Are lipid ratios and triglyceride-glucose index associated with critical care outcomes in COVID-19 patients?

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Abstract

Lipid ratios and the triglyceride and glucose index (TyG) could be a simple biochemical marker of insulin resistance (IR). The current study was carried out to examine the correlation between triglyceride to high-density lipoprotein-cholesterol (TG/HDL-C), total cholesterol to HDL-C (TC/HDL-C), low-density lipoprotein-cholesterol to HDL-C ratio (LDL-C/HDL-C), as well as TyG index with the severity and mortality of severe coronavirus disease 2019 (COVID-19). A total of 1228 confirmed COVID-19 patients were included in the current research. Regression models were performed to evaluate the correlation between the lipid index and severity and mortality of COVID-19. The TyG index and TG/HDL-C levels were significantly higher in the severe patients (P < 0.05). TG/HDL-C, LDL-C/HDL-C, TC/HDL-C ratios, and TyG index were significantly lower in survivor cases (P < 0.05). Multivariate logistic regression analysis demonstrated that predictors of the severity adjusted for age, sex and BMI were TyG index, TG/HDL-C ratio (OR = 1.42 CI:1.10–1.82, OR = 1.06 CI: 1.02–1.11, respectively). This analysis showed that TG/HDL-C, TC/HDL-C, LDL-C/HDL-C ratios, and TyG index statistically are correlated with COVID-19 mortality (OR = 1.12 CI:1.06–1.18, OR = 1.24 CI:1.05–1.48, OR = 1.47 CI:1.19–1.80, OR = 1.52 CI:1.01–2.31, respectively). In summary, the TyG index and lipid ratios such as TC/HDL-C, TG/HDL-C, LDL-C/HDL-C could be used as an early indicator of COVID-19 mortality. Furthermore, the study revealed that TyG index and TG/HDL-C indices are biochemical markers of COVID-19 severe prognosis.

Introduction

In December 2019, a novel coronavirus (2019-nCoV) was discovered from individuals with pneumonia in Wuhan, China [1]. According to the Iranian official reports, the coronavirus disease 2019 (COVID-19) epidemic was started from 2020-02-19 in Iran [2]. The most important characteristic of the COVID-19 pandemic was the rapid spread and increasing trend of
the crisis so that this pandemic has affected almost every country in the world quickly. By December 29, 2020, a total of 6,190,000 patients with COVID-19 have been diagnosed in Iran of which 131,000 deaths have been occurred by the virus. Iran ranks tenth in the number of deaths due to COVID-19 in the world.

Patients with COVID-19 display a wide spectrum of manifestations from mild symptoms and good prognosis to severe lethal respiratory infection [3, 4]. Severe cases of COVID-19 develop acute respiratory distress syndrome and often need mechanical ventilation. So, to limit the increase of severe cases, it seems essential to recognize the factors that promote the development of COVID-19 severity [5]. Although, the severity of COVID-19 is probably to be multifactorial, accumulating evidence has shown a high risk of poor prognosis and more severe complications among peoples with COVID-19 who have comorbidities [6, 7] such as metabolic syndrome, hypertension, cardiovascular disease (CVD), and type 2 diabetes mellites (T2DM) [7]. The IR is caused by defects in insulin action in its target tissues either due to insulin receptor defects or disorders in the post-receptor insulin signaling cascade [8]. It is worse nothing that insulin plays a vital role in normal lung function as well as the management of people with COVID-19 [9]. It is believed that disturbance in metabolic health especially IR is the key risk factor for severe COVID-19 [9–14]. So, early diagnosis of IR, as an important risk factor for poor prognosis of COVID-19, plays a crucial role in predicting the severity and managing the disease. Although most clinicians are conscious of the importance of IR, it is never formed in the routine clinical assessment of COVID-19 patients and causes it challenging to determine the effectiveness of IR in predicting COVID19 outcomes [14]. It is likely due to the time-consuming and expensiveness of the gold standard method of IR assessment, Hyperinsulinaemic-euglycaemic clamp technique [15], and also, lacking standardization, availability, and cost-effective of the insulin assessment method for indirect estimation of IR such as homeostasis model assessment for insulin resistance (HOMA-IR), the fasting glucose to insulin ratio (FG-IR), and the quantitative insulin sensitivity check index (QUICKI) [16]. Therefore, it seems reasonable using simple, inexpensive and more available biochemical indices for IR estimation can be helpful for determining COVID-19 prognosis [14] and can improve therapeutic strategy and disease outcomes at the time of COVID-19 diagnosis [17, 18]. In recent years, some simple and reliable biochemical markers including triglyceride (TG)-glucose (TyG) index [19], and the TG to high-density lipoprotein cholesterol (TG/HDL-C) ratio [20], the low-density lipoprotein cholesterol to HDL-C (LDL-C/HDL-C), and the total cholesterol to HDL-C (TC/ HDL-C) ratio [21] have been developed for estimating IR [22].

