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Original Article

Association of triglyceride-glucose index with prognosis of COVID-19: A population-based study

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ABSTRACT

Background: Triglyceride-glucose (TyG) index is a simple and reliable surrogate marker for insulin resistance. Epidemiology studies have shown that insulin resistance is a risk factor for various infectious diseases. We evaluated the prognostic value of TyG index measured before the COVID-19 infection in COVID-19 infected patients.

Methods: From a nationwide COVID-19 cohort dataset in Korea, we included COVID-19 patients diagnosed between Jan and Jun 2020. Based on the nationwide health screening data between 2015 and 2018, TyG index was calculated as ln [triglyceride (mg/dL) × fasting glucose level (mg/dL)/2]. Primary outcome is development of severe complications of COVID-19 defined as composite of mechanical ventilation, intensive care unit care, high-flow oxygen therapy, and mortality within two months after the diagnosis of COVID-19.

Results: This study included 3887 patients with COVID-19 confirmed by reverse transcription polymerase chain reaction. Mean ± standard deviation of TyG index was 8.54 ± 0.61. Severe complications of COVID-19 were noted in 289 (7.44%) patients. In the multivariate logistic regression, TyG index was positively associated with severe complications of COVID-19 (adjusted odds ratio: 1.42, 95% confidence interval [1.12–1.79]).

Conclusions: In COVID-19 infected patients, high TyG index was associated with increased risk for severe complications. TyG index might be useful predictor for the severity of COVID-19 infection.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The global pandemic of COVID-19 is still ongoing and the most serious threat to public health in a century. Although most COVID-19 patients show good recovery, a number of patients, especially with underlying comorbidities, have critical complications including respiratory failure that can eventually lead to death [2]. Epidemiological studies have documented that the presence and number of comorbidities correlated with poorer outcome with COVID-19 infection [3]. Along with other comorbidities, diabetes mellitus was considered as a possible risk factor for COVID-19 infection and related complications [4].

Insulin resistance is the common metabolic disorder often associated with type 2 diabetes, representing a pathological condition in which the body's cells become resistant to the hormone insulin [5]. Insulin involves multiple molecular and pathophysiological pathways, and pathologic condition of insulin resistance is closely linked to not only diabetes mellitus, but also to various medical conditions such as hypertension, dyslipidemia, liver disease, cardiovascular disease, neurodegenerative disease, malignancy, obesity, inflammatory and infectious disease [6,7]. In critically ill patients, insulin resistance has been reported to be correlated with the severity of condition and poor clinical outcome [8–10]. The triglyceride-glucose (TyG) index is a simple surrogate marker of insulin resistance, calculated using fasting triglyceride and fasting blood

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glucose [11]. High TyG index is significant indicator of adverse prognosis in general population as well as in patients with various diseases [12,13]. We investigated whether TyG index measured before the COVID-19 infection has a prognostic value to identify those at high-risk for severe complications in COVID-19 infected patients.

Material and methods

Study design and participants

We performed a retrospective observational study for prognosis of COVID-19 infection according to TyG index with a nationwide population-based COVID-19 dataset in South Korea. South Korea has a single-payer public healthcare system, called by National Health Insurance Service (NHIS). NHIS has an information for hospital visit, diagnoses (recorded based on International Statistical Classification of Diseases and Related Health Problems 10th revision), medical procedure, prescription, and mortality of the whole Korean population [14]. Recently, the Korea Centers for Disease Control and Prevention, and the Ministry of Health and Welfare, South Korea released a nationwide COVID-19-related dataset, which includes the data of Korean citizens who underwent real-time reverse transcription polymerase chain reaction (RT-PCR) assays with nasal and pharyngeal swabs to COVID-19 from January 1 to June 4, 2020 [15]. The COVID-19-related dataset contains data on result of COVID-19 test (positive or negative), national health check-up program (2015–2018), health claims data, and mortality of all people who underwent RT-PCR tests for the COVID-19 [16]. The real-time PT PCR assays kit followed the WHO guideline and was validated by the Korea Centers for Disease Control and Prevention [17].

