Triglyceride/High-Density Lipoprotein Cholesterol Ratio is associated with the mortality of COVID-19: An Observational Study

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Research Article

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Abstract

(1) Background: Triglyceride to high density lipoprotein cholesterol (TG/HDL-c) ratio is crucial when researching metabolic and vascular diseases, and its involvement in COVID-19 was sparsely elaborated on. The purpose of the study was to explore if there were any associations between the TG/HDL-c ratio and COVID-19 prognosis;

(2) Methods: A total of 262 COVID-19 patients were retrospectively investigated. The clinical features and baseline hematological parameters were recorded and analyzed;

(3) Results: Compared with the survivors, the non-survivors of COVID-19 had significantly higher levels of white blood cells (4.7 vs. 13.0 ×10^9/L; \(P<0.001\)), neutrophils (3.0 vs. 11.6×10^9/L; \(P<0.001\)), C-reactive proteins (15.7 vs. 76.7 mg/L; \(P<0.001\)) and TG/HDL-c ratio (1.4 vs. 2.5; \(P=0.001\)). The receiver operating characteristics curve [area under the curve, 0.731; 95% confidence interval, 0.609–0.853; \(P=0.001\)] suggested that the TG/HDL-c ratio could predict the mortality of COVID-19. Moreover, the TG/HDL-c ratio was positively correlated with white blood cells (\(r=0.255, P<0.001\)), neutrophils (\(r=0.243, P<0.001\)) and C-reactive proteins (\(r=0.170, P<0.006\));

(4) Conclusions: Our study demonstrated that TG/HDL-c ratio may potentially be a predictive marker for mortality in COVID-19 patients.

1. Background

As is generally known, the Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has already become a serious threat to the global public health system\(^1\). As of May 21, 2021, there were already 160 million confirmed cases of COVID-19 which has resulted in more than 3.4 million deaths worldwide\(^2\). Although most cases reported mild, severe cases can progress rapidly, culminating in respiratory failure, septic shock, or a fatal outcome. Consequently, being able to identify risk factors early is very important for COVID-19 progression. Dyslipidemia is common in strokes \(^3\), insulin resistance \(^4\), metabolic syndromes \(^5\) and cardiovascular diseases \(^6\). Increases in TG and decreases in HDL-c may be caused by inflammatory cytokines, and triglyceride (TG), and a high density lipoprotein cholesterol (HDL-c) ratio (TG/ HDL-c) was strongly correlated with inflammation\(^7\). Idiopathic pulmonary arterial hypertension (IPAH) patients with a higher TG/ HDL-c ratio were more likely to suffer from systemic inflammation\(^7\). Type B acute aortic dissection (AAD) patients with higher TG/ HDL-c ratio had greater mortality that might be explained by higher levels of inflammatory factors\(^8\). Nevertheless, the correlation between TG/HDL-c ratio and viral infections is still not clear. And this study seeks to clarify the relationship of TG/HDL-c ratio and the mortality of COVID-19 patients.

2. Methods
2.1 Study Design

Ethic approval was obtained from the Second Xiangya Hospital of Central South University (No.2020001, April 20, 2020). The enrolled COVID-19 patients, restricted to adults, were confirmed by real-time polymerase chain reactions and driven from the Tongji Medical College of Huazhong University of Science and Technology and Public Health Treatment Center of Changsha China, by March 26th 2020. Based on their survival status, the enrolled patients were divided into a survivor and non-survivor group.

2.2 Data Collection

All medical records of the patients were carefully collected and reviewed by two members of our team. We recorded the demographics, baseline characteristics, and blood test parameters when admitting patients. The medical records with incomplete information were excluded. The primary end point in this study was the occurrence of death among patients with COVID-19.

2.3 Statistical Analysis

The Mann-Whitney test and Fisher’s exact test (or χ² test) were used to analyze the continuous and categorical variables, respectively. To detect which variables best predicted the final outcome for COVID-19 patients, we performed univariate and multivariate logistic regression analyses. To evaluate how variables can predict COVID-19 prognoses, the receiver operating characteristics (ROC) were calculated. The Spearman's rank correlation coefficients were used to measure the correlation between two variables. IBM SPSS version 26 software was conducted during all analyses.

3. Results

The enrolled patients were separated into survivors and non-survivors based on clinical outcomes, and demographics and baseline characteristics for each group are provided in Table 1. A total of 262 patients aged above 18 were admitted to the study, which included 244 survivors and 18 non-survivors. Based on their age, patients were further divided into three groups, i.e., ≥ 65years (21.4%), 45 years ≤ age < 65years (36.6%), < 45years (42.0%), respectively. Comparing the survivors with the non-survivors, there were significant differences that among in the ages and comorbidities with cancer (P < 0.05).

