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Association of triglyceride/high-density lipoprotein cholesterol ratio with severe complications of COVID-19

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus can lead to serious complications such as respiratory failure, requiring mechanical ventilation or ICU care, and can even result in death, especially in older patients with comorbidities. The ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL), a biomarker of atherosclerotic dyslipidemia and insulin resistance, is related to cardiovascular mortality and morbidity. We aimed to evaluate the link between serious complications of COVID-19 and TG/HDL in the general population.

Methods: We conducted a comprehensive analysis of 3,933 COVID-19 patients from a nationwide cohort in Korea spanning from January 1 to June 4, 2020. TG/HDL ratio was calculated from the national health screening examination data underwent before the COVID-19 infection. Serious complications of COVID-19 were defined as a composite of high-flow oxygen therapy, mechanical ventilation, admission to the intensive care unit (ICU), and mortality. We employed logistic regression analysis to investigate the relationship between the TG/HDL ratio and the likelihood of developing severe complications within 2 months of the diagnosis. To visualize this association, we used a smoothing spline plot based on the generalized additive regression model. Multivariate analysis was performed with adjustment for age, gender, body mass index, lifestyle measures, and comorbidities.

Results: Among the 3,933 COVID-19 patients, the proportion of serious complications was 7.53%. Regarding individual outcomes, the number of patients who received high-flow oxygen therapy, mechanical ventilation, ICU care, and died was 84 (2.14%), 122 (3.10%), 173 (4.40%), and 118 (3.00%), respectively. In the multivariable logistic regression, a positive association was found between TG/HDL ratio and serious complications of COVID-19 (adjusted OR, 1.09; 95% CI [1.03–1.15], $p = 0.004$).

Conclusion: Our study revealed a significant positive association between TG/HDL ratio and the risk of developing severe complications in COVID-19-infected patients. While this finding

Abbreviations: COVID-19, Coronavirus disease 2019; TG/HDL ratio, Triglyceride to high-density lipoprotein ratio.

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provides valuable insight into the potential prognostic role of TG/HDL ratio in COVID-19, further studies are needed to fully elucidate the underlying mechanisms behind this relationship.

1. Introduction

The coronavirus disease 2019 (COVID-19) is a disease that became pandemic worldwide, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Most of the COVID-19 patients are asymptomatic or have mild symptoms, but some patients have serious complications such as respiratory failure, desaturation, and cyanosis [2]. A recent study analyzing 21,615 COVID-19 patients in Korea found that 19.1% experienced one or more complications related to their infection, and 4.4% required hospitalization due to severe illness [3]. Given the potential severity of the disease, identifying those at higher risk of developing serious complications is essential for effective treatment and prevention. Recent reports suggest that comorbidities, such as old age, hypertension, diabetes mellitus, cancer, chronic obstructive pulmonary disease, coronary disease, and neurological disease, may increase the likelihood of a poor prognosis [4–6]. Additionally, dyslipidemia and insulin resistance have been linked to COVID-19 prognosis, indicating a potential interaction between metabolic pathways and the immune system [7–9].

The triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio is a biomarker for atherosclerotic dyslipidemia and insulin resistance [10,11]. High TG/HDL ratio is related with cardiovascular mortality and morbidity, which has a better predictive value on cardiovascular risk than blood HDL or low-density lipoproteins cholesterol (LDL) levels [12,13]. This association is thought to be due

