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Association of Lipid Profile and Inflammatory Markers With COVID-19 Severity and Outcome

Amirhossein Khoshgoeian[1], Adele Bahar[1], Zahra Kashi[1], Mina Khasayesi[1], Shima Yahoo Torghabe[2], Mahmood Moosazadeh[3], Zahra Hosseini-khah[1*]

1. Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Basic Sciences, Faculty of Animal Sciences and Fisheries, Sari Agricultural Sciences and Natural Resources University, Sari, Iran.
3. Gastrointestinal Cancer Research Center, Non-Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.

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ABSTRACT

Background: COVID-19 is a highly contagious disease that has already affected millions of people worldwide. Proinflammatory cytokines in COVID-19 infection change lipid metabolism and profile. This study investigates the association between lipid profile and inflammatory markers with the severity and outcome of COVID-19 patients referred to a teaching hospital in Mazandaran Province, Iran, during April-May and July-August 2020.

Materials and Methods: This study was conducted on 140 patients with COVID-19 based on their clinical symptoms, imaging results, and laboratory findings. Patients were categorized as severe and non-severe groups based on the Centers for Disease Control and Prevention criteria. Blood samples (5-7 mL) were collected from patients after 12 hours of fasting. Serum triglycerides, cholesterol, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were measured using Pars Azmoon Kits (Hitachi Ltd).

Results: Of 140 COVID-19 patients, 33.57% had severe and 66.43% had non-severe disease. Patients with severe disease had a significantly lower mean LDL serum level than those with non-severe involvement (56.39±3.62 vs 70.10±3.74 mg/dL) (P=0.023). Patients in the intensive care units had significantly lower HDL, LDL, and cholesterol serum levels than those hospitalized in other parts (P=0.006, P=0.002, and P=0.002, respectively). There was a significant negative correlation between HDL serum level and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (P=0.0001 and r=-0.482) and (P=0.01 and r=-0.258), respectively. Additionally, there was a significant correlation between cholesterol level and CRP, triglycerides, and ESR (P=0.016 and P=0.02, respectively).

Conclusion: The present study highlights the potential of lipid profiling as a cost-effective and accessible marker to assess COVID-19 severity and prognosis.

*** Corresponding Author:**
Zahra Hosseini-khah, PhD.
Address: *Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran.*
Phone: *+98 (911) 1588632*
E-mail: *zahra_582005@yahoo.com*

Introduction

The COVID-19 pandemic has impacted millions of individuals worldwide. The patients were presented with different levels of severity and outcomes. Lipid profile refers to the various types of lipids, including cholesterol and triglycerides, in the bloodstream. Recent studies have investigated the association between lipid profile and the severity and outcome of COVID-19 [1]. It is necessary to study some metabolic processes and physiological functions affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19 infection. As a result of infection with SARS-CoV-2, a variety of changes occur in the host's immunological status, such as neutropenia, depletion of dendritic cells, natural killer cell depletion, decreased T (T CD4+ and CD8+) and B lymphocytes, and an increase in proinflammatory cytokines. Monocytes, macrophages, and T cells respond to inflammatory factors. They will be absorbed into the site of inflammation by creating a complex of cytokines that damage the lungs [2].

As a consequence of the cytokine storm, which includes the release of proinflammatory cytokines (tumor necrosis factor, interleukin [IL]-6, IL-8, and IL-10), and lymphopenia, patients with SARS-CoV-2 infection are considered to be at high risk of death [3]. When released cytokines and chemokines act directly on cells, they cause massive cell death, which promotes inflammation by producing macrophage-derived eicosanoids [4]. Patients with COVID-19 may have an altered lipid profile due to increased cytokine levels [5]. Moreover, proteome analysis indicates dysregulation of lipid metabolism in COVID-19 patients [6]. A high level of proinflammatory cytokines is associated with dyslipidemia and immune, respiratory, and cardiovascular system damage. Moreover, dyslipidemia is related to an increased risk of thrombotic complications, endothelial dysfunction, and higher platelet activity [7].

