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Prognostic significance of temporal changes of lipid profile in COVID-19 patients

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ABSTRACT

Background: COVID-19 is a multisystemic disease that affects many organs and has metabolic effects.
Aims: This study aims to investigate the effect of the temporal changes of lipid levels on the prognosis during the course of the disease.
Study design: Retrospective cross-sectional study.
Methods: For this single-center study, data of patients who were treated for COVID-19 were collected. Fasting lipid parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were collected within 24 h of hospitalization. For investigation of temporal changes in lipid parameters, the results of the same parameters in the one-year period before COVID-19 were collected from medical records. A total number of 324 eligible COVID-19 patients were included in this study. The association of changes of lipid parameters with COVID-19 symptom severity and in-hospital mortality were investigated.
Results: The mean age of the severe group (n = 139) was 65.4 ± 15.5 years, and 60% were male. TC, LDL-C and HDL-C levels were significantly lower compared to pre-COVID measurements in the study population. Multiple linear regression analysis determined age, acute kidney injury, hs-Troponin, D-dimer, temporal changes in TC, and TG levels were determined as independent predictors for the development of COVID-19 mortality.
Conclusion: Our findings showed that temporal changes in lipid parameters before and after COVID-19 may be associated with mortality and in-hospital adverse outcomes.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus is a new type of beta-coronavirus and causes coronavirus disease 2019 (COVID-19) infection with high mortality rates (Huang et al., 2020). COVID-19 infection is a systemic infection in which...
cardiac, enteric, neurologic, nephrotic, and hepatic involvement can be seen and can cause multi-organ failure, mainly in the respiratory system (Guan et al., 2020; Wu and McGoogan, 2020; Islamoglu et al., 2021). COVID-19 infection, a multisystemic disease, can affect many biochemical parameters according to the severity of the disease. While parameters such as ferritin, D-dimer, fibrinogen, high-sensitivity cardiac troponin I (hs-TnI), and C-reactive protein (CRP) increase in proportion to the severity of the disease, lymphocyte levels decrease (Terpos et al., 2020; Barman et al., 2020; Gungor et al., 2021). However, little is known about how lipid parameters are affected by the disease.

Lipids play a crucial role not only in the proliferation and membrane structure of many microbiological agents, but also in the pathophysiology of viral infections (Hsu et al., 2010). Lipids constitute a large part of the surfactant structure in the lung (Han and Mallampalli, 2015). All lipid parameters are significantly affected by disease, primarily due to acute infections. Generally, a decrease in total cholesterol (TC) levels and an increase in the concentration of triglyceride-rich lipoproteins are observed. Low- and high-density lipoprotein cholesterol (LDL-C, HDL-C), apolipoprotein-A1, and apolipoprotein-B levels decrease (Filippas-Ntekouan et al., 2017). These changes in lipid levels may have prognostic and diagnostic significance in some infections. Reports show that TC is lower in SARS and hepatitis C virus patients than in healthy people (Dreux et al., 2009; Wu et al., 2017).

In patients with COVID-19 infection, the disease severity increases in the presence of many comorbid conditions such as coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HT), and dyslipidemia (Hashim et al., 2020). In a recent study, the atherogenic index of plasma was demonstrated to be a predictor of mortality in patients with COVID-19 (TurgayYıldırım and Kaya, 2021). It has been shown that decreasing lipid levels during COVID-19 are associated with a poor prognosis (Ding et al., 2020; Choi et al., 2020; Chen et al., 2020).

In this study, we aim to investigate the effect of COVID-19 infection on change of lipid parameters compared to individuals’ routine check-up visits.

2. Materials and methods

Three hundred twenty-four patients diagnosed with real-time reverse transcription-polymerase chain reaction (RT-PCR) positivity and treated in the hospital for COVID-19 infection between April 1 and June 15, 2020, were included in the study. The study was retrospective and organized in a single center. Patients younger than 18 years old or with familial hypercholesterolemia and familial hypertriglyceridemia were not included in the study (Fig. 1). The study was approved by the Internal Review Board of our center and was performed under the Ethical Standards of the Declaration of Helsinki.

According to the World Health Organization guidelines, SARS-CoV-2 RNA was detected by the real-time RT-PCR method determined in the Ministry of Health Public Health Microbiology Reference Laboratory. First, an oropharyngeal swab was taken. Then, the same swab was used, and a nasal sample was taken and placed on the transport solution. The SARS-CoV-2 virus nucleic acid amplification tests were performed to determine the routine confirmation and nucleic acid sequence of the SARS-CoV-2 virus.