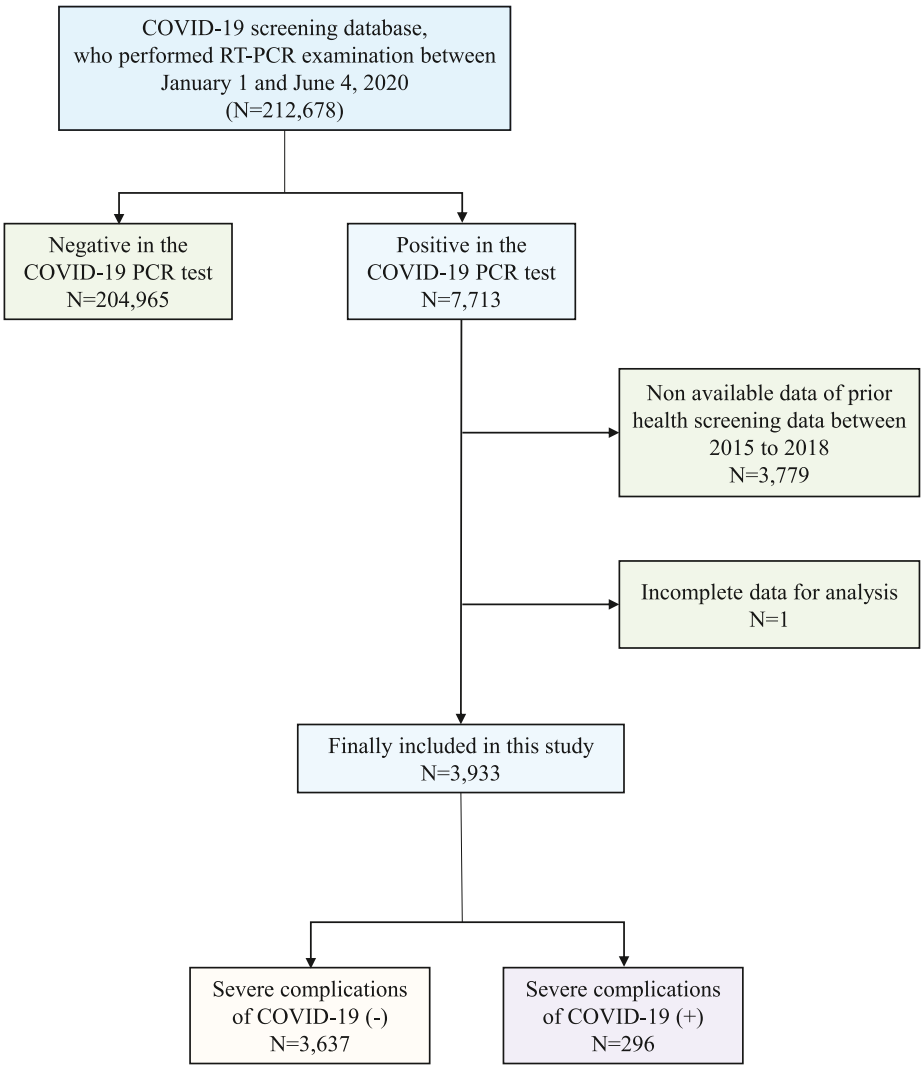

Fig. 1. Flow chart depicting the patient selection COVID-19, coronavirus disease 2019; RT-PCR, real-time reverse transcription polymerase chain reaction.

to the close relationship between metabolic pathways and immune networks [4,5]. Given these findings, we hypothesized that the TG/HDL ratio, as a simple indicator of atherosclerotic dyslipidemia and insulin resistance, could be used to predict complications in COVID-19 patients. Understanding the potential relationship between the TG/HDL ratio and COVID-19 prognosis could help inform more targeted treatment and prevention strategies for those at highest risk.

2. Subjects and methods

2.1. Study design and participants

In this study, the prognosis of COVID-19 patients was analyzed retrospectively using the Korean COVID-19 database. The Korean medical system has adopted the national health insurance system, and most citizens are subscribed to the National Health Insurance Service (NHIS). NHIS builds and provides big medical data for public health promotion and medical research [14]. The dataset provided by NHIS includes information on demographics, hospital visits, diagnoses (using the International Statistical Classification of Diseases and Related Health Problems, 10th revision code), medical practices, drugs, and mortality [15]. The Korea Centers for Disease Control and Prevention and the NHIS opened a COVID-19 dataset on who underwent the at least one real-time reverse transcription polymerase chain reaction (RT-PCR) test for the novel coronavirus infection from January 1 to June 4, 2020 [16]. For the Real-Time RT PCR assay kit, a diagnostic kit verified by the Korea Centers for Disease Control and Prevention according to the World Health Organization (WHO) guidelines was used [17]. The NHIS provides COVID-19 datasets as part of their effort to promote transparency and accountability in the management of the pandemic. By making these datasets publicly available, researchers and policymakers can access and analyze the data to gain insights into the epidemiology of COVID-19, identify patterns and trends, and develop evidence-based interventions to mitigate the spread of the virus. The COVID-19 dataset contains a wide range of information, including demographics, national health screening examination data, hospital visits, diagnoses, medications, procedures, and mortality (https://hira-covid19.net/). Health screening is an application of medical test to detect a disease or health conditions early when they are easier to manage and is a key part of disease prevention. In Korea, *a free national health screening* program was launched in the 1980s to promote early detection and diagnosis *of chronic diseases, as well as modifying health behaviors* to improve overall health outcomes [18]. Our study was conducted on patients who were diagnosed with COVID-19 by RT-PCR test and who had available data for TG and HDL from the national health examination program. Fig. 1 shows the patient selection according to the inclusion and exclusion criteria.

2.2. Study outcome

Primary outcome was the development of serious complications with COVID-19 infection, defined as a composite of high-flow oxygen therapy, ventilator treatment, ICU admission, and mortality within 2 months after diagnosis of COVID-19 [19–23]. Use of high-flow oxygen therapy, ventilator treatment, and admission to ICU were identified as the presence of related claim codes (high-flow oxygen therapy: M0046, mechanical ventilation: M5850, M5857, M5858, M5860, admission to ICU: AH110, AH150, AH180-85, 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) [24].

2.3. Data of TG/HDL ratio

TG/HDL ratio was calculated from previously performed health examination data (2015–2018) in COVID-19 patients. To reduce potential errors by extreme values, the ≥99-percentile value was substituted with the 99-percentile value, and the ≤1-percentile value was substituted with the 1-percentile value. The most recent result was used if the health checkup was performed repeatedly.

2.4. Covariate

Using the COVID-19 dataset patients' health screening and health insurance claim data, gender, age at the time of diagnosis of COVID-19, household income (quartile), body mass index (BMI), alcohol consumption, smoking, physical activity, underlying diseases (hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, stroke, asthma, and malignancy) were collected.