TyG index and covariates

As a public institution, the NHIS provides free health checkups to all Koreans aged ≥ 40 years every two years. The free health checkups program consisted of physical examination of blood pressure, body mass index (BMI), lifestyle survey (medical history, physical activity, smoking habit, alcohol consumption), and laboratory tests including fasting glucose, triglyceride, cholesterol levels [18]. The TyG index was calculated as ln [triglyceride (mg/dL) × fasting glucose level (mg/dL)/2], based on the blood chemistry data measured in the free nationwide health checkups program before the COVID-19 infection (2015–2018) [19]. In order to avoid errors due to extreme values, when the measured value ≥ the 99 percentile value or ≤ the 1 percentile value, they are replaced with the 99% percentile value or the 1 percentile value, subsequently. If study participants underwent twice or more health check-up during the period, the most recent data was used in this study.

From the health claims and health checkups program data, we also collected information for sex, age at COVID-19 diagnosis, household income level (four quartiles), alcohol consumption, smoking habit, physical activity, BMI, low density lipoprotein (LDL) cholesterol, and presence of comorbidities (hypertension, diabetes mellitus, stroke, coronary artery disease, chronic kidney disease, asthma, malignancy). BMI was calculated by one's weight (kg) divided by the square of height (m^2). Hypertension was defined when participants received prescription blood pressure lowing agents (calcium-channel blocker, diuretics, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and beta-blockers) with hypertension diagnostic codes of 'I10–15', or had blood pressure ≥ 140/90 mmHg, or positive checking in a self-report questionnaire regarding hypertension [20]. Diabetes mellitus was defined when participants had received prescription anti-diabetic agents (sulphonylurea, metformin, meglitinide, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium-glucose co-transporter 2, glucagon-like peptide-1 agonists, α-glucosidase inhibitor, and insulin) with diabetes mellitus diagnostic codes of 'E11–14', or had fasting blood glucose > 7.0 mmol/L, or positive checking in a self-report questionnaire for diabetes mellitus. Stroke was defined as the presence of corresponding stroke diagnostic codes of 'I60–I63', 'I69'. Coronary artery disease and chronic kidney disease were defined as the presence of corresponding diagnostic codes (coronary artery disease: I20–25, chronic kidney disease: N03, N05, N165, N18–19, N250, I12–13, Z490, Z491–2, Z940, Z992, E102, E112, E132, E142, or T861) [21,22]. Asthma was determined by the presence of diagnostic codes of 'J45–46' as the primary diagnosis 2 times or more [23]. Malignancy was defined by having at least three times outpatient visits or once admission with the diagnostic code of 'C00–97' with specific cancer registration code of 'V027', 'V193–4'. The data for smoking habit (current, former, never), alcohol consumption (average frequency per week: < 1 time, 1–2 times, 3–4 times or ≥5 times), and physical activity (average frequency per week: < 1 day, 1–4 days or ≥5 days) were obtained from the self-report questionnaire for lifestyles in the health check-up program.

Study outcomes

We defined the primary outcome as a composite of 1) application of mechanical ventilation, 2) admission to the intensive care unit, 3) use of high-flow oxygen therapy, and 4) mortality within 2 months after COVID-19 diagnosis. Application of mechanical ventilation was identified by claim codes for mechanical ventilation (M5850, M5857, M5858, M5860). The admission to the intensive care unit was defined using the related claim codes for intensive care (AH110, AH150, AH180–5, AH190–5, AH210, AH250, AH280–9, AH28A, AH290–9, AH380–9, AH38A, AH390–9, AH501, AJ001–AJ011, AJ020–1, AJ031, AJ100–390, AJ2A0, AJ3A0, AJ500–590, V5100, V5200, V5210–20, V5500–5520). High-flow oxygen therapy was determined by the presence of claim code for high-flow nasal cannula therapy (M0046) [24]. Mortality data are obtained by NHIS, which have previously been validated [25].

Statistical analyses

For comparison of continuous and categorical variables between groups, independent t-tests and chi-square tests were performed, respectively. To evaluate the relationship between TyG index and severe complications of COVID-19 infection, we used univariable and multivariable logistic regression analyses. To detect and measure the collinearity in a multivariable regression model, we calculated variance inflation factor (VIF) for each variable. Small value of VIF indicates low correlation among variables and it is believed acceptable if it is less than 5 [26]. The subgroup analyses were conducted according to the sex, age (dichotomized more than 60 years old), history of hypertension, and history of diabetes mellitus. The results were presented as odds ratio (OR) and 95% confidence interval (CI). To help the understanding of the association between TyG index and COVID-19 outcomes, we draw a spline curve representing OR for primary outcome according to the continuous level of TyG index. All statistics were executed using R software, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria), and SAS 9.4 version (SAS Inc., Cary, NC, USA). Two-sided *P*-values less than 0.05 were considered significant.