Table 1 Demographics and baseline characteristics of survivor and non-survivor of COVID-19 patients
|                              | No. (%)               | Survivor (n = 244) | Non-survivor (n = 18) | \( P \) value |
|------------------------------|-----------------------|--------------------|-----------------------|--------------|
| **Age, %**                   |                       |                    |                       |              |
| \( \geq 65 \text{y} \)      | 56(21.4)              | 45(18.4)           | 11(61.1)              | \(<0.001\)   |
| 45\( \leq \)age\(< 65 \)   | 96(36.6)              | 89(36.5)           | 7(38.9)               |              |
| \( < 45 \text{y} \)        | 110(42.0)             | 110(45.1)          | 0(0.0)                |              |
| **Gender, %**                |                       |                    |                       | 0.774        |
| Male                         | 137(52.3)             | 127(52.0)          | 10(55.6)              |              |
| Female                       | 125(47.7)             | 117(48.0)          | 8(44.4)               |              |
| **Symptoms**                 |                       |                    |                       |              |
| Fever, %                     | 181(78.6)             | 165(67.6)          | 16(88.9)              | 0.060        |
| Cough, %                     | 212(80.9)             | 197(80.7)          | 15(83.3)              | 0.787        |
| Myalgia, %                   | 26(9.9)               | 25(10.2)           | 1(5.6)                | 0.521        |
| Fatigue, %                   | 114(43.5)             | 109(44.7)          | 5(27.8)               | 0.164        |
| Headache, %                  | 33(12.6)              | 32(13.1)           | 1(5.6)                | 0.352        |
| Diarrhoea, %                 | 58(22.1)              | 54(22.1)           | 4(22.2)               | 0.993        |
| Abdominal pain, %            | 7(2.7)                | 7(2.9)             | 0(0.0)                | 0.467        |
| Shortness of breath, %       | 90(34.3)              | 83(34.0)           | 7(38.9)               | 0.675        |
| **Comorbidities**            |                       |                    |                       |              |
| Hypertension, %              | 53(20.2)              | 48(19.7)           | 5(27.8)               | 0.410        |
| Cardiovascular disease, %    | 18(6.9)               | 15(6.1)            | 3(16.7)               | 0.089        |
| Diabetes, %                  | 25(9.5)               | 23(9.4)            | 2(11.1)               | 0.815        |
| COPD, %                      | 1(0.0)                | 1(0.0)             | 0(0.0)                | 0.786        |
| Chronic bronchitis, %        | 20(7.6)               | 20(8.1)            | 0(0.0)                | 0.527        |
| Cerebrovascular disease, %   | 9(3.4)                | 8(3.2)             | 1(5.5)                | 0.609        |
| Cancer, %                    | 5(1.9)                | 2(1.0)             | 3(16.7)               | \(<0.001\)   |

Abbreviation: COVID-19, Coronavirus disease 2019; COPD, chronic obstructive pulmonary disease.

\( P \) values indicate differences between survivor and non-survivor of COVID-19 patients. \( P < 0.05 \) was considered statistically significant.
The non-survivor COVID-19 patients had significantly higher white blood cells (WBC) (4.7 vs. 13.0 ×10⁹/L; \(P<0.001\)), neutrophils (3.0 vs. 11.6 ×10⁹/L; \(P<0.001\)), C-reactive proteins (CRP) (15.7 vs. 76.7mg/L; \(P<0.001\)), and TG/HDL-c ratio (1.4 vs. 2.5; \(P=0.001\)) levels than survivors, but the levels of lymphocytes (1.1 vs. 0.6 ×10⁹/L; \(P<0.001\)), and low density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio (LDL-c/HDL-c) (3.2 vs. 2.2; \(P=0.010\)) were lower than non-survivors when compared with survivors (Table 2).