Although some studies showed dyslipidemia and its potential association with the outcome of COVID-19 [23–26], it seems that lipid ratios and TyG index can be considered as a better indicator of COVID-19 severity than blood level of lipid profile alone at the time of COVID-19 diagnosis [27, 28]. Given the insufficient studies regarding the correlation between lipid ratios and TyG index and the critical care outcomes of COVID-19 in the large affected population, we aimed to evaluate the possible association of TG/HDL-C, TC/HDL-C, LDL-C/ HDL-C, and TyG indices, as a surrogate of estimating IR, with disease severity in non-vaccinated hospitalized COVID-19 patients at the time of diagnosis in Iranian ethnicity.

**Material and methods**

**Study population**

The present study employed a cross-sectional design. Since the beginning of the outbreak in Iran, a local registration system was created in Shahroud, Iran, in the administration of Shahroud University of Medical Sciences (SHMU). A comprehensive electronic medical record
including epidemiological, demographic, anthropometric, chronic medical histories, clinical, and laboratory data was created, from people admitted to SHMU hospitals due to a SARS-CoV-2 infection within February 20, 2020, and March 20, 2021. Only data from hospitalized and non-vaccinated cases with a COVID-19 diagnosis confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from oro- and nasopharyngeal swab specimens were included in our analysis. Patients who lacked sufficient data were excluded from the study. Finally, a total of 1228 cases were incorporated in the analysis (S1 Fig). This research was approved by the Ethics Committee of Shahroud University of Medical Sciences (IR.SHMU.REC.1398.160) and was conducted in accordance with the declaration of Helsinki. Informed consent was received from all the cases before registration in the study.

Clinical and laboratory assessments

Body mass index (BMI) was determined via standard calculation [body weight (kg)/height squared (m2)]. Blood specimens were taken from patients who had been fasting ten-hour at the baseline (COVID-19 diagnosis). Biochemical markers such as fasting blood glucose (FBG), TC, TG, LDL-C, HDL-C, C-reactive protein (CRP) and lactate dehydrogenase (LDH), and ferritin were assessed using calorimetric methods via the commercially available kits (Pars Azmoon, Tehran, Iran). The white blood cell (WBC) and lymphocyte count were also performed. The TG/HDL-C, TC/HDL-C, LDL-C/HDL-C and TyG indices were calculated via the following formulas respectively: TG (mg/dL)/HDL-C (mg/dL), TC (mg/dL)/HDL-C (mg/ dL), LDL-C (mg/dL)/HDL-C (mg/ dL), and Ln [TG (mg/dL) × FBG (mg/dL)]/2.

People with COVID-19 are considered to have the severe disease if they have: 1. respiratory rate > 30/min, 2. oxygen saturation ≤ 93%, 3. Patients with shock, or respiratory failure requiring mechanical ventilation, or with other organ failure admission to intensive care unit (ICU). The deceased cases were also considered as severe patients.

Statistical analysis

Statistical analysis was performed using SPSS software version 23. The chi-squared, Fisher exact test, and Student’s t-test were used to compare differences between two groups. The cut-off values were assessed according to the receiver operating characteristic (ROC) curves and a minimum sensitivity of 50%. univariate and multivariate logistic regression analyses adjusted to age, sex, and BMI also were used. Statistically significant differences were considered with p-values < 0.05.

Results

A total of 1228 confirmed patients were incorporated in the current study, with a mean age of 58.8 ± 16.2 years old. 611 (49.8%) of patients were males. Demographic and clinical features are exhibited in Table 1. Regarding the history of comorbidities, 23.7% had CVD, 24.7% had T2DM, and 6.2% had chronic kidney disease. The most common comorbidities were CVD (24.7%) and T2DM (23.7%) so that they were 2 and 1.3 times higher in severe cases than mild cases, respectively. Also, severe patients had a significantly lower saturated rate of O2. Moreover, deceased patients had a higher value of heart rate and a lower saturated rate of O2 (All P < 0.05) (Table 1).

Laboratory findings and lipid ratios of cases according to the severity and mortality have been shown in Table 2. Severe and deceased patients showed statistically significant higher values of FBS, neutrophil/lymphocyte ratio, ESR, WBC, CRP, LDH, and ferritin when compared with mild and survivor groups, respectively (p < 0.05). Regarding the lipid profile, TG level did not demonstrate a significant difference between groups. Serum concentrations of TC,
Table 1. The basic features of patients with COVID-19 in accordance with the severity and mortality.

