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CLINICAL STUDY

The relationship of lipid profile with severity of disease and mortality in patients with COVID-19

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ABSTRACT
OBJECTIVES: Serum total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol may be associated with a poor prognosis in COVID-19 patients.
BACKGROUND: We think it may be essential to understand the role of lipids in the pathophysiology of COVID-19.
METHODS: One hundred eighty-nine patients admitted to the emergency department between 20th January and 20th February 2021 and later decided to be hospitalized to an inpatient clinic or intensive care unit were included in the study. The patients were determined to be hospitalized to the inpatient clinic or intensive care unit according to the Turkish Ministry of Health COVID-19 guidelines. A demographic information form was established for each patient.
RESULTS: The primary findings we have obtained were as follows: (1) CRP, PCT, D-Dimer levels were found to be high, while Albumin, TC, HDL-c, and LDL-c levels were found to be low in critical type patients; (2) CRP, PCT, and D-Dimer levels were higher in the patients who were intubated compared to those who were not intubated. Albumin and HDL levels were low; (3) DH was found to have a significantly negative relationship with TC and HDL-c, and (4) Sensitivity of LDL-c in predicting mortality was found as 69 % and specificity as 70 %. It was observed that patients with low LDL-c levels had higher mortality rates.
CONCLUSION: We think that hypocholesterolaemia may be an indicator of the impending danger. Our study examined COVID-19 in terms of lipid metabolism and offers a different perspective on the disease *(Tab. 4, Ref. 23)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, lipid, mortality.

Introduction

Coronavirus Disease 2019 (COVID-19) has spread to hundreds of countries worldwide, affecting millions of people. This infection may be asymptomatic or progress to acute respiratory failure, multiple organ failure, and septic shock (1, 2). Therefore, early identification of risk factors leading to severe cases of COVID-19 is essential.

Lipids have a critical place in the pathophysiology of viral infections and lung biology. For example, pulmonary surfactant consists of 90 % lipid and 10 % protein (3). Also, lipids take part in many cellular processes. One of these is to regulate the entry of viruses into the host cell. Lipids are essential components of the viral cell membrane. Therefore, it is indispensable in the viral replication of the virus (4).

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In general, lipoprotein levels change during viral infections. It was shown that especially critically ill patients with septic conditions have hypolipidemia (5, 6). Patients with dyslipidemia may be more or less tend to SARS-CoV-2 infection than the normal population. However, many studies have reported an increase in C-reactive protein (CRP) and pro-inflammatory cytokine levels and a decrease in lymphocyte, total protein, albumin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein (LDL-c) in COVID 19 patients (7, 8, 9). Studies have shown that one of the risk factors for severe COVID-19 cases is lipid disorders (10, 11).

Besides, in another study examining the relationship between duration of hospitalization and lipid disorders, it was shown that there was a negative correlation between TC and LDL-c levels at admission and duration of hospitalization (11). The duration of hospitalization for COVID-19 patients is also essential. Long-term hospitalizations come with higher costs and higher consumption of medical resources. The duration of hospitalization reflects the patient's recovery time. The prolongation of the hospitalization is, to some extent, related to the severity of the disease.

In light of this information, we aimed to examine the relationship between lipid disorders in COVID-19 patients and duration of hospitalization (DH), disease severity, and 28-day mortality.

Methods

Study design and settings

This prospective study was conducted in Erzurum Faculty of Medicine, Turkey. The local ethics committee approved the study (The name of the chairperson of the ethics committee was Prof. Dr. Ali KURT, the protocol number that was attributed by the ethics committee was 2021/02-41, and the date of approval by the ethics committee was 18 January 2021), which was carried out following the VMA Declaration of Helsinki, 1964, and later revisions. Informed consent was obtained from all participants or their relatives for the study. The inclusion criteria of the study were RT-PCR positivity and being older than 18 years of age. Pre-arrest cases were excluded from the study. A demographic information form was established for each patient. Demographic data were recorded by the physician responsible for the patient. One hundred eighty-nine patients admitted to the emergency department between 20th January and 20th February 2021 and later decided to be hospitalized at the inpatient clinic or intensive care unit were included in the study. The patients were determined to be hospitalized at the inpatient clinic or intensive care unit according to the Turkish Ministry of Health COVID-19 guidelines. Clinical cases were defined as follows in the guideline:

(a) Uncomplicated COVID-19 case: Patients with symptoms such as fever, muscle/joint pain, cough, sore throat, without respiratory distress (with a respiratory rate of < 30/minute, SpO2 level of > 93 % at room air) and with normal chest radiography and/or tomography findings.