Results

Participants and demographics

The Korean nationwide COVID-19 cohort consisted of 212,678 participants aged ≥ 20 years who received RT-PCR test for COVID-19. Among them, 7713 patients who tested positive in the COVID-19 PCR test were included in this study, excluding those who tested negative

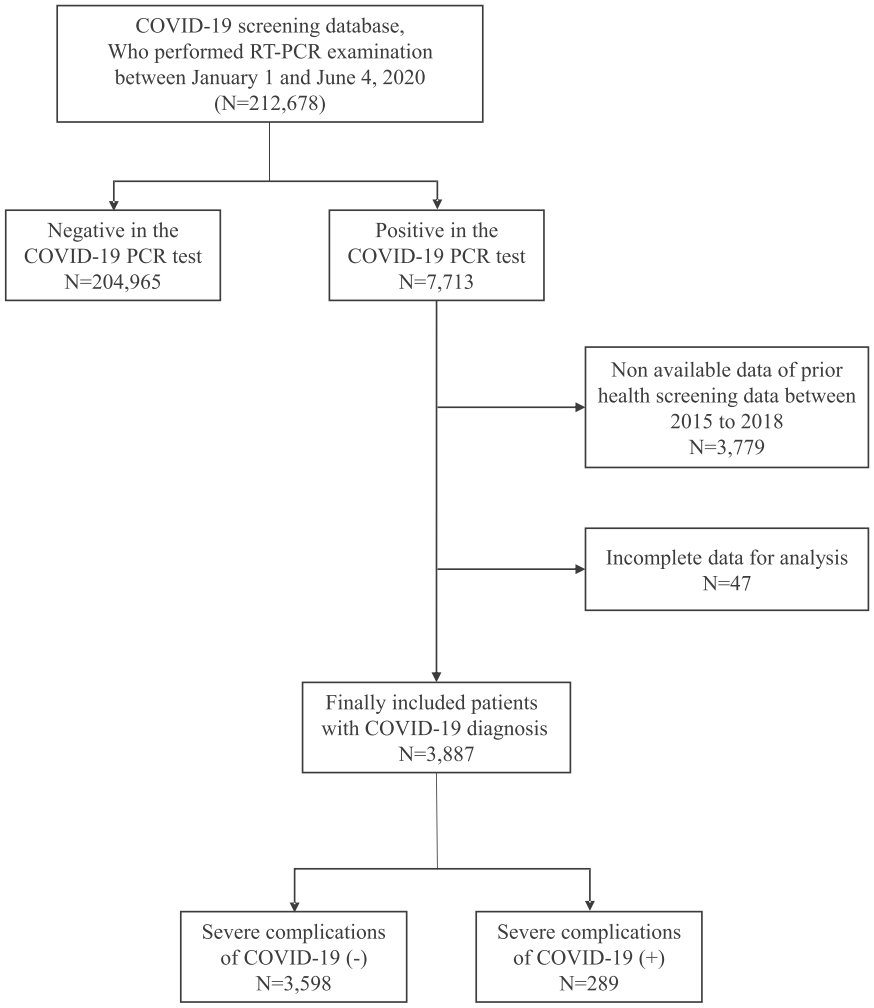

Fig. 1. Flowchart depicting patient inclusion and exclusion. COVID-19, coronavirus disease 2019; RT-PCR, real-time reverse transcription polymerase chain reaction.

in the COVID-19 PCR test (n = 204,965). Among these 7713 patients, there were 3934 patients who had an available data for national health screening program in 2015–2018. We additionally excluded 47 patients with incomplete data for analysis. Finally, 3887 patients with confirmed COVID-19 diagnosis were included in this study (Fig. 1).