|                | Normal range | Survivor     | Non-survivor | \(P\) value |
|----------------|--------------|--------------|--------------|-------------|
| **WBC, \(\times10^9/L\)** | 3.5-9.5      | 4.7(3.6-6.0) | 13.0(7.8-17.8)| \(<0.001\) |
| **Lymphocytes, \(\times10^9/L\)** | 0.8-4.0      | 1.1(0.8-1.5) | 0.6(0.4-0.7) | \(<0.001\) |
| **Neutrophils, \(\times10^9/L\)** | 1.8-6.3      | 3.0(2.2-3.8) | 11.6(6.9-16.6)| \(<0.001\) |
| **CRP, mg/L**   | 0-8          | 15.7(4.5-35.3)| 76.7(36.8-229.0) | \(<0.001\) |
| **TC/HDL-c ratio** | /            | 4.5(3.8-5.6) | 5.0(3.4-5.6) | 0.899 |
| **LDL-c/HDL-c ratio** | /            | 3.2(2.5-4.1) | 2.2(1.4-3.4) | \(0.010\) |
| **TG/HDL-c ratio** | /            | 1.4(0.9-2.1) | 2.5(1.5-4.8) | \(0.001\) |

Abbreviation: COVID-19, Coronavirus disease 2019; WBC, white blood cells; CRP, C-reactive proteins; TC/HDL-c ratio, total cholesterol-to-high-density lipoprotein cholesterol ratio; LDL-c/HDL-c ratio, low-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio; TG/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio.

\(P\) values indicate differences between smoking and non-smoking COVID-19 patients. \(P<0.05\) was considered statistically significant.

The mortality of COVID-19 patients was associated with age [odds ratio (\(OR\)) = 1.108; 95% confidence interval (\(CI\)) 1.060-1.159; \(P<0.001\)], cancer (\(OR = 24.200; 95\% CI, 3.754-156.023; P = 0.001\)), WBC (\(OR = 1.451; 95\% CI, 1.267-1.661; P<0.001\)), lymphocytes (\(OR = 0.006; 95\% CI, 0.001-0.059; P<0.001\)), neutrophils (\(OR = 1.493; 95\% CI, 1.294-1.724; P<0.001\)), CRP (\(OR = 1.023; 95\% CI, 1.014-1.032; P<0.001\)), LDL-c/HDL-c ratio (\(OR = 0.551; 95\% CI, 0.327-0.927; P = 0.025\)), and TG/HDL-c ratio (\(OR = 1.291; 95\% CI, 1.066-1.564; P = 0.009\)) (Table 3). However, only TG/HDL-c ratio (\(OR = 1.730; 95\% CI, 1.044-2.866; P = 0.033\)) and cancer (\(OR = 44.973; 95\% CI, 2.059-982.524; P = 0.016\)) were the independent risk factors affected mortality in COVID-19 patients (Table 4).
Table 3 Univariate analysis of risk factors related to the mortality of COVID-19 patients

| Variables         | Odds Ratio (95% CI)       | Pvalue |
|-------------------|---------------------------|--------|
| Age               | 1.108(1.060-1.159)        | <0.001 |
| Cancer            | 24.200(3.754-156.023)     | 0.001  |
| WBC               | 1.451(1.267-1.661)        | <0.001 |
| Lymphocytes       | 0.006(0.001-0.059)        | <0.001 |
| Neutrophils       | 1.493(1.294-1.724)        | <0.001 |
| CRP               | 1.023(1.014-1.032)        | <0.001 |
| LDL-c/HDL-c ratio | 0.551(0.327-0.927)        | 0.025  |
| TG/HDL-c ratio    | 1.291(1.066-1.564)        | 0.009  |

Abbreviation: COVID-19, Coronavirus disease 19; CI, confidence interval; WBC, white blood cells; CRP, C-reactive proteins; LDL-c/HDL-c ratio, low-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio; TG/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio.

*P* values indicate differences between the survivor and non-survivor COVID-19 patients. *P* < 0.05 was considered statistically significant.

Table 4 Multivariate analysis of risk factors related to the mortality of COVID-19 patients

|          | B   | SE  | Wald | P    | OR   | 95% CI       |
|----------|-----|-----|------|------|------|--------------|
| Age      | 0.050 | 0.039 | 1.703 | 0.192 | 1.052 | 0.975-1.134  |
| Cancer   | 3.806 | 1.574 | 5.851 | **0.016** | 44.973 | 2.059-982.524 |
| WBC      | 0.919 | 1.322 | 0.484 | 0.487 | 0.399 | 0.030-5.319  |
| Lymphocytes | 3.388 | 2.375 | 2.035 | 0.154 | 0.034 | 0.000-3.550  |
| Neutrophils | 1.055 | 1.358 | 0.604 | 0.437 | 2.872 | 0.201-41.096 |
| CRP      | 0.007 | 0.007 | 1.113 | 0.292 | 1.007 | 0.994-1.021  |
| LDL-c/HDL-c ratio | 0.323 | 0.307 | 1.111 | 0.292 | 0.724 | 0.397-1.321  |
| TG/HDL-c ratio | 0.548 | 0.258 | 4.522 | **0.033** | 1.730 | 1.044-2.866  |

Abbreviation: COVID-19, Coronavirus disease 19; CI, confidence interval; WBC, white blood cells; CRP, C-reactive proteins; LDL-c/HDL-c ratio, low-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio; TG/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio.
P values indicate differences between the survivor and non-survivor COVID-19 patients. P < 0.05 was considered statistically significant.