Demographic characteristics of the patients, such as gender, age, smoking history, history of statin use, HT and DM, and laboratory data were obtained from medical records. The lipid parameters TC, LDL-C, HDL-C, and triglyceride (TG) values of the patients in the last year before hospitalization were obtained from their electronic medical records. In the first 24 h of hospitalization, laboratory data such as complete blood count, biochemical parameters including urea, creatinine, and electrolytes, liver and kidney function

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**Fig. 1. Flowchart of the study.**
tests, CRP, procalcitonin, lactate dehydrogenase, D-dimer, and hs-TnI were evaluated in addition to lipid parameters. Lipid parameters were taken from peripheral venous blood samples after 12 h of fasting. Serum biochemical measurements were performed in the hospital clinical laboratory using routine automatic techniques. The patients were compared with the severe/non-severe group according to the severity of the disease and then divided into non-survivors and survivors.

2.1. Definitions

The severe COVID-19 group was defined as having any of the following: (Huang et al., 2020) respiratory distress (respiratory rate ≥30 breaths per min); (Guán et al., 2020) oxygen saturation at rest ≤93%; (Wu and McGoogan, 2020) a ratio of the partial pressure of arterial oxygen (PaO₂) to the fractional concentration of oxygen inspired air (FiO₂) (PaO₂/FiO₂ ≤300 mmHg); or (Islamoglu et al., 2021) a critical complication (respiratory failure and mechanical ventilation (MV) required, septic shock, and/or multiple organ dysfunction/failure and required intensive care unit (ICU) admission) (Holshue et al., 2020). Acute cardiac injury (ACI) was characterized as hs-TnI serum levels above the 99th percentile upper reference limit (Thygesen et al., 2019). Acute respiratory distress syndrome (ARDS) was defined according to the Berlin Definition (Force et al., 2012). Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition (Kellum et al., 2012).

2.2. Endpoints

The primary endpoint was accepted as death. ARDS, AKI, ACI, MV, and ICU admission were accepted as the secondary endpoint. The relationship between lipid levels and endpoints was evaluated.

2.3. Statistical analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyze the normality of the data. Continuous data are expressed as mean ± SD, and categorical data are expressed as percentages. A chi-square test was used to assess differences in categorical variables between groups. The student’s t-test or Mann–Whitney U test was used to compare unpaired samples as needed. Comparisons of lipid parameters for individuals before and after COVID-19 were performed by paired samples t-test and/or Wilcoxon signed-rank test. Univariate and multivariate logistic regression analyses were used to identify independent variables of mortality. After performing univariate analysis, significantly obtained variables were selected into the multivariate logistic regression analysis with the stepwise regression method. The results of univariate and multivariate regression analyses were presented as an odds ratio with 95% CI. Significance was assumed at a 2-sided p < 0.05.

3. Results

The clinical and demographic characteristics of 324 COVID-19 positive patients included in the study are shown in Table 1. Patients were divided into two groups according to mortality, and 64 patients were included in the non-survivor group. While there was no statistical difference between the groups in terms of gender, the mean age was higher in the non-survivor group. The mean age of patients with non-survivor group was 67.67 ± 15.9, while the mean age of the non-severe patient group was 56.14 ± 18.2, and there was a statistically significant difference (p < 0.001). There was no statistically significant difference between the groups in terms of smoking. While a statistically significant difference was found between the groups in terms of HT (p = 0.004) and atrial fibrillation (p = 0.017), there was no statistically significant difference in terms of CAD, DM and hyperlipidemia. The patients were examined in terms of the drugs they used, no difference was observed in terms of Statins, Fibrates, and Glucose-lowering drugs, while patients using blood pressure-lowering drugs were more frequently observed in the non-survivor group (p = 0.004). While a statistically significant difference was found between the two groups in terms of heart rate (HR) and oxygen saturation (SpO₂) measurements at the time of admission between the severe and non-severe patient groups (p < 0.001), there was no statistically significant difference between the two groups in systolic blood pressure measurements (p = 0.272). Similarly, when laboratory tests were compared, a statistically significant difference was found between both groups in terms of HDL-C (p < 0.001), LDL-C (p < 0.001), TG (p < 0.001), blood urea nitrogen (p < 0.001), CRP (p = 0.006), hs-TnI (p < 0.001), hemoglobin (p < 0.001), D-dimer (p < 0.001), procalcitonin (p < 0.001), and LDH (p < 0.001) values. Finally, when the patients were compared in terms of ARDS and AKI development, ICU admission, severity of COVID-19, length of stay in hospital and MV need, it was found that the non-survivor group showed a statistically significant difference compared to the survivor group (p < 0.001) (Table 1). In addition, 324 COVID-19 positive patients included in the study were grouped as severe (n = 139) and non-severe (n = 185), and their clinical and demographic characteristics are shown in Table 1.