At the health screening examination, BMI was assessed by one's weight (kg) divided by the square of height (m^2), BMI >25 (kg/m^2) was defined as overweight [25]. Hypertension was identified as the presence of the diagnostic code (I10-15) with concurrent prescription of anti-hypertensive medications (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker, calcium-channel blocker, diuretics) in the health claim data, or blood pressure ≥140/90 mmHg or self-reports of the known hypertension at the time of health examination [26]. Diabetes mellitus was defined as the presence of the diagnostic code (E11-E14) with prescription of hypoglycemic agents (α-glucosidase inhibitor, metformin, meglitinide, sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist, sodium-glucose co-transporter 2, and insulin), or fasting blood glucose >7.0 mmol/L, or self-reports of the known diabetes at the time of health examination [27]. Chronic kidney disease was defined as the presence of diagnostic codes (N03, N05, N16.5, N18–9, N25.0, I12-3, Z49.0, Z49.1–2, Z94.0, Z99.2, E10.2, E11.2, E13.2, E14.2, or T86.1) [28,29]. Ischemic heart disease and stroke were also defined as the related diagnostic codes in the claims data (ischemic heart disease: I20–I25, stroke: I60–I63, and I69) [30,31]. Asthma was defined as a case in which the diagnosis code 'J45-46' was claimed as the main diagnosis code more than twice [32]. Malignancy was identified as the presence of diagnostic code (C00-97) and cancer-specific registration codes (V027 and V193-4) with ≥2 outpatient visits or ≥1 inpatient visits [33]. Information on alcohol

consumption, smoking, and physical activity were collected by a self-reported questionnaire. To calculate the total alcohol consumption per week, we multiplied the weekly frequency and pure alcohol amount per occasion, and subsequently converted the result to the daily amount of alcohol intake. The alcohol consumption was classified into 3 groups: none or mild (<15 g per day), moderate (15–29.9 g per day), or heavy (≥30 g per day), according to the Dietary Guidelines for Americans [34,35]. In the self-reported questionnaire, usual frequency per week of light, moderate, vigorous physical intensity with duration were collected, and 3.0, 4.0, and 8.0 metabolic equivalent of task (MET) were assigned, respectively. Participants were categorized according to the levels of physical activity per week as follows: inactive (0 MET-min/week), insufficiently active (1–499 MET-min/week), active (500–999 MET-min/week), highly active (≥1000 MET-min/week)] [36]. Based on the self-reported questionnaire, participants were evaluated whether they were current smokers.

Table 1
Baseline characteristics of patients according to the presence of severe complications of COVID-19.

Variable	Total	Presence of severe complications[a]		*P*-value[b]
		Without severe complications of COVID 19	With severe complications of COVID 19	
N	3933	3637	296	
Sex, male, n (%)	1471 (37.40)	1290 (35.47)	181 (61.15)	<0.001
Age, years, n (%)				<0.001
<60	2392 (60.82)	2328 (64.01)	64 (21.62)	
≥60	1541 (39.18)	1309 (35.99)	232 (78.38)	
Household income, n (%)				0.003
Q1, lowest	1345 (34.20)	1261 (34.67)	84 (28.38)	
Q2	924 (23.49)	863 (23.73)	61 (20.61)	
Q3	707 (17.98)	653 (17.95)	54 (18.24)	
Q4, highest	957 (24.33)	860 (23.65)	97 (32.77)	
Alcohol consumption (g/day), n (%)				0.572
none or mild: <15	3522 (89.55)	3258 (89.58)	264 (89.19)	
moderate: 15 to 30	228 (5.80)	213 (5.86)	15 (5.07)	
heavy: ≥30	183 (4.65)	166 (4.56)	17 (5.74)	
Current smoking, n (%)				0.434
Yes	3635 (92.42)	3358 (92.33)	277 (93.58)	
No	298 (7.58)	279 (7.67)	19 (6.42)	
Physical activity, metabolic equivalent task minutes per week, n (%)				0.413
0	1326 (33.71)	1213 (33.35)	113 (38.18)	
1–499	920 (23.39)	856 (23.54)	64 (21.62)	
500–999	844 (21.46)	784 (21.56)	60 (20.27)	
≥1000	843 (21.43)	784 (21.56)	59 (19.93)	
Body mass index (kg/m^2), n (%)				<0.001
Body mass index <25	2538 (64.53)	2378 (65.38)	160 (54.05)	
Body mass index ≥25	1395 (35.47)	1259 (34.62)	136 (45.95)	
Comorbidities, n (%)				
Hypertension	1324 (33.66)	1130 (31.07)	194 (65.54)	<0.001
Diabetes mellitus	613 (15.59)	511 (14.05)	102 (34.46)	<0.001
Stroke	158 (4.02)	124 (3.41)	34 (11.49)	<0.001
Coronary artery disease	210 (5.34)	173 (4.76)	37 (12.50)	<0.001
Chronic kidney disease	281 (7.14)	233 (6.41)	48 (16.22)	<0.001
Asthma	216 (5.49)	189 (5.20)	27 (9.12)	0.004
Malignancy	336 (8.54)	292 (8.03)	44 (14.86)	<0.001
Lipid profile, means (SD)				
Total cholesterol, mg/dL	194.94 ± 37.51	195.56 ± 37.26	187.27 ± 39.77	<0.001
Triglyceride, mg/dL	120.35 ± 73.87	118.55 ± 72.69	142.50 ± 84.19	<0.001
HDL, mg/dL	56.53 ± 14.05	56.91 ± 13.98	51.85 ± 14.03	<0.001
TG/HDL ratio	2.44 ± 2.29	2.35 ± 1.89	3.11 ± 2.33	<0.001
Clinical outcome, n (%)				
Mechanical ventilation	122 (3.10)			
Intensive care unit care	173 (4.40)			
High-flow oxygen therapy	84 (2.14)			
Death	118 (3.00)			

COVID-19, coronavirus disease 2019; HDL, High-density lipoprotein cholesterol; Q, quartile; SD, standard deviation; TG, triglyceride.
Data are presented as the number of participants (%) or mean ± standard deviation.