Therefore, it is likely that lipid dysregulation contributes to COVID-19 infection-related morbidity and mortality. Lipids play a role in structural components, energy resources, signaling mediators, and infection, particularly viral infections [8, 9]. It has been observed that lipid metabolism plays a pivotal role in pulmonary infections and inflammatory states due to its dependence on macrophage regulation and immune modulatory pathways [6, 10]. It had been noted that coronaviruses affect lipid metabolism and serum lipid profiles before the current pandemic. Lipid profiles of COVID-19 patients have been found to change significantly in several studies [2, 11]. There is much uncertainty as to whether the lipid profiles of COVID-19 patients can predict the severity of the disease, mortality, and how lipids change over time. This study evaluates changes in lipid profiles and inflammatory markers of patients with COVID-19 infection referred to a teaching hospital in Sari City, Iran, to determine the association of lipid profiles with clinical manifestations, severity, and disease outcome.

Materials and Methods

This cross-sectional study was conducted on 140 patients with COVID-19 infection referred to teaching hospitals at Mazandaran University of Medical Sciences during March-April and June-July 2020. COVID-19 was confirmed according to clinical symptoms, imaging results, laboratory, and molecular (positive real-time PCR) findings. Individuals with dyslipidemia, heart disease, hypertension, diabetes, malignancies, anti-lipid drug users, and those who did not consent to sampling were excluded.

The data were collected through a questionnaire, which included demographic information such as age, gender, education level, history of underlying disease including heart disease, lung disease, kidney disease, lung disease, and liver disease, laboratory findings, hospitalization, and mortality rate and was recorded from the patient's file.

According to the centers for disease control and prevention, the disease's severity has been categorized into severe and non-severe [12]. The severe group includes patients who represent severe and critical symptoms, such as a respiratory rate exceeding 30 breaths per minute, SpO_2 level lower than 94%, invasive mechanical ventilation, displaying mild and moderate symptoms, such as fever, chills, dry cough, body aches, tiredness, and SpO_2 equal to or exceeding 94%.

About 5-7 mL of blood was collected from each patient after 12 hours of fasting. The lipid profile test in patients with COVID-19 is typically conducted within the first 5 days of hospitalization. Samples were stored at -20°C until they were tested. Blood samples were centrifuged at 1500 xg for 10 minutes, and serums were separated. After measuring hematological and biochemical parameters, serum levels of triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were evaluated using Pars Azmoon Kits (Hitachi Ltd) following the standard protocol.

Table 1. Patients' demographics with severe and non-severe COVID-19

Demographic Characteristic		Mean±SD/No. (%)		P
		COVID-19 Patients (Severe) (n=47)	COVID-19 Patients (Non-severe) (n=93)	
Age (y)		62.31±2.6	54.27±1.7	0.01*
Gender	Male	28(37.3)	47(62.7)	0.15
	Female	17(26.2)	48(73.8)	
BMI (kg/m^2)		27.65±0.77	28.32±0.67	0.55
Marital status	Single	2(16.7)	10(83.3)	0.22
	Married	38(33.9)	74(66.1)	
Education	High school	25(44.6)	31(55.4)	0.01*
	Diploma and higher	21(24.4)	65(75.6)	
Location	Urban	32(36)	57(64)	0.07
	Rural	8(20)	32(80)	
Blood group	Type A	7(29.2)	7(70.8)	0.80
	Type B	13(41.9)	18(58.1)	
	Type AB	2(33.3)	4(66.7)	
	Type O	11(36.7)	19(63.3)	
Smoking		5(71.4)	2(28.6)	0.03*
Opium		7(43.8)	9(56.2)	0.44

*Significant

The statistical analyses for this study were conducted using SPSS software, version 20. Graphics were created using GraphPad Prism software, version 8.0.2. Evaluation of data normality was done by the Kolmogorov-Smirnov test. The normally distributed qualitative and quantitative variables were analyzed using the chi-square and student t-tests, respectively. Additionally, we used Spearman's rank correlation test for non-normally distributed data. Data were reported as Mean±SD. P<0.05 were considered significant.