Among the finally included 3887 patients, 1451 (37.33%) were male and 1520 (39.10%) were ≥ 60 years of age. The mean ± standard deviation of fasting glucose and triglyceride was 100.44 ± 22.87 mg/dL and 120.04 ± 73.46 mg/dL, respectively. Demographics, comorbidities, and laboratory findings are presented in Table 1. Compared to the group without severe complications, the severe complications of COVID-19 group were older and had a higher BMI (24.79 ± 3.43 vs. 23.91 ± 3.27 kg/m^2, p < 0.001). Comorbidities such as hypertension, diabetes mellitus, stroke, and coronary artery disease, chronic kidney disease, asthma, and malignancy were more commonly noted in severe complications of COVID-19 group. The severe complications of COVID-19 group had a higher TyG index than the group without severe complications (8.81 ± 0.61 vs. 8.51 ± 0.61, p < 0.001), and fasting glucose level (111.64 ± 29.65 vs. 99.54 ± 22.00 mg/dL, p < 0.001) and triglyceride (142.58 ± 84.51 vs. 118.22 ± 72.20 mg/dL, p < 0.001) were higher (Table 1).

Association of TyG index with severe complications of COVID-19

Primary outcome for severe complications of COVID-19 was noted in 289 (7.44%) patients including mechanical ventilation in 119 (3.06%) patients, intensive care unit care in 171 (4.40%) patients, high-flow oxygen therapy in 83 (2.14%) patients, and mortality in 114 (2.93%) patients, respectively. After adjusting sex, age, household income, alcohol consumption, smoking habit, physical activity, BMI, hypertension, diabetes mellitus, stroke, coronary artery disease, chronic kidney disease, asthma, malignancy, and LDL cholesterol, TyG index was positively associated with severe complications of COVID-19 (OR: 1.42, 95% CI [1.12 – 1.79], p = 0.003) (Table 2). In a testing for multicollinearity with VIF, all values are < 2 indicating absence of high multicollinearity.

Distribution of TyG index according to the presence of severe complications of COVID-19 are demonstrated in Fig. 2. A spline curve demonstrated the positive association between TyG index and severe complications of COVID-19 (Fig. 3). In subgroup analysis by sex, age, hypertension, and diabetes mellitus, the positive association of TyG index with severe complications of COVID-19 was consistently noted (all p for interaction > 0.05, Fig. 4).

Discussion

The key finding of our study based on a nationwide population-based COVID-database in South Korea is that high TyG index, which represents insulin resistance, was associated with the increased risk for severe complications of COVID-19 patients.

In a previous hospital-based study with 151 COVID-19 positive patients, the TyG index levels were significantly higher in the patients with severe complication or mortality [27]. Among patients

Table 1
Baseline characteristics of COVID-19 patients according to prognosis.

Variable	Total	Primary outcome[a]		*P*-value[b]
		Without Severe complications of COVID-19	With Severe complications of COVID-19	
Number of patients	3887	3598	289	
Sex, male	1451 (37.33)	1275 (35.44)	176 (60.90)	< 0.001
Age, years				< 0.001
< 60	2367 (60.90)	2307 (64.12)	60 (20.76)	
≥ 60	1520 (39.10)	1291 (35.88)	229 (79.24)	
Household income				0.002
Q1, lowest	1320 (33.96)	1241 (34.49)	79 (27.34)	
Q2	912 (23.46)	852 (23.68)	60 (20.76)	
Q3	705 (18.14)	651 (18.09)	54 (18.69)	
Q4, highest	950 (24.44)	854 (23.74)	96 (33.22)	
Alcohol consumption, frequency per week				< 0.001
< 1 time	2656 (68.33)	2442 (67.87)	214 (74.05)	
1–2 times	921 (23.69)	880 (24.46)	41 (14.19)	
3–4 times	225 (5.79)	198 (5.50)	27 (9.34)	
≥ 5 times	85 (2.19)	78 (2.17)	7 (2.42)	
Smoking habit				< 0.001
None	3018 (77.64)	2840 (78.93)	178 (61.59)	
Former smoker	573 (14.74)	481 (13.37)	92 (31.83)	
Current smoker	296 (7.62)	277 (7.70)	19 (6.57)	
Physical activity, frequency per week				0.020
< 1 day	806 (20.74)	730 (20.29)	76 (26.30)	
1–4 days	1693 (43.56)	1586 (44.08)	107 (37.02)	
≥ 5 days	1388 (35.71)	1282 (35.63)	106 (36.68)	
Anthropometric measurements				
Body mass index (kg/m^2)	23.97 ± 3.29	23.91 ± 3.27	24.79 ± 3.43	< 0.001
Comorbidities				
Hypertension	1304 (33.55)	1115 (30.99)	189 (65.40)	< 0.001
Diabetes mellitus	601 (15.46)	502 (13.95)	99 (34.26)	< 0.001
Stroke	156 (4.01)	123 (3.42)	33 (11.42)	< 0.001
Coronary artery disease	209 (5.38)	172 (4.78)	37 (12.80)	< 0.001
Chronic kidney disease	278 (7.15)	230 (6.39)	48 (16.61)	< 0.001
Asthma	212 (5.45)	185 (5.14)	29 (9.34)	0.003
Malignancy	333 (8.57)	289 (8.03)	44 (15.22)	< 0.001
Laboratory findings				
Fasting glucose, mg/dL	100.44 ± 22.87	99.54 ± 22.00	111.64 ± 29.65	< 0.001
Triglyceride, mg/dL	120.04 ± 73.46	118.22 ± 72.20	142.58 ± 84.51	< 0.001
LDL cholesterol, mg/dL	114.23 ± 33.03	114.83 ± 32.84	106.74 ± 34.46	< 0.001
TyG index	8.54 ± 0.61	8.51 ± 0.61	8.81 ± 0.61	< 0.001
Clinical outcome				
Mechanical ventilation	119 (3.06)			
Intensive care unit care	171 (4.40)			
High-flow oxygen therapy	83 (2.14)			
Mortality	114 (2.93)			