[a] Severe complications of COVID-19 include high-flow oxygen therapy, mechanical ventilation, admission to intensive care unit, and death within 2 months after COVID-19 diagnosis.

[b] P-value is derived from the independent *t*-test or chi-square test between patient groups according to severe complications of COVID-19.

2.5. Ethics statement

As this study is a retrospective study using a fully anonymized dataset, informed consent was not taken from the individual. The Institutional Review Board of Seoul Hospital Ewha Womans University College of Medicine approved the conduct of the study (#2020-10-021).

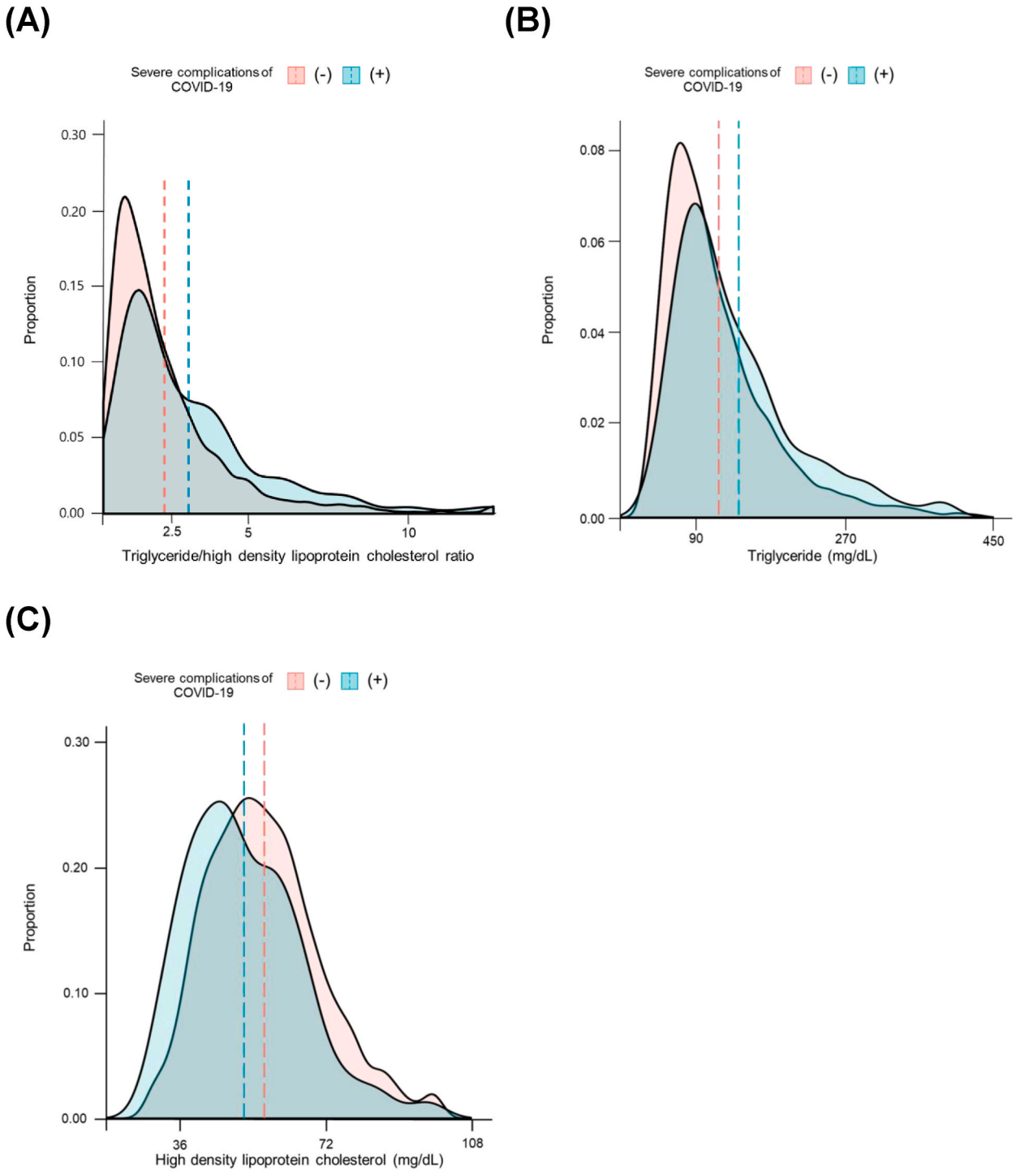

Fig. 2. Distribution of (A) triglyceride/high-density lipoprotein cholesterol ratio, (B) triglyceride, and (C) high-density lipoprotein cholesterol levels according to the presence of severe complications in COVID-19 patients. The vertical dotted line indicates the mean value.