(b) COVID-19 case with mild to moderate pneumonia: Patients with symptoms such as fever, muscle/joint pain, cough, sore throat, respiratory rate of < 30/minute, SpO2 level of > 90 % in room air, and mild to moderate pneumonia findings on chest radiography or tomography.

(c) COVID-19 case with severe pneumonia: Patients with symptoms such as fever, muscle/joint pain, cough, sore throat, tachypnea (respiratory rate of ≥ 30/minute), SpO2 level of ≤ 90 % in room air, and bilateral diffuse pneumonia findings on chest radiography or tomography.

(d) COVID-19 cases in need of intensive care: Having one or more of the following criteria in COVID-19 cases with severe pneumonia; Respiratory rate of ≥ 30/min, PaO2/FiO2 of < 300, Oxygen need increasing during follow-up, SpO2 of < 90 % or PaO2 of < 70 mmHg despite 5 L/min oxygen therapy, Hypotension (systolic blood pressure of < 90 mmHg and decrease from usual SBP more than 40 mmHg and mean arterial pressure < 65 mmHg), the presence of skin disorders such as cutis marmorata, acute kidney damage, acute disorders in liver function tests, confusion, acute bleeding diathesis, development of acute organ dysfunction, arrhythmia, those who needed mechanical ventilation.

Tab. 1. Demographic data and laboratory assessments in COVID-19 patients.

	COVID-19 severity			Severe		
	Severe (n=108)	Critical (n=80)	p	Surviving (n=29)	Non-Surviving (n=51)	p
Age1,years, M (SS)	65.18 (11.30)	70.16 (12.70)	**<0.001***	73.82 (13.48)	68.07 (11.87)	**0.04****
Sex3						
Female, n (%)	57 (53)	35 (44)	0,24	12 (34)	23 (66)	0.87
Male, n (%)	51 (47)	45 (56)		17 (38)	28 (62)	
IMV, n (%)	0 (0)	32 (100)	**<0.001***	15 (47)	17 (53)	0.15
HLO2, day, Median (IQR)	13 (9-19)	30 (18-44)	**<0.001***	22 (36)	34 (19)	0.28
Comorbid diseases						
DM, n (%)	25 (56)	20 (44)	0.86	7 (35)	13 (65)	1
HT, n (%)	56 (60)	37 (40)	0.46	13 (35)	24 (65)	1
PD, n (%)	25 (58)	18 (42)	1	7 (39)	11 (61)	0.78
HF, n (%)	3 (33)	6 (67)	0.17	3 (50)	3 (50)	0.66
CAD, n (%)	15 (40)	23 (60)	**<0.01***	9 (39)	14 (61)	0.80
DL, n (%)	5 (71)	2 (29)	0,71	0 (0)	2 (100)	0.50
Laboratory findings						
CRP2, Median(IQR)	40 (71)	90 (101)	**0.01***	62 (137)	90 (101)	0.66
PCT2, Median (IQR)	0.7 (0.6)	1 (1.40)	**<0.001***	1.20 (1.80)	1 (1.10)	0.86
D-Dimer2, Median (IQR)	757 (2279)	1178 (3935)	**0.04****	2792 (5139)	825 (3545)	0,42
BUN2, Median(IQR)	17 (12)	27 (25)	**<0.001***	32 (23)	24 (19)	**0.01****
Creatinine2, Median (IQR)	0,9 (0.4)	1 (0.6)	**0.02****	1 (0,65)	1 (0,60)	0.66
ALT2, Median (IQR)	29 (23)	34 (43)	0.23	49 (55)	31 (31)	0.06
AST2, Median (IQR)	33 (26)	46 (56)	**<0.001***	48 (86)	45 (50)	0.31
Albumin2, Median (IQR)	41 (7)	39 (5)	**<0.001***	37 (7)	39 (5)	**0.01****
TC2, Median (IQR)	163 (66)	147 (53)	**<0.001***	143 (58)	151 (51)	0.74
TG2, Median (IQR)	141 (70)	135 (60)	0.74	115 (107)	136 (53)	0.52
LDL-C2, Median (IQR)	107 (62)	94 (68)	**<0.001***	73 (50)	101 (72)	**0.02****
HDL-C2, Median (IQR)	40 (21)	34 (15)	**<0.001***	34 (11)	34 (17)	0.88