Results

Demographic characteristics of patients

An analysis of 140 patients with COVID-19 revealed that 75 patients (53.6%) were men and 65(46.4%) were women. The patients were categorized into severe and non-severe groups. Of 140 patients, 47(33.57%) demonstrated severe symptoms, and 93(66.43%) were non-severe. The severe group had an average body mass index (BMI) of 27.65±0.77 kg/m^2, while the non-severe group had an average BMI of 28.32±0.67 kg/m^2 (P=0.55). Table 1 provides demographic information of the patients.

Comorbidities in patients with severe and non-severe COVID-19 infection

The results showed that the most prevalent comorbidities in patients were hypertension (severe group=38.1%, non-severe group=35.9%), diabetes (severe group=30.2%, non-severe group=32.1%), and cardiovascular disease (severe group=23.8%, non-severe group=21.8%). There was no significant association between comorbidities and the severity of the disease (P>0.05).

Symptoms of patients with severe and non-severe COVID-19 infection

The most common symptoms in patients were dyspnea (58.9%), cough (45.5%), and fever (42.9%). The preva-

Table 2. Comparing lipid profile levels between severe and non-severe COVID-19 patients

Lipid Profile	Mean±SEM		P
	COVID-19 Patients (Severe) (n=46)	COVID-19 Patients (Non-severe) (n=96)	
LDL (mg/dL)	56.39±3.62	70.10±3.74	0.02*
HDL (mg/dL)	35.80±1.45	37.75±1.59	0.44
TG (mg/dL)	190.1±22.59	172.6±11.45	0.23
Cholesterol (mg/dL)	124.4±6.05	141.5±6.63	0.10

Abbreviations: LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides.

*Significant.

lence of dyspnea among patients with severe disease was significantly higher than that among patients with non-severe disease (79.5% vs 47.9%) (P=0.001).

Association between lipid profile and severity of COVID-19

The average lipid profile, including cholesterol, triglyceride, LDL, and HDL in patients with COVID-19 was 136.04±4.9 mg/dL, 182.6±12.3 mg/dL, 65.66±2.83 mg/dL, and 36.45±0.85 mg/dL respectively. The results showed that the triglyceride level was higher than the normal range, and the HDL level was lower than the normal range in patients with COVID-19.

Severe and non-severe cases of COVID-19 disease were compared according to lipid profiles, including cholesterol, triglycerides, LDL, and HDL. There was no significant difference between the two groups for cholesterol, triglycerides, and HDL (P>0.05). Patients with severe disease had significantly lower serum LDL levels compared to non-severe patients (56.39±3.62 vs 70.10±3.74 mg/dL) (P=0.023) (Table 2).

Association between lipid profile and outcome of patients with COVID-19

The association between the outcome of the disease and the level of lipid profile in patients with COVID-19 showed that the serum level of HDL in the patients who were hospitalized in intensive care units (ICU) was

Table 3. Association between lipid profile and disease outcome of COVID-19 patients

Lipid Profile	Mean±SD							
	Outcome Yes (n=29), No(n=113)							
	ICU Hospitalization	P	Ventilation	P	ARDS	P	Death	P
LDL (mg/dL)	Yes:50.65±3.3 No:69.51±3.3	0.002*	Yes:56.66±6.3 No:68.18±3.7	0.36	Yes:61.33±10.1 No:67.36±3.6	0.776	Yes:47.33±5.81 No:63.50±4.06	0.081
HDL (mg/dL)	Yes:32.10±1.3 No:38.97±1.9	0.006*	Yes:32.66±3.1 No:36.98±1.08	0.24	Yes:34.66±5.04 No:36.67±1.05	0.746	Yes:32.66±1.79 No:36.10±2.06	0.45
TG (mg/dL)	Yes:181.93±31.83 No:198.31±23.53	0.673	Yes:223±91.91 No:181.8±15.09	0.458	Yes:416.3±185.62 No:178.56±10.21	0.496	Yes:150.20±23.52 No:171.61±17.43	0.585
Cholesterol (mg/dL)	Yes:112.89±5.2 No:160.58±5.9	0.002*	Yes:120.88±11.3 No:141.94±6.6	0.342	Yes:139.00±24.4 No:140.15±6.3	0.975	Yes:109.86±9.01 No:128.63±7.02	0.235

Abbreviations: ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides.