2.6. Statistical analysis

We performed chi-square tests to evaluate the difference in categorical variables between groups. Independent t-tests were done to compare continuous variables between two groups. To evaluate the association between TG/HDL ratio and prognosis after COVID-19 infection, we used logistic regression analysis for the development of severe complications within 2 months. To better describe the relationship between TG/HDL ratio and severe complications of COVID-19, we illustrated smoothing spline plot based on the generalized additive regression model. In the multivariable analysis, age, gender, body mass index, alcohol consumption, smoking, physical activity, household income, hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, stroke, asthma, malignancy, and level of total cholesterol were adjusted. Data manipulation and statistical analyses were performed using SAS 9.4 version (SAS Inc., Cary, NC, USA) and R 3.3.3 version (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographics of study patients

In the COVID-19 screening dataset, there were 212,678 participants who underwent at least one COVID-19 RT-PCR test from January 1, 2020 to June 4, 2020. According to the inclusion and exclusion criteria, this study finally included 3,933 COVID-19 infected patients with an available TG/HDL ratio (Fig. 1). Table 1 shows the demographics of the included patients with COVID-19 infection. Among the study patients, 37.40% were males, and 39.18% were aged ≥60. The mean ± standard deviation of TG/HDL ratio in the study patients was 2.44 ± 2.29.

Table 2
Factors associated with the occurrence of severe complications in COVID-19 patients.

Variable	Univariate OR [95% CI]	P-value	Adjusted OR [95% CI][a]	P-value
Sex, male	2.86 [2.25–3.65]	<0.001	2.66 [2.02–3.50]	<0.001
Age, years				
<60	1 (Ref)	–	1 (Ref)	–
≥60	6.45 [4.85–8.57]	<0.001	3.96 [2.90–5.42]	<0.001
Household income				
Q1, lowest	1 (Ref)	–	1 (Ref)	–
Q2	1.06 [0.76–1.49]	0.733	1.12 [0.78–1.61]	0.555
Q3	1.24 [0.87–1.77]	0.232	1.14 [0.78–1.67]	0.485
Q4, highest	1.69 [1.25–2.30]	<0.001	1.38 [0.99–1.91]	0.057
Alcohol consumption (g/day)				
none to mild: <15	1 (Ref)	–	1 (Ref)	–
moderate: 15 to 30	0.87 [0.51–1.49]	0.610	0.77 [0.43–1.39]	0.383
heavy: ≥30	1.26 [0.76–2.12]	0.372	0.90 [0.51–1.59]	0.717
Current smoker				
No	1 (Ref)	–	1 (Ref)	–
Yes	0.83 [0.51–1.34]	0.435	0.52 [0.31–0.88]	0.016
Physical activity, MET minutes per week				
0	1 (Ref)	–	1 (Ref)	–
1–499	0.80 [0.58–1.10]	0.176	0.95 [0.67–1.34]	0.765
500–999	0.82 [0.59–1.14]	0.237	0.81 [0.57–1.16]	0.248
≥1000	0.81 [0.58–1.12]	0.201	0.76 [0.53–1.08]	0.122
Body mass index (kg/m^2)				
<25	1 (Ref)	–	1 (Ref)	–
≥25	1.61 [1.27–2.04]	<0.001	1.09 [0.84–1.41]	0.540
Comorbidities				
Hypertension	4.22 [3.29–5.42]	<0.001	1.89 [1.42–2.51]	<.001
Diabetes mellitus	3.22 [2.49–4.16]	<0.001	1.38 [1.02–1.86]	0.037
Stroke	3.68 [2.47–5.48]	<0.001	1.34 [0.87–2.07]	0.190
Coronary artery disease	2.86 [1.96–4.17]	<0.001	1.16 [0.76–1.77]	0.482
Chronic kidney disease	2.83 [2.02–3.96]	<0.001	1.28 [0.87–1.87]	0.216
Asthma	1.83 [1.20–2.79]	0.005	1.30 [0.82–2.06]	0.261
Malignancy	2.00 [1.42–2.82]	<0.001	1.40 [0.96–2.03]	0.079
Laboratory findings				
Total cholesterol, mg/dL	0.79 [0.70–0.90]	<0.001	0.91 [0.80–1.04]	0.176
TG/HDL ratio	1.16 [1.11–1.22]	<0.001	1.09 [1.03–1.15]	0.004

Data are derived from logistic regression analysis for severe complications in COVID-19. Severe complications is a composite of high-flow oxygen therapy, mechanical ventilation, admission to intensive care unit, and death within 2 months after COVID-19 diagnosis. OR, odds ratio; CI, confidence interval; Q, quartile; TG, triglyceride; HDL, high-density lipoprotein cholesterol.

[a] Adjusted for sex, age, household income, alcohol consumption, smoking, physical activity, body mass index, hypertension, diabetes mellitus, stroke, coronary artery disease, chronic kidney disease, asthma, malignancy, and total cholesterol.

3.2. Prognosis after COVID-19 infection

During the two months from the COVID-19 diagnosis, the number of patients with primary outcome (development of serious complications) was 296 (7.53%). Regarding individual outcomes, the numbers of patients who received mechanical ventilation, admission to ICU, high-flow oxygen therapy, and who died were 122 (3.10%), 173 (4.40%), 84 (2.14%), and 118 (3.00%), respectively.