Data are represented as number of patients (%) or mean ± standard deviation. Q, quartile; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TyG index is calculated by the following formula: ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].
[a] Primary outcome is composite of mechanical ventilation, intensive care unit care, high-flow oxygen therapy, and mortality within two months after COVID-19 diagnosis
[b] P-value is derived from independent t-test or Chi's square test between patient groups according to primary outcome.

hospitalized for COVID-19, those with critical COVID-19 presented higher levels of fasting glucose, triglycerides, both of which are components of the TyG index [28]. Another hospital-based case-control study with 43 patients revealed that biochemical markers of insulin resistance may be related with severe complications of COVID-19 [29].

Our result is in lines with these previous studies for the potential role of TyG index and markers of insulin resistance as an indicator for the severe complications of COVID-19 [27]. Unlike the prior studies, we calculated TyG index based on a nationwide health screening data measured before the COVID-19 infection. It has been known that COVID-19 infection itself can induce insulin resistance and lipid metabolic dysregulation [30,31]. The previous case series demonstrated that COVID-19 infection triggered uncontrolled hyperglycemia and insulin resistance in acute phase [32–34]. Therefore, worse prognosis of COVID-19 patients with high TyG index measured in acute phase might be due to that critical illness with COVID-19 infection itself cause further insulin resistance [35]. We found that the TyG index measured before the COVID-19 infection also had a significant association with COVID-19 prognosis. This result added evidence that underlying insulin resistance in health condition is one of determinant for the prognosis of COVID-19 infection. Regarding the interplay between inflammation and insulin resistance, baseline insulin resistance may hold key to improving immune responses against COVID-19 [36]. In addition, our study showed that TyG index easily calculated from a pre-existing blood test can serve as a simple tool to predict the risk of severe complications from COVID-19 without additional test. It will be applicable to screening those at high-risk in general population who need to pay more attention to COVID-19 infection and determining priority group for COVID-19 vaccination.

Although our study is not a study for the mechanism, we may allow proposing hypotheses that may explain the association between the TyG index and severe COVID-19 outcome. TyG index was associated with metabolic syndrome, dyslipidemia, future development of diabetes mellitus, subclinical coronary artery disease, arterial stiffness, and occurrence of major cardiovascular events [11,37,38]. Epidemiologic data have documented that individuals with high TyG index are at increased risk for nonalcoholic fatty liver disease, which is also closely related to obesity and insulin resistance [39,40]. It has been established that the presence and number of these comorbidities in COVID-19 patients, which closely related with

Table 2
Association factors for occurrence of severe complications in COVID-19 patients.