When the lipid values of the patients included in the study were examined before the COVID-19 infection and during hospitalization, it was found that there was a statistically significant decrease in the TC, HDL-C, and LDL-C values (p < 0.001). However, it was observed that the change in TG levels did not reach statistical significance in all groups (Table 2) (Fig. 2).

The changes in lipid values measured before infection and during hospitalization of the patients included in the study were examined. It was found that changes in TC, LDL-C, and TG values did not have a statistically significant effect on the severity of the disease, need for MV, ICU requirement, ARDS and AKI development, or death. It was observed that changes in HDL-C values did not have a statistically significant effect on the severity of the disease, the need for ICU, or the development of ARDS and AKI (p > 0.05). It was found that there was a statistically significant effect on death (p = 0.007) and the need for MV (p = 0.026) (Table 3).

Parameters affecting the mortality were evaluated by univariate and multivariate analysis with logistic regression analysis. Many parameters such as age, gender, HT, CAD, AKI, HR, SpO₂, changes in HDL-C, TC, and TG levels, glucose, hs-TnI, D-dimer, and CRP
were first evaluated in univariate analysis. In univariate analysis, statistically significant differences in age, HT, AKI, heart rate, SpO₂, changes in HDL-C, TC, and TG levels, hs-TnI, D-dimer and CRP values were evaluated by multivariate analysis. They were found to be statistically significant independent predictors, respectively, in terms of predicting the development of mortality (age: OR = 1.042, p < 0.001; D-dimer: OR = 1.130, p = 0.014) (Table 4).

4. Discussion

In this study, we aimed to show the effect of lipid levels on the severity of COVID-19 infection and the change in lipid levels throughout the course of the disease. The main findings of our study are: i) TC, TG, and HDL-C levels decreased compared with levels before COVID-19; ii) this decrease was observed more prominently in those who had severe disease or died; iii) in the multivariate analysis method, age, AKI, hs-TnI, D-dimer, changes in TC, and TG levels were determined as independent predictors for the mortality.

There has been substantial evidence that cardiovascular risk factors such as HT, diabetes, and dyslipidemia are closely related to the severity of COVID-19 infection (Chen et al., 2020). In a limited number of studies on this topic, the change in lipid levels after the diagnosis of infection has been examined (Ding et al., 2020; Choi et al., 2020; Chen et al., 2020), and the pre-infection lipid levels of the patients are not known. At this point, evaluations on dyslipidemia and the severity of infection do not reach the desired level. In
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TC, HDL, LDL, and monocyte/HDL ratios were lower in COVID-19 patients (Hu et al., 2020). In a study conducted by Ding et al., HDL- whose prognosis worsened (Wei et al., 2020). In a study by Hu et al., COVID-19 patients were compared with the control group, and

degrees decreased as the severity of the disease increased, and hypolipidemia was observed to become more pronounced in patients

19 patients may indicate improvement (Chen et al., 2020). In a study by Wei et al., 597 COVID-19 patients were included, and lipid

patic LDL receptors (LDL-R). Low levels of apolipoprotein E (ApoE) and apolipoprotein C-III (ApoC-III) in HDL result in a decrease in

lipid transport and disruption of the reverse cholesterol transport (RCT) pathway, and decreases cholesterol es-
terification by lecithin-cholesterol acyltransferase (LCAT). The return of cholesteryl esters to the liver is reduced either directly

through the hepatic scavenger receptor-B1 (SR-B1) receptors or indirectly through cholesteryl ester transfer protein (CETP) and he-

patic LDL receptors (LDL-R). Low levels of apolipoprotein E (ApoE) and apolipoprotein C-III (ApoC-III) in HDL result in a decrease in

lipoprotein lipase (LPL) activity, leading to the accumulation of very-low-density lipoprotein (VLDL) and TGs. Consequently, it is

thought that SARS-CoV-2 infection may cause liver damage associated with dyslipidemia and oxidative stress (Bruzzone et al., 2020;

Shen et al., 2020; Mechanick et al., 2020).