[1] independent sample t-test, [2]Mann Whitney U Test,[3] chi-square test, * p<0.01, ** p<0.05

Note: IMV, invasive mechanical ventilation; HLO, hospital length of stay; DM, diabetes mellitus; HT, hypertension; HF, heart failure; CAD, coronary artery disease; DL, dyslipidemia; CRP, C-reactive protein; PCT, procalcitoin; BUN, blood urea nitrogen; ALT, alanine amino transferase; AST, aspartate amino transferase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol.

Among the patient groups specified in this guideline, only COVID-19 cases with severe pneumonia requiring hospitalization and COVID-19 cases in need of intensive care were included in the study. COVID-19 cases with severe pneumonia were called severe type, and COVID-19 cases in need of intensive care were called critical type. A definitive outcome (discharged, continued treatment, or died) was determined for all patients before analyzing the data.

Demographic information form

The Demographic Information Form contains various information about the individuals who participated in the study. These forms included parameters such as participants' gender, age, place of hospitalization, comorbid diseases (DM, HT, Pulmonary Disease, Heart failure, Coronary Artery Disease, and dyslipidemia), blood test parameters (CRP, Procalcitonin, D-Dimer, Bun, Creatinine, ALT, AST, Albumin, Total Cholesterol, Triglyceride, HDL-C, and LDL-C), whether the patient was intubated, duration of hospitalization, and death within 28 days.

Statistical analysis

SPSS 22.0 package program was used for statistical analysis. Before analyzing the data, the data's conformity to the normal distribution in continuous variables was examined using Kolmogorov-Smirnov or Shapiro-Wilk tests, depending on the number of samples within the group. In descriptive statistics, normally distributed data for continuous variables were presented with mean and standard deviation in brackets, and non-normally distributed data were shown with the median and IQR in parentheses. Categorical variables were defined with frequency and percentage in brackets. Pearson's chi-square test was used to analyze categorical variables in interpretative analyses. Continuous variables showing normal distribution were analyzed with the independent sample t-test, and mean differences within groups were analyzed using the Mann–Whitney U test for non-normally distributed variables. The statistical significance level was considered below 0.05.

Results

One hundred eighty-eight patients, 96 male and 92 female, were included in the study. When the patients were examined in terms of age, there was a significant relationship between severe and critical groups. This relationship appeared as the high mean age in the critically ill group. Besides, there was a significant relationship between deceased and survivors and age in the critically ill group. The mean age of the patients who died was lower.

Regarding the duration of hospitalization, it was observed that critical type patients stayed longer in the hospital.

The relationship between the groups and comorbid diseases was examined. Coronary artery disease was observed to be more common in the critical patient group. Except for coronary artery disease, there was no significant difference between the groups in terms of comorbid diseases.

Severe and critical groups were examined in terms of laboratory findings. CRP, procalcitonin (PCT), D-Dimer, Blood urea nitrogen (BUN), creatinine, and aspartate aminotransferase (AST) levels were found to be high in critical type patients, while Albumin, TC, HDL-c, and LDL-c were found to be lower. These differences were statistically significant. Also, the subgroups of critically ill patients as deceased and survived showed a significant difference in albumin and LDL-c levels. According to this relationship, albumin and LDL-c levels were higher in the patient group who did not die (Tab. 1).

Thirty-two of all patients were intubated. All of the patients who were intubated were in the critical group. The CRP, PCT, D-Dimer, BUN, Creatinine, and AST levels of the intubated patients were higher than those who were not intubated. Albumin and HDL-c levels were low, and these differences were also statistically significant (Tab. 2).

The relationship between duration of hospitalization and age and laboratory findings was examined. It was determined that DH had a significantly negative relationship with TC and HDL-c. According to this relationship, patients with low TC and HDL-c levels stayed in the hospital for a more extended period of time (Tab. 3).