3.3. TG/HDL ratio and severe complication of COVID-19

Fig. 2 demonstrates TG/HDL ratio distribution in the patients with and without severe COVID-19 complications. To evaluate the association between TG/HDL ratio and risk of serious complications in COVID-19 patients, we performed univariate and multivariable logistic regression analysis (Table 2). In univariate analysis, TG/HDL ratio was related with serious complications of COVID-19 (odds ratio (OR): 1.16; 95% confidence interval (CI): 1.11–1.22, $\boldsymbol{P} < 0.001$). This finding persisted in the multivariable model (adjusted OR: 1.09; 95% CI: 1.03–1.15, $\boldsymbol{P} = 0.004$). Fig. 3 shows a spline curve for OR according to TG/HDL ratio, with the median value of TG/HDL ratio (1.81) as a reference. In the spline curve, the prevalence of serious COVID-19 complications tended to increase as TG/HDL ratio increased.

3.4. TG/HDL ratio and mortality

As a secondary outcome, we further analyzed the relationship between TG/HDL ratio and mortality within two months from COVID-19 diagnosis (Table 3). In the multivariable model, TG/HDL ratio had positive correlation with mortality (adjusted OR: 1.12; 95% CI: 1.04–1.22, $\boldsymbol{P} = 0.006$).

In the subgroup analysis, a positive relationship between TG/HDL ratio and serious complications of COVID-19 was consistent regardless of sex, age, hypertension, and diabetes mellitus (Fig. 4).

4. Discussion

The main finding of our study is that a high blood TG/HDL ratio, which represents atherosclerotic dyslipidemia and insulin resistance, was linked with a higher risk of serious complications in COVID-19 infected patients. The identifying of laboratory biomarker, simply calculated from routine lipid profiles, on COVID-19 prognosis would help to classify patients according to the risk of serious complication, which in turn enables timely and proper treatment for the high-risk groups, such as early use of antiviral agents and intensive monitoring [37,38].

Multiple studies have investigated the relationship between dyslipidemia, cholesterol levels, and COVID-19 outcomes. A recent meta-analysis found that dyslipidemia was associated with a higher risk of severe complications from COVID-19, (relative risk: 1.39) [8], while another study found that blood cholesterol levels may be related to COVID-19 severity [39]. A multicenter cohort study found that increased TG and decreased HDL levels were significantly associated with poor prognosis in COVID-19 patients [40]. In a

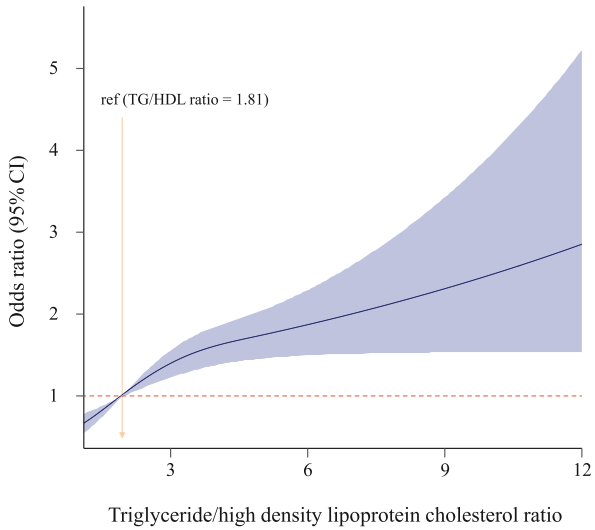

Fig. 3. Spline curves of the association between triglyceride/high-density lipoprotein cholesterol ratio and severe complications of COVID-19. The blue lines and shadows represent the odds ratio and 95% confidence intervals for the presence of severe complications of COVID-19 (composite of mechanical ventilation, intensive care unit care, high-flow oxygen therapy, and death), with the median value of triglyceride/high-density lipoprotein cholesterol ratio (1.81) as reference (odds ratio = 1.0). TG/HDL, triglyceride/high-density lipoprotein cholesterol; CI, confidence interval.

Table 3
Associated factors for occurrence of mortality in COVID-19 patients.