Lipid levels are affected due to the inflammation that develops in most infectious diseases. Decreased HDL-C and LDL-C levels

have been observed in HIV infections and hepatitis B patients with cirrhosis (Baker et al., 2010; Cao et al., 2019). In a study con-
ducted by Chen et al., serum lipid levels in COVID-19 patients were low at admission. They found that low LDL-C was an independent

predictor of prolongation of hospitalization. They suggested that the increase in lipid levels during hospitalization in severe COVID-

19 patients may indicate improvement (Chen et al., 2020). In a study by Wei et al., 597 COVID-19 patients were included, and lipid

levels decreased as the severity of the disease increased, and hypolipidemia was observed to become more pronounced in patients

whose prognosis worsened (Wei et al., 2020). In a study by Hu et al., COVID-19 patients were compared with the control group, and

TC, HDL, LDL, and monocyte/HDL ratios were lower in COVID-19 patients (Hu et al., 2020). In our study conducted by Ding et al., HDL-

C levels were found to be low in 65.2% of the patients whose PCR test positivity time was longer than 14 days, and HDL-C was

thought to be an independent predictor affecting virus clearance (Ding et al., 2020). In our study, a decrease was found in TC, LDL-C,

HDL-C, and TG levels in the course of infection compared with the period before COVID-19. The temporal changes in lipid levels (TC,

HDL-C) in the pre-illness period and after COVID-19 are an independent predictor of mortality.

The mechanism of this change in lipid parameters in COVID-19 patients is not entirely known. Current research shows that in pa-

tients with severe COVID-19 infection, plasma cholesterol levels, including HDL-C and LDL-C, are reduced, and this reduction is

related to the severity of the disease (Choi et al., 2020). Immune system dysfunction may be the cause of the change in lipid levels, as it

is a critical factor associated with the severity of the disease in COVID-19 patients (Zhang et al., 2020).

This study has some limitations. The lipid levels of patients diagnosed with COVID-19 were measured in the first 24 h after hospi-
talization. Recurrent lipid levels were not measured during the follow-up of the patients during their hospitalization. As the study in-
volved a limited number of patients who used statins, the cause for the shift in lipid levels could be due to the use of statins. In addi-
tion, the study design, the study site, the sample size, and the number of covariates include other limitation of the study.

In conclusion, metabolic changes are frequently observed in patients with COVID-19, and the changes that occur may have an im-

pact on the prognosis of the disease. Decreased levels of TC, TG, and HDL-C indicate worse outcomes and severe types of COVID-19. More data are needed to reveal the mechanism underlying the association of TC, TG, and HDL-C levels with COVID-19 disease. Therefore, early evaluation of serum lipid levels may be required, especially in patients with comorbidities.

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Fig. 2. Temporal changes of lipid profile in severe and non-severe COVID-19 patients.
Table 3
Relationship between changes in lipid levels and clinical outcomes.

|                        | TOTAL CHOLESTEROL DIFFERENCE (MG/DL) | P     | HDL DIFFERENCE (MG/DL) | P     | TRIGLYCERIDE DIFFERENCE (MG/DL) | P     |
|------------------------|--------------------------------------|-------|------------------------|-------|-------------------------------|-------|
| SEVERE DISEASE         | Yes 44 (−7/90.5)                    | 0.969 | 14 (−2.5/28)          | 0.556 | 9 (−76/66.5)                  | 0.814 |
|                        | No 39 (−4/95)                       | 0.069 | 22 (5/35.5)           | 0.007 | 32 (−97/94)                   | 0.536 |
| NON-SURVIVOR           | Yes 84 (13/113)                     | 0.152 | 16.5 (7/31)           | 0.026 | 12 (−109/87)                  | 0.469 |
|                        | No 34 (−10/83)                      | 0.354 | 7 (−4/7/19.7)         | 0.103 | 10 (−43/69)                   | 0.874 |
| TRIGLYCERIDE DIFFERENCE| INTENSIVE CARE                      |       |                        |       |                               |       |
|                        | Yes 58 (9/99.7)                     | 0.803 | 16.5 (1/297)          | 0.122 | 12 (−83/101)                  | 0.874 |
|                        | No 31.5 (−7.9/88)                   | 8.5 (−4.2/20) |                           |       |                               |       |
| MV                     | Yes 49.5 (4/110)                    | 0.152 | 16.5 (7/31)           | 0.026 | 12 (−109/87)                  | 0.469 |
|                        | No 31.5 (−16/86)                    | 7 (−4.7/19.7) |                           |       |                               |       |
| INTENSIVE CARE         | Yes 58 (9/99.7)                     | 0.303 | 16.5 (1/297)          | 0.122 | 12 (−83/101)                  | 0.874 |
|                        | No 31.5 (−7.9/88)                   | 8.5 (−4.2/20) |                           |       |                               |       |
| AKI                    | Yes 54 (20/88)                      | 0.445 | 15 (1/30)             | 0.163 | 7 (−86/76)                    | 0.583 |
|                        | No 29 (−12/102)                     | 9 (−5/20) |                          |       |                               |       |
| ARDS                   | Yes 89 (−4/116)                     | 0.208 | 16 (−2.7/30)          | 0.301 | 84 (−175/90)                  | 0.122 |
|                        | No 37 (−7.5/86)                     | 9 (−2.5/21.2) |                          |       |                               |       |