| Variables               | Mild (n = 945) | Severe (n = 283) | P-value  | Survivor (n = 1140) | Deceased (n = 88) | P-value |
|-------------------------|----------------|------------------|----------|---------------------|------------------|---------|
| Demographic             |                |                  |          |                     |                  |         |
| Gender                  | Male           | 455(48.1)        | 156(55.1)| 0.023               | 558(48.9)        | 53(60.2) | 0.041   |
|                         | Female         | 490(51.9)        | 127(44.9)|                      | 582(51.1)        | 35(39.8) |         |
| Age(years)              |                | 56.1±0.51        | 67.3±0.87| <0.001              | 57.68(1.332)     | 71.52(0.47) | <0.001 |
| Comorbidities           |                |                  |          |                     |                  |         |
| T2DM                    |                | 216(22.9)        | 87(30.7) | 0.007               | 275(24.1)        | 28(31.8) | 0.107   |
| CVD                     |                | 185(19.6)        | 106(37.5)| <0.001              | 254(22.3)        | 37(42)  | <0.001  |
| Cancer                  |                | 10(1.1)          | 11(3.9)  | 0.003               | 16(1.4)          | 5(5.7)  | 0.014   |
| COPD                    |                | 6(0.6)           | 4(1.4)   | 0.252               | 8(0.7)           | 2(2.3)  | 0.157   |
| Asthma                  |                | 24(2.5)          | 16(5.7)  | 0.010               | 80(2.8)          | 8(9.1)  | 0.006   |
| Chronic Liver Disease   |                | 16(1.7)          | 4(1.4)   |                      | 20(1.8)          | 0(0)    | 0.391   |
| Chronic Kidney Disease  |                | 47(5)            | 29(10.2) | 0.001               | 65(5.7)          | 11(12.5)| 0.011   |
| Neurological Diseases   |                | 28(3.0)          | 20(7.1)  | 0.002               | 39(3.4)          | 9(10.2) | 0.005   |
| Seizures                |                | 7(0.7)           | 1(0.4)   | <0.001              | 92.7±0.48        | 91.4±0.83| 0.014   |

Clinical finding

| Variables                          | Mild (n = 945) | Severe (n = 283) | P-value  | Survivor (n = 1140) | Deceased (n = 88) | P-value |
|------------------------------------|----------------|------------------|----------|---------------------|------------------|---------|
| Respiratory rate                   | 12.53±0.79     | 13.16±0.81       | 0.582    | 15.72±1.86          | 12.65±0.59       | 0.147   |
| Heart rate                         | 81.13±1.05     | 84.04±1.18       | 0.072    | 82.13±0.81          | 89.09±3.53       | 0.017   |
| Systolic blood pressure            | 115.79±1.27    | 117.35±1.31      | 0.396    | 116.8±0.95          | 114.7±3.5        | 0.533   |
| Diastolic blood pressure           | 74.08±0.86     | 74.5±0.92        | 0.743    | 74.5±0.65           | 72.29±2.5        | 0.341   |
| BMI                                | 27.84±0.15     | 27.92±0.3        | 0.806    | 27.89±0.14          | 27.33±0.52       | 0.279   |
| SaO 2                              | 95.68±0.15     | 90.2±0.74        | <0.001   | 92.7±0.48           | 91.4±0.83        | 0.014   |

Data were expressed as mean ± standard error of mean or number (percent).

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Table 2. Laboratory findings, Lipid profile and lipid ratios of patients with COVID-19.

| Variables                | Mild (n = 945) | Severe (n = 283) | P-value  | Survivor (n = 1140) | Deceased (n = 88) | P-value |
|--------------------------|----------------|------------------|----------|---------------------|------------------|---------|
| FBG (mg/dl)              | 129.94±2.28    | 143.94±4.56      | 0.006    | 131.37±2.08         | 159.45±9.65      | 0.006   |
| TG (mg/dl)               | 105.38±1.98    | 111.8±3.65       | 0.118    | 106.65±1.8          | 109.10±5.7       | 0.713   |
| TC (mg/dL)               | 134.13±1.16    | 127.81±2.61      | 0.028    | 133.4±1.1           | 123.92±4.75      | 0.03    |
| HDL-C (mg/dL)            | 33.59±0.32     | 31.70±0.63       | 0.008    | 33.53±0.3           | 28.25±1.12       | <0.001  |
| LDL-C (mg/dL)            | 76.11±0.72     | 70.39±1.42       | <0.001   | 75.24±0.66          | 69.05±2.72       | 0.014   |
| Tg/HDL-C                 | 3.61±0.11      | 4.08±0.19        | 0.039    | 3.63±0.09           | 4.83±0.46        | 0.012   |
| TC/HDL-C                 | 4.24±0.05      | 4.24±0.09        | 0.976    | 4.21±0.04           | 4.65±0.20        | 0.038   |
| LDL-c/HDL-C              | 2.43±0.03      | 2.41±0.06        | 0.817    | 2.40±0.03           | 2.75±0.15        | 0.021   |
| TyG                      | 8.63±0.023     | 8.78±0.05        | 0.008    | 8.65±0.022          | 8.83±0.1         | 0.101   |
| ESR                      | 34.25±0.82     | 40.71±2.1        | 0.005    | 34.99±0.8           | 45.1±4           | 0.016   |
| WBC (×10^3/L)            | 32.75±0.54     | 45.82±1.94       | <0.001   | 34.45±0.59          | 52.16±3.9        | <0.001  |
| Lymphocytes (x10^9/mL)    | 26.04±0.37     | 22.04±0.75       | <0.001   | 25.5±0.35           | 20.14±1.4        | <0.001  |
| NLR                      | 3.73±0.1       | 5.62±0.43        | <0.001   | 4.02±0.13           | 6.04±0.56        | 0.001   |
| CRP (mg/dl)              | 25.55±0.92     | 33.37±1.9        | <0.001   | 26.77±0.87          | 34.16±3.24       | 0.025   |
| Lactate dehydrogenase, U/L LDH | 453.55±6.8  | 598.82±18.1      | <0.001   | 471.03±6.86         | 689.78±30.11     | <0.001  |
| Ferritin                 | 292.94±18.3    | 454.05±37.14     | <0.001   | 318.54±17.6         | 478.84±53.36     | 0.012   |

Data were expressed as mean ± standard error of mean.