Variable	Univariate OR [95% CI]	*P*-value	Adjusted OR [95% CI][a]	*P*-value
Sex, male	2.84 [2.22–3.63]	< 0.001	2.40 [1.72–3.34]	< 0.001
Age, years				
< 60	1 (Ref)	–	1 (Ref)	–
≥ 60	6.82 [5.09–9.14]	< 0.001	3.89 [2.81–5.37]	< 0.001
Household income				
Q1, lowest	1 (Ref)	–	1 (Ref)	–
Q2	1.11 [0.78–1.57]	0.568	1.15 [0.79–1.66]	0.474
Q3	1.30 [0.91–1.87]	0.148	1.17 [0.80–1.72]	0.422
Q4, highest	1.77 [1.30–2.41]	< 0.001	1.42 [1.02–1.99]	0.040
Alcohol consumption, frequency per week				
< 1 time	1 (Ref)	–	1 (Ref)	–
1–2 times	0.53 [0.38–0.75]	< 0.001	0.52 [0.35–0.77]	0.001
3–4 times	1.56 [1.02–2.38]	0.042	0.95 [0.58–1.57]	0.851
≥ 5 times	1.02 [0.47–2.25]	0.953	0.46 [0.20–1.07]	0.072
Smoking habit				
None	1 (Ref)	–	1 (Ref)	–
Former smoker	3.05 [2.33–4.00]	< 0.001	1.53 [1.07–2.21]	0.021
Current smoker	1.09 [0.67–1.78]	0.718	0.67 [0.38–1.17]	0.155
Physical activity, frequency per week				
< 1 day	1 (Ref)	–	1 (Ref)	–
1–4 days	0.65 [0.48–0.88]	0.006	0.77 [0.55–1.07]	0.124
≥ 5 days	0.79 [0.58–1.08]	0.142	0.80 [0.57–1.12]	0.199
Anthropometric measurements				
Body mass index (kg/m^2)	1.08 [1.04–1.12]	< 0.001	1.01 [0.97–1.06]	0.586
Comorbidities				
Hypertension	4.21 [3.27–5.42]	< 0.001	1.78 [1.33–2.39]	< 0.001
Diabetes mellitus	3.21 [2.48–4.17]	< 0.001	1.20 [0.87–1.66]	0.261
Stroke	3.64 [2.43–5.46]	< 0.001	1.25 [0.80–1.96]	0.326
Coronary artery disease	2.93 [2.01–4.27]	< 0.001	1.21 [0.79–1.85]	0.386
Chronic kidney disease	2.92 [2.08–4.09]	< 0.001	1.27 [0.86–1.88]	0.225
Asthma	1.90 [1.25–2.90]	0.003	1.33 [0.84–2.12]	0.222
Malignancy	2.06 [1.46–2.90]	< 0.001	1.36 [0.93–1.99]	0.115
Laboratory findings				
LDL cholesterol, mmol/L	0.87 [0.82–0.93]	< 0.001	0.93 [0.86–0.99]	0.032
Triglyceride/glucose index	2.11 [1.75–2.54]	< 0.001	1.42 [1.12–1.79]	0.003

Data are derived from logistic regression analysis for severe complications of COVID-19. Severe complications of COVID-19 are composite of mechanical ventilation, intensive care unit care, high-flow oxygen therapy, and mortality.
OR, odds ratio; CI, confidence interval; Q, quartile; LDL, low-density lipoprotein.
[a] Adjusted for sex, age, household income, alcohol consumption, smoking status, physical activity, body mass index, hypertension, diabetes mellitus, stroke, coronary artery disease, chronic kidney disease, asthma, malignancy, and LDL cholesterol.

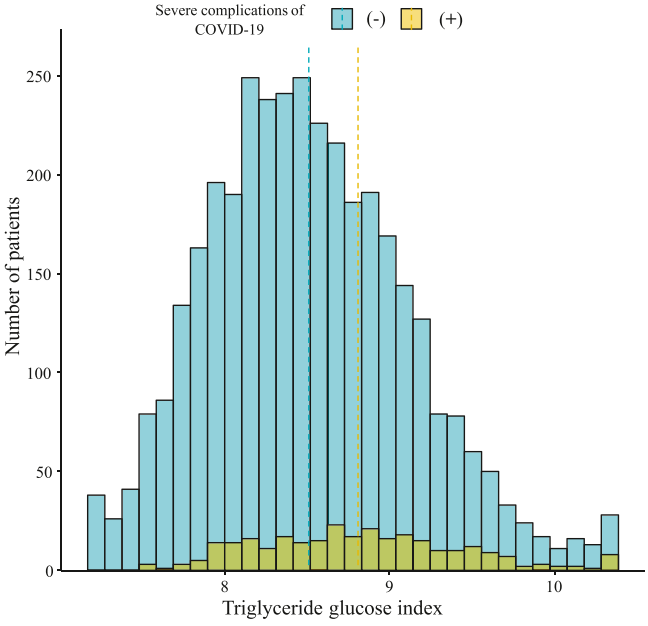

Fig. 2. Distribution of triglyceride-glucose index according to presence of severe complications of COVID-19. Vertical dotted lines present the mean values of triglyceride-glucose index in each groups with and without severe complications of COVID-19.