*Significant.

Table 4. Laboratory findings in patients with severe and non-severe COVID-19 patients

Laboratory Findings	Mean±SD		P
	COVID-19 Patients (Severe)	COVID-19 Patients (Non-severe)	
WBC (×10^9/L)	10190±671.59	8111.23±488.64	0.015*
Lymphocytes (/µL)-	14.11±2.05	20.64±1.65	0.019*
PLT (µL)	247606.82±19099	231548.81±12170.53	0.46
Hb (g/dL)	10.79±0.36	11.29±0.28	0.28
Ca (mg/dL)	8.31±0.21	8.39±0.12	0.73
Alb (g/dL)	3.48±0.10	3.70±0.07	0.088
Ca corrected with Alb (mg/dL)	8.73±0.21	8.72±0.09	0.94
Phosphorus (mg/dL)	3.41±0.09	3.77±0.1	0.015*
Na (mmol/L)	134.54±0.85	135.70±0.61	0.27
K (mmol/L)	4.29±0.11	4.23±0.058	0.60
Mg (mmol/L)	2.03±0.07	2.01±0.05	0.87
CPK (units/L)	324.18±130.69	362.77±93.61	0.80
LDH (U/L)	606.20±31.88	738.55±120.33	0.44
Troponin (ng/L)	18.79±6.07	29.91±18.09	0.64
Ferritin (µg/dL)	535.70±161.97	336.51±41.23	0.23
ALT (U/L)	30.78±4.29	44.07±6.06	0.076
AST (U/L)	38.92±4.65	55.23±8.12	0.085
ALP (U/L)	248.78±21.79	283.26±34	0.47

Abbreviations: WBC: White blood cell; PLT: Platelet; Hb: hemoglobin; Ca: Calcium; Alb: albumin; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase.

*Significant.

significantly lower than in the patients in other wards (32.10±1.3 vs 38.97±1.9 mg/dL), (P=0.006). Also, patients hospitalized in the ICU had lower total cholesterol and LDL serum levels (P=0.002 and P=0.002, respectively) (Table 3).

In addition, the patients with more severe disease and hospitalized in the ICU had a significantly higher LDL level than those with non-severe disease (52.10 20.03±47.44±12.55, P=0.046).

Serum inflammatory markers (CRP, ESR) and COVID-19 severity and outcome

The Mean±SD values of the inflammatory marker, CRP, in patients with COVID-19, were 50.46±5.05, 54.24±5.4 and 7.74±47.94 mg/dL in the three phases of admission, hospitalization, and discharge, respectively. Also, the serum level of erythrocyte sedimentation rate (ESR) was 48.13±2.7, 58.86±7.32, and 8.9±53.50 mg/dL in the three phases of admission, hospitalization, and discharge, respectively. The results showed that the level of inflammatory markers was higher than the normal range in patients with COVID-19, which decreased after hospitalization and treatment. Also, the results of this study showed that the mean serum levels of CRP and ESR were higher in patients with severe disease than in the non-severe group. Still, this difference was not statistically significant (P>0.05) (Table 4).