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HDL-C, and LDL-C were lower in severe and deceased groups in comparison with mild and survivor groups, respectively (p < 0.05). The severe group showed a significant increase in TG/HDL-C ratio and TyG index compared to the mild patients (p < 0.05). Also, all lipid ratios and TyG index were significantly higher in the deceased group than in the survivor group (p < 0.05) (Table 2).

Multivariate logistic regression analysis revealed that predictors of severity adjusted for age, sex and BMI were TyG index, TG/HDL-c ratio, and TG. Notably, TyG was markedly correlated to higher odds of severe disease (OR = 1.42 CI: 1.10–1.82). This analysis showed that all lipid ratios and TyG index statistically are correlated with COVID-19 mortality (Table 3).

In addition, the prediction for severity and mortality was also determined by Area Under Curve (AUC). According to AUC, the prediction of lipid ratios and TyG index for death are better than severity. Lipid ratios and TyG index could significantly predict the odds of death more than lipid profile alone. So, increasing each unit in TyG and LDL-C/HDL-C ratio increased the odds of death by 52% and 47% (Table 3).

Cut-off points accordance with a minimum sensitivity of 50% shown in Table 4. Categorical TyG, HDL-C, LDL-C, and their ratio predict the death significantly based on cutoff (Table 4).

Cut-offs 8.77 and 2.44 for the TyG and LDL-C/HDL-C ratio increased odds of death significantly (OR = 2.04 and 1.66)

Table 3. Odds ratios for severe and deceased cases associated with lipid profile, TyG index, and lipid ratios.

| Variables      | Severity          | Mortality         |
|----------------|-------------------|-------------------|
|                | OR(CI)            | P-value | AUC | OR(CI)            | p-value | AUC |
| TG (mg/dl)     | 1.004(1.001–1.006) | `.003`  | 0.707 | 1.004(1.001–1.008) | .069 | 0.783 |
| TC (mg/dL)     | 0.99(0.99–1.00)   | `.586`  | 0.706 | 0.99(0.98–1.01)   | .493 | 0.787 |
| HDL-C (mg/dL)  | 0.98(0.97–1.00)   | `.054`  | 0.707 | 0.95(0.92–0.97)   | `<.001` | 0.782 |
| LDL-C (mg/dL)  | 0.99(0.98–1.00)   | `.062`  | 0.714 | 0.99(0.98–1.00)   | `.415` | 0.771 |
| TG/HDL-C       | 1.06(1.02–1.11)   | `.007`  | 0.705 | 1.12(1.06–1.18)   | `<.001` | 0.787 |
| TC/HDL-C       | 1.02(0.91–1.14)   | `.684`  | 0.713 | 1.24(1.05–1.48)   | `.011` | 0.794 |
| LDL-C/HDL-C    | 1.03(0.88–1.2)    | `.682`  | 0.705 | 1.47(1.19–1.80)   | `<.001` | 0.779 |
| TyG            | 1.42(1.10–1.82)   | `.006`  | 0.706 | 1.52(1.01–2.31)   | `.047` | 0.781 |

Regression models adjusted for age sex and BMI.

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Table 4. Analysis of the ROC curve of the lipid profile, TyG index, and lipid ratios with mortality in patients with COVID-19.

| Variables      | Cut off*  | Sensitivity | Specificity | P-value** | AUC | Univariate OR(CI) |
|----------------|-----------|-------------|-------------|-----------|-----|--------------------|
| TG (mg/dl)     | 98.50     | 50          | 56.3        | 0.349     | .531 | 1.28(0.82–1.98)    |
| TC (mg/dL)     | 126.50    | 50          | 46.5        | 0.097     | .441 | 0.75(0.48–1.16)    |
| HDL-C (mg/dL)  | 29.50***  | 54.5        | 36.8        | `<.001`   | .625 | 0.48(0.31–0.75)    |
| LDL-C (mg/dL)  | 65.50***  | 50          | 35.8        | `.009`    | .583 | 0.56(0.36–0.86)    |
| TG/HDL-C       | 3.22      | 53.7        | 57.8        | `.019`    | .578 | 1.27(0.82–1.97)    |
| TC/HDL-C       | 4.24      | 50.7        | 57.7        | `.039`    | .558 | 1.13(0.72–1.76)    |
| LDL-C/HDL-C    | 2.44      | 50          | 60.4        | `.103`    | .552 | 1.66 (1.08–2.58)   |
| TyG            | 8.77      | 60.9        | 63.5        | `.040`    | .596 | 2.04(1.31–3.17)    |

* Greater than or equal to the cut-off values based on a minimum sensitivity of 50%.
** p-value for Significant differences with 0.5.
***less than or equal to cut off for HDL.