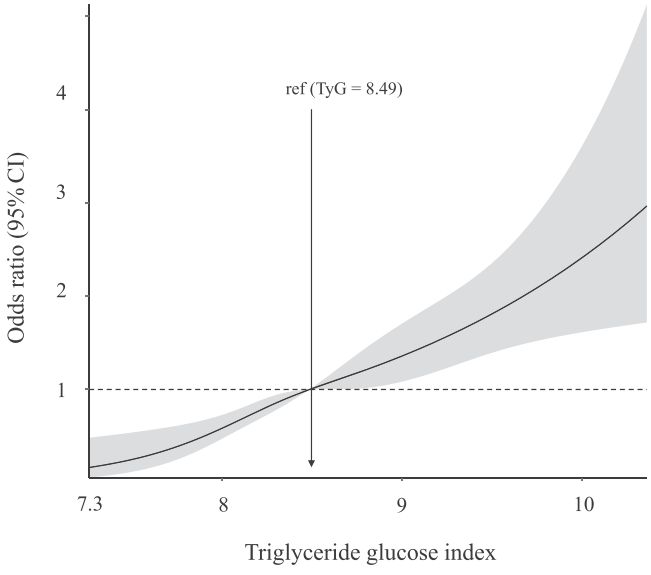

Fig. 3. Spline curve of the association between triglyceride-glucose index and severe complications of COVID-19. The black lines and gray shadows represent the odds ratio and 95% confidence intervals for the presence of severe complications of COVID-19 (composite of mechanical ventilation, intensive care unit care, high-flow oxygen therapy, and mortality). Ref indicates median value (8.49) of triglyceride-glucose index. TyG, triglyceride-glucose index; CI: confidence interval.

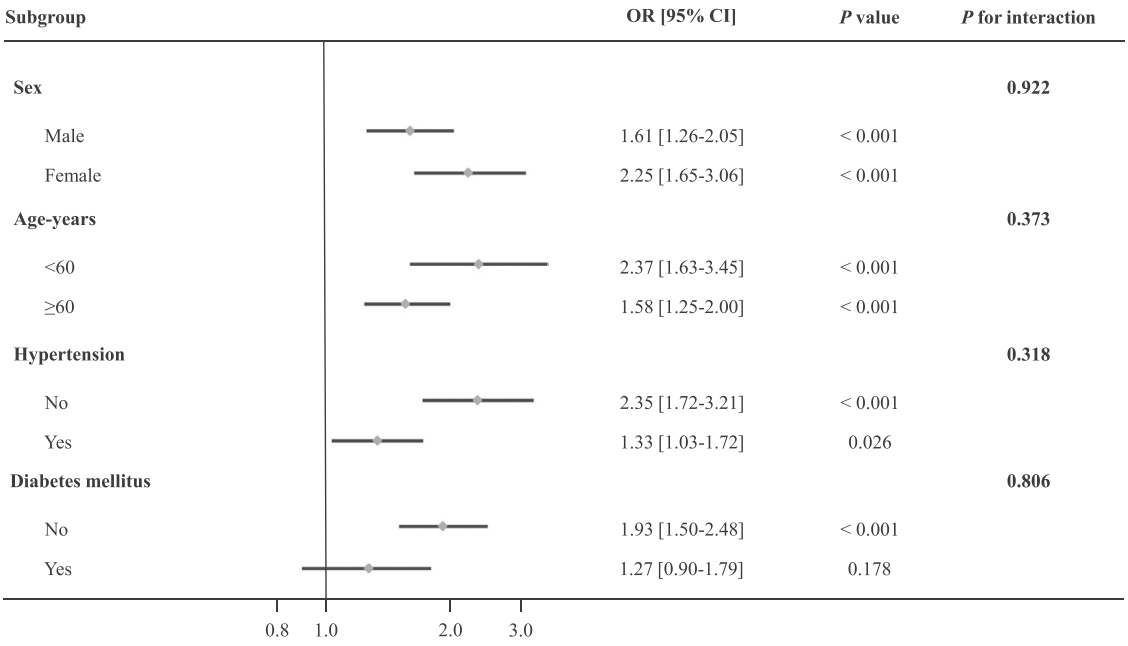

Fig. 4. Triglyceride-glucose index on the severe complications of COVID-19 in each subgroup by risk factor. Data include odds ratio (OR) and 95% confidence intervals (CI) for triglyceride-glucose index derived from logistic regression model for presence of severe complications in COVID-19 patients. *P*-values for interaction are calculated between each risk factor and triglyceride-glucose index.