Variable	Univariate OR [95% CI]	P-value	Adjusted OR [95% CI][a]	P-value
Sex, male	3.82 [2.58–5.67]	<0.001	3.36 [2.17–5.20]	<0.001
Age, years				
<60	1 (Ref)	–	1 (Ref)	–
≥60	14.65 [8.04–26.71]	<0.001	7.49 [3.95–14.19]	<0.001
Household income				
Q1, lowest	1 (Ref)	–	1 (Ref)	–
Q2	1.47 [0.87–2.50]	0.155	1.70 [0.96–3.00]	0.069
Q3	1.58 [0.90–2.78]	0.108	1.48 [0.81–2.69]	0.1991
Q4, highest	1.20 [1.22–3.27]	0.006	1.64 [0.97–2.79]	0.065
Alcohol consumption (g/day)				
none to mild: <15	1 (Ref)	–	1 (Ref)	–
moderate: 15 to 30	0.99 [0.46–2.16]	0.983	0.73 [0.31–1.76]	0.486
heavy: ≥30	0.35 [0.09–1.41]	0.139	0.19 [0.04–0.81]	0.024
Current smoker				
No	1 (Ref)	–	1 (Ref)	–
Yes	1.40 [0.76–2.57]	0.282	0.94 [0.47–1.90]	0.871
Physical activity, MET minutes per week				
0	1 (Ref)	–	1 (Ref)	–
1–499	0.82 [0.51–1.31]	0.404	0.97 [0.58–1.62]	0.894
500–999	0.67 [0.40–1.18]	0.123	0.62 [0.36–1.08]	0.093
≥1000	0.63 [0.37–1.07]	0.090	0.57 [0.32–1.00]	0.050
Body mass index (kg/m^2)				
<25	1 (Ref)	–	1 (Ref)	–
≥25	1.79 [1.24–2.59]	0.002	1.11 [0.74–1.66]	0.613
Comorbidities				
Hypertension	6.72 [4.38–10.33]	<0.001	2.28 [1.42–3.68]	<0.001
Diabetes mellitus	4.41 [3.03–6.41]	<0.001	1.50 [0.97–2.32]	0.069
Stroke	5.81 [3.52–9.60]	<0.001	1.95 [1.13–3.39]	0.017
Coronary artery disease	3.16 [1.85–5.39]	<0.001	1.01 [0.56–1.84]	0.963
Chronic kidney disease	3.74 [2.36–5.92]	<0.001	1.40 [0.83–2.37]	0.210
Asthma	1.81 [0.96–3.42]	0.068	1.12 [0.56–2.25]	0.745
Malignancy	2.71 [1.69–4.33]	<0.001	1.76 [1.05–2.95]	0.031
Laboratory findings				
Total cholesterol, mg/dL	0.84 [0.76–0.92]	<0.001	0.85 [0.70–1.05]	0.130
TG/HDL ratio	1.20 [1.13–1.29]	<0.001	1.12 [1.04–1.22]	0.006

Data are derived from logistic regression analysis for death within 2 months after COVID-19 diagnosis. OR, odds ratio; CI, confidence interval; Q, quartile; TG, triglyceride; HDL, High-density lipoprotein cholesterol.

[a] Adjusted for sex, age, household income, alcohol consumption, smoking, physical activity, body mass index, hypertension, diabetes mellitus, stroke, ischemic heart disease, chronic kidney disease, asthma, malignancy, and total cholesterol.

retrospective case series study, TG/HDL ratio was increased in COVID-19 patients with cardiovascular complication and poor outcomes [41]. A recent study in China (n = 262) also showed worse clinical outcome with elevated TG/HDL ratio in COVID-19 patients [42]. A systematic review and meta-analysis of 19 studies found that total cholesterol, HDL, and LDL were decreased in patients with severe COVID-19 [43]. On the other hand, insulin resistance and diabetes have been linked to worse outcomes in COVID-19 patients [44,45], by increasing membrane expression of ACE2 [46,47]. Also, insulin resistance and hyperglycemia can cause inflammation releasing pro-inflammatory cytokines and activating inflammatory pathways [48,49]. Our results support the results of these previous studies. The positive relationship between TG/HDL ratio and serious complications of COVID-19 may provide additional information that dyslipidemia and insulin resistance might have connection with severe complications of COVID-19 in a nation-wide cohort study.

Although our study did not explore the mechanism, we propose theories that may justify the link between TG/HDL ratio and COVID-19 outcomes. Lipids and lipid metabolites *participate* in multiple *cellular* processes and signaling pathways, that are associated with the immunologic and inflammatory response [50,51]. Accumulating evidence have shown that lipid profiles have a prognostic value in the development, disease activity, and progression of various clinical disorders including cardiovascular, metabolic, malignant, inflammatory, and infectious diseases [52–54]. TG/HDL ratio is a representative biomarker of atherogenic dyslipidemia and is closely associated with insulin resistance [55,56]. COVID-19 patients are known to have a poor prognosis when they have cardiovascular disease and dyslipidemia, which are related to an atherogenic process [8]. Because a higher TG/HDL ratio is considered to have a more severe atherogenic process and a higher cardiovascular disease burden, which is also related to a higher likelihood of poor prognosis of COVID-19, our results of the positive relationship between TG/HDL ratio and severe COVID-19 complications can be explained. In patients with extensive lung injury due to previous MERS-CoV or SARS-CoV infection, the cytokine level in the blood was significantly elevated. This cytokine storm caused hyperactivation of neutrophils, macrophages, lymphocytes, Th1/Th17, and Toll-like receptor pathways in the adaptive immune system. Because insulin resistance is known to be involved in the inflammatory response associated with this cytokine storm [57,58], the results of our study can be explained. In patients with insulin resistance or diabetes mellitus accompanied by hyperinsulinemia, insulin can increase the activity of angiotensin-converting enzyme 2, which functions as a receptor for the COVID-19 spike protein that causes infection of cells located in the lungs. Thus, viremia can be exacerbated by insulin