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Discussion

Accumulating evidence indicates that loss of metabolic health is a key risk factor for the severity of COVID-19 [9, 29]. It is well characterized that IR and related metabolic disorders especially metabolic syndrome, CVD, and T2DM are correlated with poor prognosis of COVID-19 [30, 31]. In accordance with previous studies [32, 33], the current study also demonstrated that the presence of comorbidities such as T2DM, cancer, asthma, chronic kidney disease, neurological diseases, and CVD are related to more severe illness in COVID-19 patients.

The current study revealed significantly decreased levels of TC, HDL-C, and LDL-C in the severe group and deceased group when compared with the mild group and survivor group respectively. In this regard, meta-analysis researches also demonstrated similar results [34, 35]. It is likely due to the raised usage of cholesterol for pulmonary surfactant synthesis, and/or decreased cholesterol synthesis in the liver due to liver dysfunction in severe cases of COVID-19. Increased pro-inflammatory cytokines may be another reason for these changes in lipid profile through upregulation of the scavenger receptor class B type 1 in COVID-19 infection [35]. While the current study and several other studies established the correlation between lipid profile, biomarkers of metabolic state and disease severity in COVID-19 cases [23, 35, 36], the correlation between IR markers and COVID-19 outcomes has hardly been investigated so far.

It is worth noting that, direct and indirect methods for IR assessment are technically demanding, time-consuming and expensive [18, 37]. Recently, several researchers have suggested that lipid ratios could be valuable alternative biomarkers for estimating IR in several disorders and populations because of their analytical and economic advantages [22, 37–39]. Our result revealed that an increase in TG/HDL-C ratio and TyG index at the time of admission positively correlated with disease severity among Iranian diagnosed people with coronavirus infection after adjusting for BMI, sex, and age. More importantly, we demonstrated for the first time that an increase in TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and TyG indices, as reliable surrogate markers of IR, positively associated with COVID-19 mortality. Previous researches have revealed that the TyG and lipid ratios such as TC/HDL-C, TG/HDL-C, LDL-C/HDL-C may predict the development of T2DM [40, 41], cancer [12, 42], metabolic syndrome [38, 39]. These indices are predictive markers for the severity of a non-alcoholic fatty liver disease (NAFLD) [43]. TyG is also associated with the severity of cardiovascular outcomes in patients with non-ST and ST-segment elevation myocardial infarction [44, 45]. Moreover, the positive correlation between TG/HDL-C ratio and pulmonary disease is described in asthma, obstructive sleep apnea [46, 47], and idiopathic pulmonary arterial hypertension [48]. It has also been demonstrated that the LDL-C/HDL-C ratio is associated with PaO2 levels and severity of pulmonary alveolar proteinosis (PAP). PAP patients had higher TC/HDL-C and TG/HDL-C than the control group [49].

Nevertheless, there is limited information about the importance of lipid ratios in COVID-19. In accordance with our results, Ren et al. revealed that the TyG index is related to a high risk of severity and death in COVID-19 cases [27]. Alcantara-Alonso et al also demonstrated the positive association of TG/HDL-C ratio with LDH, the severity of disease, and the necessity of invasive mechanical ventilation in COVID-19 patients [28]. To our knowledge, the present study is the first study evaluating the association between TC/HDL-C and LDL-C/HDL-C ratios and COVID-19 outcomes. Although our results did not show a significant correlation between TC/HDL-c and LDL-C/HDL-C ratios and disease severity, we revealed that TC/HDL-C and LDL-C/HDL-C indices can predict mortality of COVID-19.

It has been accepted that hyperinsulinemia due to IR promotes SARS-CoV-2 viremia through membrane upregulation of angiotensin-converting enzyme 2 (ACE2) in pneumocytes
which in turn is involved in SARS-CoV-2 cell infection [14]. Hyperinsulinemia rises inflammatory markers, impairs fibrinolysis, and increased the risk of coagulation and thrombosis [50]. Although further studies are required to correlate the IR with severity and outcomes of COVID-19, the present study revealed a correlation between IR and COVID-19 severity and mortality through IR estimation. Therefore, it is recommended that consideration can be given to evaluating biochemical markers of IR estimation including TyG index and lipid ratios for prognostic utility in the routine clinical assessment of COVID-19 patients. Also, therapeutic interventions can be used to improve insulin sensitivity and COVID-19 outcomes.

This study is the first comprehensive study with a relatively large sample size that was performed to explore the correlation between TyG index and all lipid ratios including TC/HDL-C, TG/HDL-C, LDL-C/HDL-C with COVID-19 severity and outcomes and to determine the prognostic utility of these markers COVID-19 patient in Iran. However, several limitations in the current study need to be considered. First, lack of data about the lipid profile of the COVID-19 cases before infection. It has been revealed that SARS-CoV-2 can affect metabolic states and lipid profile since the early stages of infection [25]. So, it is not possible to ignore a viral effect on the lipid profile at the time of COVID-19 diagnosis. Second, non-hospitalized patients were not included in our study. Third, direct or indirect methods of IR assessing were not carried out to evaluate the correlation between IR and TyG and lipid ratios indices among our study population.