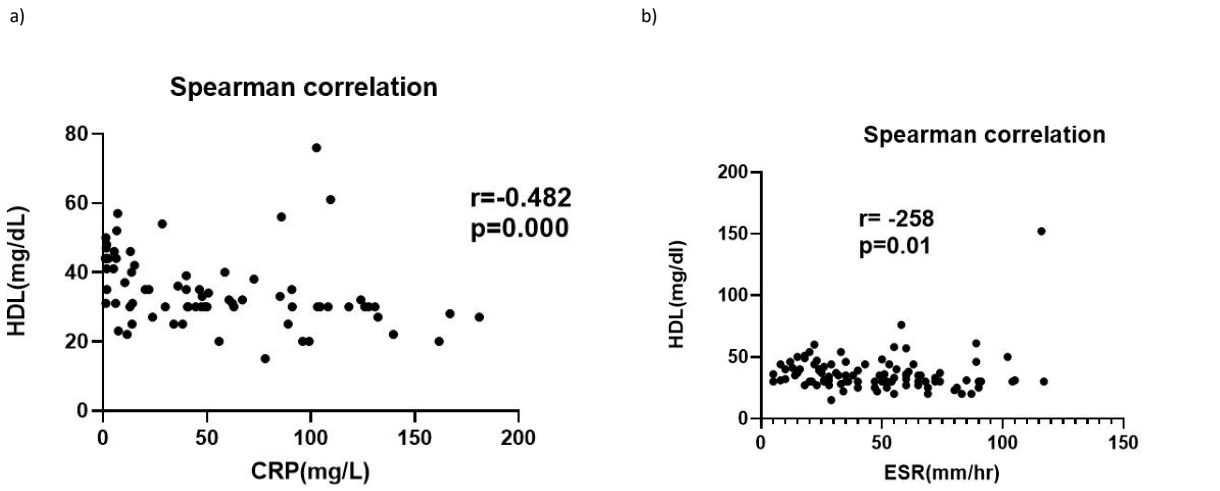

Figure 1. Correlation between HDL and inflammation markers (CRP, ESR) in COVID-19 patients

a) HDL & CRP, b) HDL & ESR

Abbreviations: HDL: High-density lipoprotein; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

The results of evaluating the level of inflammatory markers in the three phases, initial, hospitalization, and discharge, did not show a significant relationship with the outcome of the disease (admission to ICU, need for ventilation, and death) (P>0.05). Also, there was no significant association between inflammatory markers and disease outcome between severe and non-severe groups (P>0.05).

Laboratory findings in severe and non-severe patients with COVID-19

The comparison of laboratory findings between two groups of patients with severe and non-severe disease is shown in Table 4. The results showed a significant relationship between the number of white blood cells (P=0.023), serum albumin (P=0.049), and phosphorus (P=0.043) between the severe and non-severe groups.

Correlation of serum level of lipid profile with inflammatory markers (CRP, ESR) in COVID-19 patients

There was a significant negative correlation between HDL and CRP (P=0.0001, r=-0.482). Also, a significant negative correlation was observed between HDL and ESR (P=0.01, r=-0.258) (Figures 1a and 1b).

In addition, the correlation of serum total cholesterol and CRP was negative and significant (P=0.016, r=-0.277) (Figure 2a), and the correlation of serum triglyceride (TG) and ESR was positive and significant (P=0.02, r=0.23) (Figure 2b).

Correlation between lipid profile and clinical and laboratory parameters

Furthermore, a significant relationship was found between LDL serum level and SpO_2 (r=0.20, P=0.048), WBC (r=-0.18, P=0.040), lymphocyte count (r=0.22, P=0.024), CPK (r=0.278, P=0.013) and LDH (r=0.236, P=0.025). There was a significant positive correlation between serum cholesterol levels and LDH (r=0.241, P=0.022), CPK (r=0.245, P=0.028), and lymphocyte counts (r=0.26, P=0.009). HDL levels were also significantly correlated to lymphocyte counts (r=0.29, P=0.002), and TG levels were directly related to ferritin levels (r=0.273, P=0.001).

Discussion

The current study evaluated the association between lipid profile and severity and outcome of COVID-19 infection in patients referred to a teaching hospital in Mazandaran Province, Iran. The result showed a higher TG level and a lower HDL level than the normal range in patients with COVID-19. Also, LDL serum levels were significantly lower in patients with severe disease than in patients with non-severe disease. The results showed that patients hospitalized in the ICU had lower serum levels of LDL, HDL, and cholesterol than those hospitalized in other wards. Furthermore, patients with severe involvement and hospitalized in the ICU had significantly lower LDL levels than the severe group hospitalized in other wards.