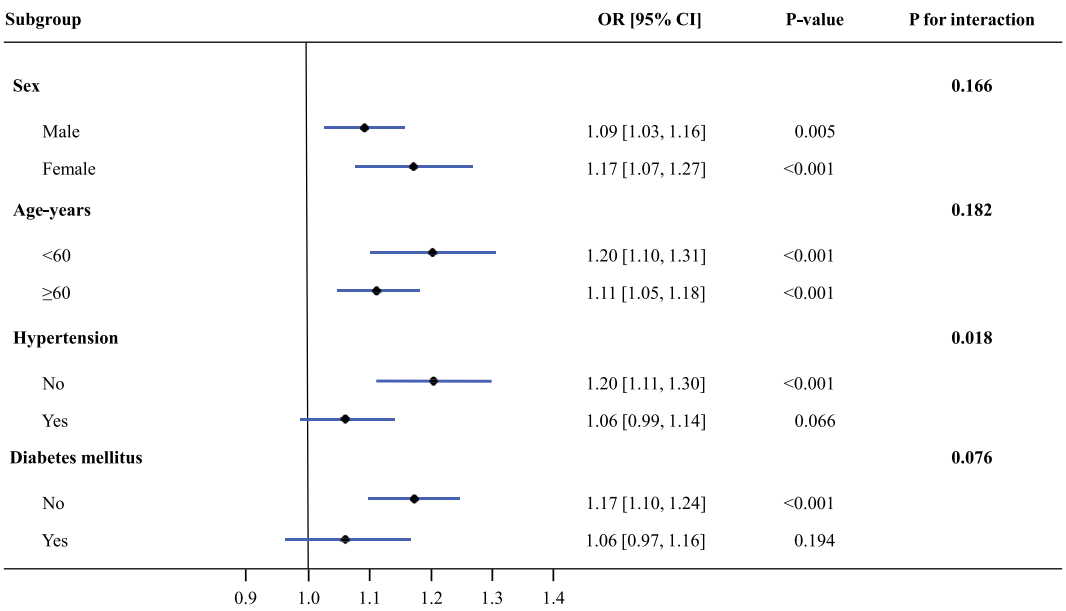

Fig. 4. Association of triglyceride to high-density lipoprotein cholesterol ratio on the severe complications of COVID-19 in each subgroup by risk factor. Data include odds ratio (OR) and 95% confidence intervals (CI) for triglycerides to high-density lipoprotein cholesterol ratio, derived from logistic regression model for severe complications of COVID-19. P-values for interaction are based on the interaction between risk factors and triglyceride to high-density lipoprotein cholesterol ratio.

resistance, and it can lead to severe complications in COVID-19 [59,60]. The insulin resistance is considered one explanation for the higher risk of severe COVID-19 in the diabetes compared to non-diabetic patients [61]. In addition, insulin resistance aggravates systemic inflammation and increases the risk of thrombosis by adversely affecting the coagulation pathway and increasing the level of plasminogen activator type 1. Therefore, this thrombotic condition may have influenced poor outcomes [62].

4.1. Limitations

This study has several limitations. At first, a causal relationship could not be established, because of a retrospective design of current study. Second, due to the lack of health screening data at a young age, those aged <40 years could not be included. The predictive value of TG/HDL in young COVID-19 patients should be further evaluated. Third, there may be potential confounding effects on COVID-19 prognosis with concomitant medications, which were not assessed in this study. Fourth, since our dataset consists only of Koreans, it is difficult to generalize the results. Fifth, because the lipid profile was checked before COVID-19 infection, we could not evaluate serial data or changes in the lipid profile after COVID-19, and we did not include information on C-reactive protein, an important biomarker for inflammatory condition [63]. Sixth, in our nationwide COVID-19 dataset, the clinical outcomes or prognosis of COVID-19 PCR test-negative participants were not available. Therefore, we could not compare the differences in outcomes between the positive and negative COVID-19 participants. Seventh, we could not directly assess beta-cell function and insulin resistance because insulin level was not measured in the national health screening program of Korea. Eighth, OR for primary outcome and TG/HDL ratio was small, and the difference of crude and adjusted ORs were also small. This may be due to the fact that the impact of TG/HDL ratio on outcomes is also influenced by other critical factors, such as old age and other comorbidities. Lastly, our study results revealed a notable decrease or increase in the OR values (cOR & aOR) after adjusting for the TG/HDL ratio, leading to loss of significance for several comorbidities, including stroke (from 3.68 to 1.34), coronary artery disease (from 2.86 to 1.16), and chronic kidney disease (from 2.83 to 1.28). Since several covariates are also closely related to the outcome, there is a possibility that the impact, or OR, was lowered during multivariable analysis.

5. Conclusion

This study showed TG/HDL ratio assessed before COVID-19 infection was positively correlated with an increased risk of serious complications with COVID-19. There is a need for further studies for the prognostic role of TG/HDL ratio in COVID-19 and the mechanism underlying the relationship.

Author contribution statement

Yoonkyung Chang: Analyzed and interpreted the data; Wrote the paper.

Jimin Jeon: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Tae-Jin Song: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jinkwon Kim: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data. The COVID-19 dataset supporting the conclusions of this study is available on the homepage of the National Health Insurance Sharing Service [http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do]. To gain access to the data, a completed application form, a research proposal, and the applicant's approval document from the institutional review board should be submitted to and reviewed by the inquiry committee of research support in the NHIS. Currently, the use of NHIS data is only allowed for Korean researchers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17428.

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