Conclusion

In summary, our results showed that the TyG and lipid ratios such as TC/HDL-C, TG/HDL-C, LDL-C/HDL-C were remarkably high in deceased COVID-19 cases. Furthermore, the present study revealed that TyG and TG/HDL-C indices are biochemical indicators of severe prognosis in COVID-19 patients. Our finding also highlighted the high risk of critical care outcomes among COVID-19 cases with insulin resistance.

Supporting information
S1 Fig. Flow chart for patients’ enrollment.
(PNG)

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References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet. 2020; 395(10223):507–13. https://doi.org/10.1016/S0140-6736(20)30211-7 PMID: 32007143

2. Pourmalek F, Hemami MR, Janani L, Moradi-Lakeh M. Rapid review of COVID-19 epidemi estimation studies for Iran. BMC public health. 2021; 21(1):1–30. https://doi.org/10.1186/s12889-020-10013-y PMID: 3338037

3. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research. 2020; 2020. https://doi.org/10.34133/2020/240296 PMID: 32377638

4. Salari A, Mahdavi-Roshan M, Ghorbani Z, Mortazavi SS, Naghsbandi M, Faraghnia F, et al. An investigation of risk factors of in-hospital death due to COVID-19: a case-control study in Rasht, Iran. Irish Journal of Medical Science (1971-). 2021;1–13.

5. Qu J, Sumali B, Lee H, Terai H, Ishii M, Fukunaga K, et al. Finding of the factors affecting the severity of COVID-19 based on mathematical models. Scientific Reports. 2021; 11(1):24224. https://doi.org/10.1038/s41598-021-03632-x PMID: 34930966

6. COVID C, Team R, COVID C, Team R, COVID C, Team R, et al. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. Morbidity and Mortality Weekly Report. 2020; 69(13):382. https://doi.org/10.15585/mmwr.mm6913e2 PMID: 32240123

7. Javanmardi F, Keshavarzi A, Akbarnia, Emami A, Pirbonyeh N. Prevalence of underlying diseases in died cases of COVID-19: A systematic review and meta-analysis. PloS one. 2020; 15(10):e0241265. https://doi.org/10.1371/journal.pone.0241265 PMID: 33095835

8. Boucker J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol. 2014; 6(1):a009191. https://doi.org/10.1101/cshperspect.a009191 PMID: 24384568.

9. Santos A, Magro DO, Evangelista-Poderoso R, Saad MJA. Diabetes, obesity, and insulin resistance in COVID-19: molecular interrelationship and therapeutic implications. Diabetology & Metabolic Syndrome. 2021; 13(1):23. https://doi.org/10.1186/s13098-021-00639-2 PMID: 33648564

10. Iacobellis G, Penaherrera CA, Bermudez LE, Mizrachi EB. Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes. Diabetes research and clinical practice. 2020; 164:108185. https://doi.org/10.1016/j.diabres.2020.108185 PMID: 32360710

11. Kim MK, Jeon J-H, Kim S-W, Moon JS, Cho NH, Han E, et al. The clinical characteristics and outcomes of patients with moderate-to-severe coronavirus disease 2019 infection and diabetes in Daegu, South Korea. Diabetes & metabolism journal. 2020; 44(4):602–13. https://doi.org/10.4093/dmj.2020.0146 PMID: 32794386

12. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. Endocrine Practice. 2020; 26(6):668–74. https://doi.org/10.4158/EP-2020-0108 PMID: 32570702

13. Zhang J-j, Dong X, Cao Y-y, Yuan Y-d, Yang Y-b, Yan Y-q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75(7):1730–41. https://doi.org/10.1111/all.14236 PMID: 32077115

14. Finucane FM, Davenport C. Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection? Frontiers in Public Health. 2020; 8(184). https://doi.org/10.3389/fpubh.2020.00184 PMID: 32574268

15. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. American Journal of Physiology-Endocrinology And Metabolism. 1979; 237(3):E214. https://doi.org/10.1152/ajpendo.1979.237.3.E214 PMID: 382871

16. Conwell LS, Trost SG, Brown WJ, Batch JA. Indexes of insulin resistance and secretion in obese children and adolescents: a validation study. Diabetes care. 2004; 27(2):314–9. https://doi.org/10.2337/diacare.27.2.314 PMID: 14747208
17. Schwartz B, Jacobs DR, Moran A, Steinberger J, Hong C-P, Sinaiko AR. Measurement of insulin sensitivity in children: comparison between the euglycemic-hyperinsulinemic clamp and surrogate measures. Diabetes care. 2008; 31(4):783–8. https://doi.org/10.2337/dc07-1376 PMID: 18174496

18. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. World journal of diabetes. 2010; 1(2):36. https://doi.org/10.4239/wjdd.v1.i2.36 PMID: 21537426

19. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and insulin ratio as risk markers of insulin resistance. Cardiovascular diabetes. 2014; 13(1):1–10.