ROC analysis indicated that the TG/HDL-c ratio was able to significantly predict death in COVID-19 patients (P = 0.001), and the area under the curve (AUC) was 0.731 (95% CI, 0.609-0.853) with sensitivity and specificity of 0.722 and 0.656, respectively. (Figure 1) Moreover, bivariate correlations indicated that TG/HDL-c ratio positively correlated with WBC (r = 0.255, P < 0.001), neutrophils (r = 0.243, P < 0.001) and CRP (r = 0.170, P < 0.006), but no significant correlations existed between TG/HDL-c ratio and lymphocytes (r = -0.004, P = 0.949).

4. Discussion

Our study primarily contributed to three findings. First, TG/HDL-c ratio of non-survivors had risen when compared with the survivors. Furthermore, TG/HDL-c ratio levels at admission positively correlated with inflammatory indicators, such as WBC, neutrophils, and CRP. Finally, TG/HDL-c ratio at admission might be able to predict and measure COVID-19 mortality.

TG/HDL-c ratio integrates predictive risks of two parameters into a single risk factor, and it is simple, non-invasive, and easily measured. Previous studies revealed that higher TG/HDL-c ratio was frequently seen in insulin resistance and cardiovascular diseases. Studies have supported that TG/HDL-c ratio might serve as an inflammatory factor in IPAH and type-B AAD patients. However, there is little literature investigating the function of TG/HDL-c ratio on viral infections. It was discovered that the expression of TG levels rose during the period of infection and inflammation. Inflammatory cytokines contribute to TG synthesis and reduce TG hydrolysis under septic conditions and also increase the angiopoietin-like protein 4 expressions which suppress the TG-rich lipoprotein metabolism. The tumor necrosis factor (TNF)-α was reported to produce a rapid rise in TG concentrations through increasing hepatic production. Without doubt, due to social isolation and long periods at home, people were more likely to have an imbalanced diet and be less active, which worsened their metabolic and lipid files and led to hypertriglyceridemia. Hypertriglyceridemia induces endothelial dysfunctionality, causing COVID-19 patients to become more susceptible to complications related to cardiovascular diseases. It was reported that TG levels significantly increased in COVID-19 patients with poor prognoses.

The most striking function of HDL was participating in reverse cholesterol transport from tissues to the liver. HDL particles are crucial to the immune system and fighting infectious diseases, which mitigate inflammatory responses during sepsis, and function against RNA and DNA viruses. In addition, HDL has the greatest affinity for binding and neutralizing lipopolysaccharides and lipoteichoic acid and exert antithrombotic and antioxidant effects. Previous studies using genetic variants as risk factors showed that increasing genetically determined levels of HDL-c exhibited an association with reduced mortality from sepsis. Other studies suggested that cholesteryl ester transfer protein (CETP) variant rs1800777 was related to the degree of HDL-C in septic patients, and CETP inhibitors might be a
potential therapy for sepsis\textsuperscript{24}. Some viral infections causing inflammation also resulted in dyslipidemia, in which human immunodeficiency virus (HIV) patients had a decreased HDL-c levels\textsuperscript{25, 26}, and patients with hepatitis B in the cirrhosis phase showed lower HDL-c levels\textsuperscript{27}. Recent studies demonstrated that COVID-19 patients with declined HDL-c concentrations had longer viral nucleic acid turning negative time than normal\textsuperscript{28}, and lower HDL-c levels exhibited an association with the severity of COVID-19 in patients\textsuperscript{29}. A marked decrease in HDL-c concentrations during the acute phase response is well documented, however, the mechanisms underlying this decrease are not clearly defined. Apolipoprotein-1 (ApoA-1), a major structural protein of HDL-c, reportedly decreased together with lower HDL-c when proinflammatory cytokines, such as interleukin-6 (IL-6) and CRP inhibited the activity of apolipoprotein synthesis enzymes\textsuperscript{15, 17}. Serum amyloid A (SAA)-enriched HDL displaced and decreased ApoA-1 levels and scavenged HDL more rapidly which was significantly higher in patients with a severe COVID-19 diagnosis\textsuperscript{11, 15}. Paraoxonase 1 (PON1), an antioxidant enzyme of HDL, could be inactivated under oxidative stresses and further weaken HDL functions\textsuperscript{30}. Moreover, hemodilution, consumption of HDL particles, and capillary leaks explain the decreased HDL concentration might be applicable to COVID-19 patients as well\textsuperscript{17, 31}. Impaired antioxidant properties of HDL cause lipid oxidation inducing inflammation and accentuating tissue damage\textsuperscript{14}. Consequently, HDL-c deficiency induces cytokine overproduction, in turn, cytokine can prime the depletion of HDL-c, which promotes a vicious cycle in severe patients. Overall, systemic inflammatory responses can cause hypertriglyceridemia and decreased HDL-c, resulting in an increase in levels of TG/HDL-c ratio.