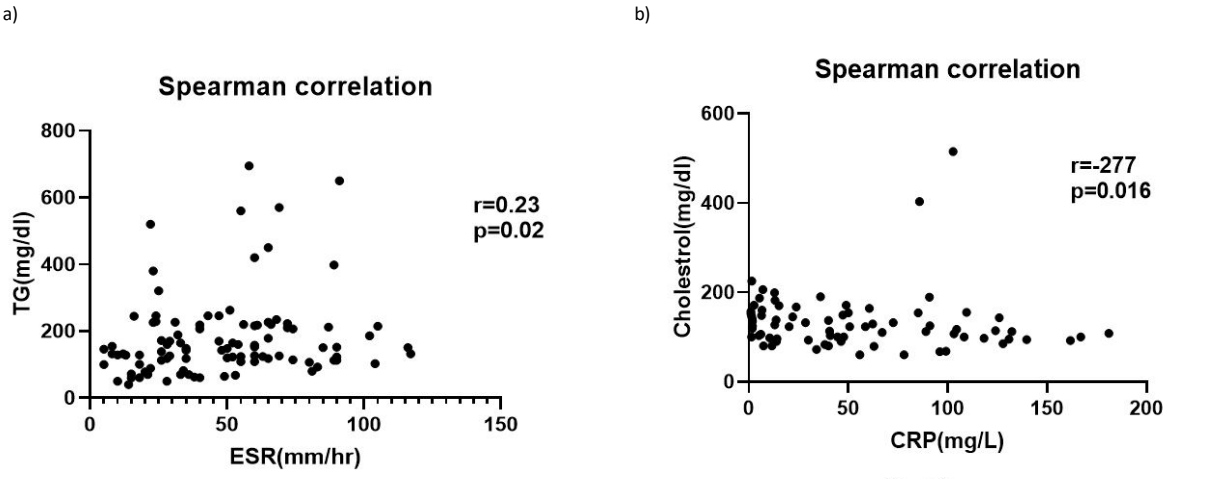

Figure 2. Correlation between total cholesterol serum level and CRP in patients with COVID-19
a) Correlation between serum TG, b) ESR levels in patients with COVID-19
Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TG: Triglyceride.

Various studies have investigated the association between COVID-19 and lipid profiles [13]. In a cross-sectional study carried out on 1411 patients with COVID-19, low HDL-C, and high TG before infection and upon admission were considered strong predictors of disease severity [14]. According to another large study, total cholesterol (TC) and LDL-C decreased with the progression of COVID-19, and HDL-C was abnormally low in critical cases [15]. An analysis of 248 COVID-19 patients' lipid profiles by Qin et al. found decreased levels of TC and LDL-C, and patients' length of stay in the hospital was negatively correlated with TC and LDL-C. In addition, they found that the patients' TC and LDL-C levels were lower than the normal range at the time of admission but slowly would reach normal as their clinical condition improved [16]. Retrospective research on 102 patients in Mexico indicates that low levels of TC and LDL-C predict more severe involvement [17]. These findings are in line with our study.

Several studies have described rapid changes in lipid profile in response to COVID-19 and disease progression. For this reason, there may be a large gap between dyslipidemia before infection and when lipid disorders occur during hospitalization. In this study, patients with more severe diseases had lower levels of LDL-C than the group of non-severe patients; some explanations for this issue have been proposed, including the hypercatabolic state and nutritional deficiency in acute infections, including COVID-19. In addition, patients hospitalized in the ICU and experienced a more severe disease had lower levels of HDL-C and LDL, indicating that factors related to the severity of COVID-19 affect lipid parameters. Furthermore, the possible effects of treatments for COVID-19 should also be considered. Most patients with severe COVID-19 were on corticosteroid treatment, which may be responsible for the high triglyceride levels; however, the lipid profile, which includes LDL and HDL cholesterol levels, is usually determined at the time of admission, which may explain the lack of evaluation effect of drugs on these levels.

In this study, there was no significant correlation between inflammatory markers and the severity and outcome of the disease. However, the results showed a significant negative correlation between HDL serum level and CRP and ESR.

According to several studies, LDL and HDL are inversely related to CRP as a marker of disease severity [14, 18]. Huang et al., in a meta-analysis, confirmed that lactate dehydrogenase (LDH), CRP, and procalcitonin (PCT) levels are associated with the severity of COVID-19; moreover, levels of leukocytosis, lymphocytopenia, and aspartate aminotransferase (AST) are linked with varying degrees of severity of COVID-19 [19]. Additionally, it has been reported in several studies that the ESR increased in COVID-19 patients [20-22]. According to some studies, the early stages of COVID-19 have been linked to significant elevations in both ESR and CRP levels. However, the level of CRP is more sensitive to the severity of the disease [23]. In a study by Xiong et al. on 42 COVID-19 patients, findings indicated that pneumonia severity considered in the initial CT scan correlated significantly with ESR, and an elevated level

of ESR, CRP, and LDH could indicate inflammation or extensive tissue damage [24].