20. McLaughlin T, Reaven G, Abbasi F, Lamendola C, Saad M, Waters D, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? The American journal of cardiology. 2005; 96(3):399–404. https://doi.org/10.1016/j.amjcard.2005.03.085 PMID: 16054467

21. Jeppesen J, Facchini F, Reaven G. Individuals with high total cholesterol/HDL cholesterol ratios are insulin resistant. Journal of internal medicine. 1998; 243(4):293–8. https://doi.org/10.1046/j.1365-2796.1998.00301.x PMID: 9627143

22. Zhang L, Chen S, Deng A, Liu X, Liang Y, Shao X, et al. Association between lipid ratios and insulin resistance in a Chinese population. PLoS One. 2015; 10(1):e0116110. https://doi.org/10.1371/journal.pone.0116110 PMID: 25635876

23. Choi GJ, Kim HM, Kang H. The potential role of dyslipidemia in COVID-19 severity: An umbrella review of systematic reviews. Journal of Lipid and Atherosclerosis. 2020; 9(3):435. https://doi.org/10.12997/jla.2020.9.3.435 PMID: 33024735

24. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020; 14(5):1463–5.

25. Bellia A, Andreadi A, Giudice L, De Taddeo S, Maiorino A, D’Ippolito I, et al. Atherogenic Dyslipidemia on Admission Is Associated With Poorer Outcome in People With and Without Diabetes Hospitalized for COVID-19. Diabetes Care. 2021; 44(9):2149–57. https://doi.org/10.2337/dc20-2838 PMID: 34253561

26. Nie S, Zhao X, Zhao K, Zhang Z, Zhang Z, Zhang Z. Metabolic disturbances and inflammatory dysfunction predict severity of coronavirus disease 2019 (COVID-19): a retrospective study. MedRxiv. 2020.

27. Ren H, Yang Y, Wang F, Yan Y, Shi X, Dong K, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovascular diabetes. 2020; 19:1–8. https://doi.org/10.1186/s12933-019-0977-z PMID: 31910850

28. Alcântara-Alonso E, Molinar-Ramos F, González-López JA, Alcântara-Alonso V, Muñoz-Pérez MA, Lozano-Nuevo JJ, et al. High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clinical Nutrition ESPEN. 2021. https://doi.org/10.1016/j.clinesp.2021.04.020 PMID: 34305002

29. León-Pedroza JI, Rodríguez-Cortés O, Flores-Mejía R, Gaona-Aguas CV, González-Chávez A. Impact of Metabolic Syndrome in the Clinical Outcome of Disease by SARS-COV-2. Arch Med Res. 2021; 52(7):738–45. Epub 04/12. https://doi.org/10.1016/j.arcmed.2021.04.001 PMID: 33926762.

30. Perpiñañ C, Bertran L, Terra X, Aguilar C, Lopez-Dupla M, Albilbic A, et al. Predictive Biomarkers of COVID-19 Severity in SARS-CoV-2 Infected Patients with Obesity and Metabolic Syndrome. Journal of personalized medicine. 2021; 11(3). Epub 2021/04/04. https://doi.org/10.3390/jpm11030227 PMID: 33809913; PubMed Central PMCID: PMC8004138.

31. Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews Endocrinology. 2021; 17(1):11–30. https://doi.org/10.1038/s41574-020-00435-4 PMID: 33188364

32. Baradaran A, Ebrariahinzadeh MH, Baradaran A, Kachooei AR. Prevalence of comorbidities in COVID-19 patients: a systematic review and meta-analysis. Archives of Bone and Joint Surgery. 2020; 8(Suppl 1):247. https://doi.org/10.22038/abjs.2020.47754.2346 PMID: 32733980

33. Atkins JL, Masoli JA, Delgado J, Pilling LC, Kuo C-L, Kuchel GA, et al. Preexisting comorbidities predicting COVID-19 and mortality in the UK biobank community cohort. The Journals of Gerontology: Series A. 2020; 75(11):2224–30.

34. Mahat RK, Rathore V, Singh N, Singh N, Singh SK, Shah RK, et al. Lipid profile as an indicator of COVID-19 severity: A systematic review and meta-analysis. Clinical Nutrition ESPEN. 2021; 45:91–101. https://doi.org/10.1016/j.clinesp.2021.07.023 PMID: 34620375

35. Zinelu A, Palogiannis P, Fois AG, Solidoro P, Carru C, Mangoni AA. Cholesterol and Triglyceride Concentrations, COVID-19 Severity, and Mortality: A Systematic Review and Meta-Analysis With Meta-Regression. Front Public Health. 2021; 9:705916. Epub 2021/09/08. https://doi.org/10.3389/fpubh.2021.705916 PMID: 34490188; PubMed Central PMCID: PMC8417431.
36. Atmosudigdo IS, Lim MA, Rabi B, Henrina J, Yonas E, Vania R, et al. Dyslipidemia increases the risk of severe COVID-19: a systematic review, meta-analysis, and meta-regression. Clinical Medicine Insights: Endocrinology and Diabetes. 2021; 14:1179551421990675. https://doi.org/10.1177/1179551421990675 PMID: 35173508

37. Kheirollahi A, Teimouri M, Karimi M, Vatannejad A, Moradi N, Borumandnia N, et al. Evaluation of lipid ratios and triglyceride-glucose index as risk markers of insulin resistance in Iranian polycystic ovary syndrome women. Lipids Health Dis. 2020; 19(1):235–. https://doi.org/10.1186/s12944-020-01410-8 PMID: 33161896.