Inflammatory cells release a large amount of cytokines in the pathophysiological processes during SARS-CoV-2 infection, thus leading to a cytokine storm which induces rapid development in multiple organ dysfunctions or even death\textsuperscript{32}. Abundant evidence indicates that compromised immune functions and an excessive inflammatory response are closely related with mortality from COVID-19\textsuperscript{33-35}. In the current study, the TG/HDL-c ratio was positively related to the levels of WBC, neutrophils, and CRP, similar to the study mentioned, within which IPAH patients with elevated TG/HDL-c ratio had elevated levels of interleukin-1\textbeta, monocyte chemoattractant protein-1, and IL-6\textsuperscript{7}. Zhang et al.\textsuperscript{36} also reported that the levels of IL-6 in non-survivors of COVID-19 were higher than that of the survivors, and increasing IL-6 concentrations were accompanied by increasing TG/HDL-c ratio. In our further analysis, we generated a ROC curve and found that TG/HDL-c ratio was probably a choice of prognostic predictors for COVID-19. Based on the findings presented above, we can speculate that inflammation might serve a beneficial role in predicting the poor outcomes of COVID-19 patients who had elevated TG/HDL-c ratio, but further investigations are required for specific mechanisms.

The study has some limitations. First, due to the retrospective analysis, we were unable to identify variables, such as BMI which might cause bias. Next, TG and HDL-c levels haven't been detected over hospitalization stays, while dynamic monitoring might be a better characterization for dyslipidemia. Finally, the lipid metabolism can be affected by various factors, such as dietary preferences and habits, and the mechanisms should be further studied.
5. Conclusions

In conclusions, this study demonstrated that higher TG/HDL-c ratio might help identify patients who have a high likelihood of developing a poor outcome.

Abbreviations

TG/HDL-c: triglyceride to high density lipoprotein cholesterol
COVID-19: Coronavirus disease 2019
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
TG: triglyceride
HDL-c: high density lipoprotein cholesterol
TG/ HDL-c: triglyceride, and a high density lipoprotein cholesterol ratio
IPAH: idiopathic pulmonary arterial hypertension
AAD: acute aortic dissection
ROC: receiver operating characteristics
WBC: white blood cells
CRP: C-reactive proteins
TC/HDL-c ratio: total cholesterol-to-high-density lipoprotein cholesterol ratio
LDL-c/HDL-c ratio: low-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio
OR: odds ratio
95% CI: confidence interval
AUC: area under the curve
TNF: tumor necrosis factor
CETP: cholesteryl ester transfer protein
ApoA-1: Apolipoprotein-1
IL-6: interleukin-6
SAA: Serum amyloid A
PON1: Paraoxonase 1
HIV: human immunodeficiency virus

Declarations

Ethics approval and consent to participate

Ethic approval was obtained from the Second Xiangya Hospital of Central South University (No.2020001, April 20, 2020).

Consent for publication

Patient consent was waived due to the retrospective study.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contribution

Conceptualization, YJ. Z. and SJ. W.; methodology, F.P.; software, F.P.; validation, YJ. Z. and SJ. W.; formal analysis, F.P.; investigation, Q.Z. and S.L.; resources, Q.Z., S.L. and YJ. Z.; data curation, Q.Z. and S.L.; writing—original draft preparation, F.P.; writing-review and editing, YJ. Z. and SJ. W.; visualization, F.P.; supervision, YJ. Z. and SJ. W.; project administration, YJ. Z. and SJ. W.; funding acquisition, SJ. W. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image_url)

**Figure 1**
Receiver operating characteristic curve of TG/HDL-c ratio for predicting the mortality of COVID-19.