We found a negative correlation between total cholesterol level and CRP. Many studies have investigated the association between total cholesterol and CRP in COVID-19 patients. Similar to our study, a retrospective study showed that serum total cholesterol level was negatively correlated with serum CRP level in COVID-19 patients [25]. Another study reported that patients with COVID-19 had lower total cholesterol levels than healthy individuals [26]. Also, a systematic review showed that low levels of total cholesterol are associated with increased severity and mortality of COVID-19 [27]. Overall, these studies suggest lower levels of total cholesterol may be associated with higher levels of CRP and more severe cases of COVID-19.

Also, the results of our study showed a significant positive correlation between serum triglyceride levels and ESR. According to our research, a retrospective study demonstrated that TG was positively correlated with ESR in COVID-19 patients [27]. This study also showed that TG level has a positive correlation with other inflammatory markers such as CRP, LDH, and IL-10 in COVID-19 patients. This finding suggests a potential link between TG and overall inflammation in COVID-19.

Typically, severe COVID-19 disease is related to a cytokine storm known as an exaggerated inflammatory response characterized by elevated interleukins, leukocytes, neutrophils, CRP, and ferritin levels [28]. Severe disease and fatal outcomes are associated with elevated CRP, PCT, LDH, and liver function indices [29]. The underlying mechanism of the relationship between lipid profile and inflammatory markers, such as ESR and CRP, is still unclear. However, there are hypotheses about potential mechanisms. Lipids, especially HDL, can have anti-inflammatory effects by inhibiting the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines. HDL can also prevent the activation of immune cells, such as monocytes and macrophages, which play a crucial role in inflammation [13]. Lipid profile and inflammatory markers may be related due to common risk factors, such as obesity, diabetes, and hypertension, as these risk factors can lead to dyslipidemia and chronic low-grade inflammation diseases [25]. It is also possible that the relationship between lipid profile and inflammatory markers is bilateral, with inflammation influencing lipid metabolism and lipid metabolism influencing the grade of inflammation. For example, low HDL-C levels may contribute to inflammation, leading to further reductions in HDL-C levels [18]. Overall, the relationship between lipid profile and inflammatory markers is complex and likely involves multiple mechanisms. Additional research is needed to fully understand the underlying mechanisms and potential therapeutic targets for dyslipidemia and inflammation.

Despite the beneficial findings of our study, it had some limitations. It was impossible to measure the lipid profile of patients before the infection, compare lipid levels before and after the infection, and evaluate the lipid profile's influence on the disease progression. Another limitation of this study was the patients' lack of nutritional and lifestyle information, which can affect the association between lipid profile and disease severity. Lipid profiles can be influenced by various factors such as age, sex, diet, lifestyle, underlying diseases, and medications. These factors may make the relationship between lipid profile and disease severity challenging. Although lipid profile changes may be associated with the severity of COVID-19, they may not have sufficient predictive value to be used as independent predictors. Evaluation of other clinical and laboratory parameters and lipid profile measurements is usually recommended to assess disease severity and prognosis.

Conclusion

The present study provides valuable information regarding the use of lipid profiles as a predictor of the severity of COVID-19 infection. It highlights the potential of lipid profiles as a cost-effective and accessible marker to assess disease severity and prognosis.

Ethical Considerations

Compliance with ethical guidelines

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1399.7658).

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Authors contribution's

Conceptualization and study design: All authors; Material preparation, data collection, and data analysis: Amirhossein Khoshgoeian, Mina Khasayesi and Mah-

mood Moosazadeh; Supervision: Adele Bahar, Zahra Kashi, and Zahra Hosseini-khah; Writing the original draft: Shima Yahoo Torghabe; Review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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