38. Unger G, Benozi SF, Perruzza F, Pennacchiotti GL. Triglycerides and glucose index: a useful indicator of insulin resistance. Endocrinología y nutrición: organo de la Sociedad Española de Endocrinología y Nutrición. 2014; 61(10):533–40. Epub 2014/09/02. https://doi.org/10.1016/j.endonu.2014.06.009 PMID: 25174769.

39. Chu S-Y, Jung J-H, Park M-J, Kim S-H. Risk assessment of metabolic syndrome in adolescents using the triglyceride/high-density lipoprotein cholesterol ratio and the total cholesterol/high-density lipoprotein cholesterol ratio. Ann Pediatr Endocrinol Metab. 2019; 24(1):41–8. Epub 03/31. https://doi.org/10.6065/apem.2019.24.1.41 PMID: 30943679.

40. Navarro-González D, Sánchez-Íñigo L, Pastrana-Delgado J, Fernández-Montero A, Martínez JA. Triglyceride–glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. Preventive medicine. 2016; 86:99–105. https://doi.org/10.1016/j.ypmed.2016.01.022 PMID: 26854766.

41. Hadaegh F, Hatami M, Tohidi M, Sarbakhsh P, Saadat N, Azizi F. Lipid ratios and appropriate cut off values for prediction of diabetes: a cohort of Iranian men and women. Lipids Health Dis. 2010; 9(1):1–9. https://doi.org/10.1186/1476-511X-9-85 PMID: 20712907.

42. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Triglyceride–glucose index (TyG index) is a predictor of incident colorectal cancer: a population-based longitudinal study. BMC Endocrine Disorders. 2020; 20(1):1–7. https://doi.org/10.1186/s12902-019-0484-y PMID: 31900145.

43. Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, et al. The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. Lipids Health Dis. 2017; 16(1):1–8. https://doi.org/10.1186/s12944-016-0392-3 PMID: 28056980.

44. Mao Q, Zhou D, Li Y, Wang Y, Xu S-C, Zhao X-H. The triglyceride-glucose index predicts coronary artery disease severity and cardiovascular outcomes in patients with non-ST-segment elevation acute coronary syndrome. Disease markers. 2019;2019. https://doi.org/10.1155/2019/6891537 PMID: 31281548.

45. Luo E, Wang D, Yan G, Qiao Y, Liu B, Hou J, et al. High triglyceride-glucose index is associated with poor prognosis in patients with acute ST-elevation myocardial infarction after percutaneous coronary intervention. Cardiovascular diabetology. 2019; 18(1):150. Epub 2019/11/15. https://doi.org/10.1186/s12933-019-0957-3 PMID: 31722708; PubMed Central PMCID: PMC6852896.

46. Ko S-H, Jeong J, Baeg MK, Han K-D, Kim HS, Yoon J-s, et al. Lipid profiles in adolescents with and without asthma: Korea National Health and nutrition examination survey data. Lipids Health Dis. 2018; 17(1):1–7. https://doi.org/10.1186/s12944-017-0646-8 PMID: 29298716.

47. Silva LOe Guimaraes TM, Luz GP, Coelho G, Badke L, Almeida IR, et al. Metabolic profile in patients with mild obstructive sleep apnea. Metabolic syndrome and related disorders. 2018; 16(1):6–12. https://doi.org/10.1089/met.2017.0075 PMID: 29148894.

48. Jonas K, Magoni W, Podolec P, Kopec G. Triglyceride-to-high-density lipoprotein cholesterol ratio and systemic inflammation in patients with idiopathic pulmonary arterial hypertension. Medical science monitor: international medical journal of experimental and clinical research. 2019; 25:746. https://doi.org/10.12659/MSM.912766 PMID: 30683836.

49. Yan X, Gao Y, Zhao Q, Qiu X, Tian M, Dai J, et al. Correlation of Lipid Ratios With the Severity of Pulmonary Alveolar Proteinosis: A Cross-Sectional Study. Frontiers in Nutrition. 2021; 8(1). https://doi.org/10.3389/fnut.2021.610765 PMID: 33816536.

50. Cooper ID, Crofts CA, DiNicolantonio JJ, Malhotra A, Elliott B, Kyriakidou Y, et al. Relationships between hyperinsulinaemia, magnesium, vitamin D, thrombosis and COVID-19: rationale for clinical management. Open Heart. 2020; 7(2):e001356. https://doi.org/10.1136/openhrt-2020-001356 PMID: 32938758.