-19. Patients in the severe group exhibited higher TyG and TyG-BMI indices values compared to those in the control and moderate groups. Furthermore, the index values were also elevated in the moderate group compared to the control group. Our test analysis revealed that both indices were positively associated with COVID-19 severity and served as risk factors for the disease in the moderate and severe groups. Using ROC curves to compare the predictive ability of the TyG and TyG-BMI indices for severe COVID-19, we found that the TyG-BMI index outperformed the TyG index in terms of prediction. Therefore, TyG and TyG-BMI indices were significant predictors of COVID-19 severity.

5. Conclusion

AST, ALB, TyG, and TyG-BMI all had significant independent effects on moderate COVID-19, while smoking history, AST, ALB, TyG, and TyG-BMI influenced the severity of the disease. Notably, both TyG and TyG-BMI indices showed predictive abilities for the severity of COVID-19, with TyG-BMI index exhibiting a higher predictive value. As IR can cause glucose and lipid metabolism disorders and inflammatory changes in patients with confirmed COVID-19, it resulted in a positive correlation between TyG and TyG-BMI indices and an increased risk of severity in patients. This finding supports the importance of the TyG and TyG-BMI indices as valuable and important predictors of COVID-19 severity, and guides and alerts physicians to pay more attention to patients with high levels of these indices, to dynamically assess disease progression, and to make timely adjustments to treatment regimens.

6. Limitation

Several limitations of this study should also be addressed. First, the present study is retrospective and has limited information on the disease process. Second, this was a single-centre study with a relatively small sample size considering the complexity of the disease. Thirdly, we evaluated the relationship between TyG and TyG-BMI indices at admission and COVID-19 severity, but lacked an association test for changes in disease dynamics. Further multicentre prospective studies are needed to assess the predictive accuracy of TyG and TyG-BMI indices for COVID-19 severity.

Contribution of the Authors

All the authors participated intellectually in the preparation and revision of the manuscript before its submission.

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Conflicts of Interest

The authors declare no competing interests regarding the publication of this paper.

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