insulin resistance and TyG index, are associated with poor prognosis of COVID-19 [38,41,42]. Because TyG index is considered a good surrogate marker of the comorbidities, those with high TyG index may have more risk factors and worse clinical outcomes in COVID-19 patients [27].

In COVID-19 infection, immunologic response plays a key role to maintain health and pathogenesis [43]. Current evidence suggested that dysregulated immune response may be responsible for COVID-19 pathogenesis and related critical illness, including lymphopenia, neutrophilia, dysregulation of monocytes/macrophages, impaired type I interferon response, antibody-dependent enhancement, and cytokine storm [44,45]. Studies in insulin resistance have revealed a clear association between the chronic activation of pro-inflammatory signaling pathways/impaired immune response and decreased insulin sensitivity [46,47]. Macrophages chronically exposed to high levels of insulin result in sustained inflammatory cytokine production and altered response to pathogen [48]. It has become apparent that the impaired immune response through multiple pathways in insulin resistance can lead to systemic alterations contributing to excessive production of pro-inflammatory cytokines, also known as a cytokine storm [36,49]. Because hyperactivated inflammatory responses with cytokine storm occurring in COVID-19 are regarded major pathogenesis of critical illness with COVID-19 [50], chronic activation of pro-inflammatory signaling and altered immunologic response with insulin resistance, presented as high TG index, could be a predisposing factor for severe complications of COVID-19 [27]. Accordingly, viremia may be worsened by insulin resistance, and this increased risk of viremia may cause poor prognosis or morality after COVID-19 infection [51,52].

Our study has limitations. First, because our study had a retrospective cohort design, the causal relationship could not be proven. Second, in the health screening cohort, young people under the age of 40 could not be included, so there would be a selection bias. Third, it is difficult to generalize our results for overall ethnicity because our dataset consists of only the Korean general population. Fourth, because our dataset checked the lipid profile before the COVID-19 infection, there was a lack of the serial laboratory finding or the change of the lipid profile after COVID-19. Fifth, concurrent medications before and after COVID-19 infection might be a possible confounding factor on the prognosis, which were not evaluated in current study. Since the TyG index is the calculated product of fasting triglyceride level and fasting blood glucose level, it could be affected by the anti-diabetic or lipid-lowering agents taken at the time of health screening. Finally, since insulin levels were not measured in our nationwide screening dataset, we could not directly check the insulin resistance.

In conclusion, our study demonstrated that TyG index measured before the COVID-19 infection was significantly associated with increased risk for severe complications of COVID-19. TyG index, which is simply calculated from fasting triglyceride and fasting blood glucose, may be a useful prognostic biomarker in COVID-19 infection. Further study is need for the pathophysiologic linking between insulin resistance and COVID-19 adverse outcomes.

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Ethics approval

The NHIS data was fully anonymized for privacy protection. Due to the retrospective analysis based on the fully anonymized data from our dataset, this study was approved by the Institutional Review Board of our institution (Seoul Hospital Ewha Womans University College of Medicine 2020-10-021), and the requirement for informed consent was waived.

Data availability

The COVID-19 database used in the present study is available from the National Health Insurance Sharing Service [http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do], but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. To access the data, a complete application form, research proposal, and an approval document for research purposes from an institutional review board should be submitted to the NHIS for review by the inquiry committee of research support.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgments

This study used the COVID-19 dataset (NHIS-2021-1-347) created by NHIS.

Author's contributions

Tae-Jin Song and Yoonkyung Chang designed the research and drafted the manuscript. Jinkwon Kim and Jimin Jeon performed the statistical analysis and the interpretation of data. Tae-Jin Song and Jinkwon Kim participated in the interpretation of all data and the critical revision of the manuscript for intellectual content. All authors read and approved the manuscript.

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