Abbreviations: MV, Mechanical Ventilation; AKI, Acute kidney injury; ARDS, Acute Respiratory Distress Syndrome.

Table 4
Univariate and multivariate logistic regression analysis on the risk factors associated with COVID-19 mortality.

| Variable        | Univariate OR 95%CI                  | p     | Multivariate OR 95%CI | p     |
|-----------------|-------------------------------------|-------|-----------------------|-------|
| Age             | 1.039 1.021–1.058                   | <0.001| 1.042 1.014–1.071     | 0.003 |
| Gender          | 0.928 0.532–1.622                   | 0.794 |                       |       |
| Hypertension    | 2.262 1.276–4.002                   | 0.005 | 1.605 0.662–3.892     | 0.296 |
| CAD             | 1.136 0.601–2.145                   | 0.695 |                       |       |
| AKI             | 5.626 3.140–10.080                  | <0.001| 1.041 1.018–1.064     | <0.001|
| Heart rate      | 1.035 1.018–1.051                   | <0.001| 1.851 0.838–4.092     | 0.128 |
| SpO₂            | 0.894 0.864–0.926                   | <0.001| 0.971 0.926–1.017     | 0.209 |
| HDL-Ca          | 0.952 0.929–0.976                   | <0.001| 1.015 0.974–1.057     | 0.483 |
| Total cholesterol| 0.987 0.981–0.994                  | <0.001| 0.990 0.981–0.999     | 0.028 |
| Triglyceridea   | 0.941 0.884–0.990                   | <0.001| 0.932 0.820–0.978     | 0.003 |
| Glucose         | 1.003 1.000–1.007                   | 0.081 | 1.001 0.995–1.007     | 0.686 |
| hs-TnI          | 1.531 1.182–2.851                   | <0.001| 1.312 1.065–1.973     | <0.001|
| D-dimer         | 1.231 1.074–1.483                   | <0.001| 1.130 1.024–1.327     | 0.014 |
| CRP             | 1.271 1.083–1.673                   | 0.001 | 1.027 0.987–1.074     | 0.342 |
| Statin use      | 1.489 0.740–2.997                   | 0.264 |                       |       |

Abbreviations: CAD, Coronary artery disease; AKI, Acute kidney injury; SpO₂, Oxygen saturation; HDL-C, High-density lipoprotein cholesterol; hs-TnI, high sensitive Troponin I; CRP, C-reactive protein.

a The temporal changes in TC, HDL-C and TG levels.

CRediT authorship contribution statement

Hasan Ali Barman: Conceptualization, Methodology, Project administration, Resources, Software, Writing – original draft.
Ayse Selcen Pala: Data curation, Investigation. Omer Dogan: Data curation, Software, Writing – original draft, Writing – review & editing. Adem Atici: Formal analysis, Writing – review & editing, Writing – original draft. Mehmet Tugay Yumuk: Data curation, Investigation. Gokhan Alici: Conceptualization, Resources, Software. Omer Sit: Data curation, Formal analysis. Baris Gun- gor: Conceptualization, Methodology, Project administration. Sait Mesut Dogan: Supervision, Visualization, Writing – original draft.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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