The performance of the lipid profile was evaluated in predicting 28-day mortality in all patient groups. In particular, we found that LDL-c can be a valuable marker in predicting mortality. The sensitivity of LDL-c in predicting mortality was found to be 69 % and specificity 70 %. As a result of the analysis, it was observed that patients with low LDL-c levels had higher mortality rates. The area under the curve (AUC) for 28-day mortality was 0.641 for TC and 0.704 for LDL-c (Tab. 4).

Tab. 2. The relationship between invasive mechanical ventilation and gender, comorbid diseases and laboratory findings.

	Invasive Mechanical Ventilation		
	(Yes) (n=32)	(No) (n=156)	p
Sex1			
Female, n(%)	12 (13)	80 (87)	0.17
Male, n(%)	20 (21)	76 (79)	
Comorbid diseases			
DM1, n(%)	8 (18)	37 (82)	0.82
HT1, n(%)	18 (19)	75 (81)	0.44
PD1, n(%)	8 (17)	35 (81)	0.81
HF1, n(%)	3 (33)	6 (67)	0.18
CAD, n(%)	10 (26)	28 (74)	0.09
DL, n(%)	0 (0)	7 (100)	0.61
Laboratory findings			
CRP2, Median(IQR)	94 (119)	42 (89)	**0.01****
PCT2, Median(IQR)	1.4 (1.8)	0.8 (0.7)	**<0.00***
D-Dimer2, Median(IQR)	3409 (5433)	732 (2379)	**<0.00***
BUN2, Median (IQR)	27 (26)	20 (14)	**<0.00***
Creatinine2, Median (IQR)	1.1 (0,68)	0.9 (0.4)	**<0.00***
ALT2, Median (IQR)	36 (56)	30 (25)	0.63
AST2, Median (IQR)	45 (56)	34 (28)	**0.01****
Albumin2, Median (IQR)	36 (8)	40 (7)	**<0.00***
TC2, Median (IQR)	136 (59)	136 (50)	**0.04****
TG2, Median (IQR)	143 (104)	135 (68)	0.31
LDL-C2, Median (IQR)	86 (58)	101 (54)	0.12
HDL-C2, Median (IQR)	30 (14)	38 (19)	**<0.00***

[1]chi-square test, [2]Mann Whitney U Test, * p<0.01, ** p<0.05. DM, diabetes mellitus; HT, hypertension; PD, pulmonary disease; HF, heart failure; CAD, coronary artery disease; DL, dyslipidemia; CRP, C-reactive protein; PCT, procalcitoin; BUN, blood urea nitrogen; ALT,alanine amino transferase; AST, aspartate amino transferase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol.

Tab. 3. Relationship between length of stay, age and laboratory findings.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. HLO	-													
2. Age	.02	-												
3. CRP	.14	.06	-											
4. PCT	.02	.02	**.14***	-										
5. D-Dimer	.01	.19*	**.22***	**.15***	-									
6. BUN	.08	.10	**.32***	**.31****	**.22****	-								
7. Creatinine	-.05	.03	.04	**.44****	.03	**18***	-							
8. ALT	.00	.04	.02	-.03	05	**17***	-02	-						
9. AST	.02	.06	.00	.00	04	**24****	-01	**.90****	-					
10. Albumin	-.14	**-.24****	**-.31***	-.13	**-22****	**-36****	-07	-.06	-.09	-				
11. TC	**-.15***	-.12	-.10	**-.16***	-00	**-24****	-01	-.09	-.09	**.30****	-			
12. TG	-.04	-.11	.02	-.02	02	**15***	-10	.10	**.19****	.02	**.34****	-		
13. LDL-C	-.11	-.12	-.06	**-.14***	-03	**-28****	01	-.07	-.09	**.29****	**.83****	.12	-	
14. HDL-C	**-18***	.14	**-.23***	-.11	02	**-14***	01	-11	-.10	.10	**.44****	-.07	**.18***	

** p<0.01 * p<0.05. HLO. hospital length of stay; PCT. procalcitoin; BUN. blood urea nitrogen; ALT .alanine amino transferase; AST. aspartate amino transferase; TC. total cholesterol; TG. triglyceride; LDL-C. low-density lipoprotein cholesterol; HDL-C. High-density lipoprotein cholesterol.

Tab. 4. Diagnostic value of lipid profile in predicting 28-day mortality.

Variable	AUC	p	Cutoff Point	95% CI	Sensitivity	Specificity
TC	0.641	**0.01***	≤150	0.54–0.74	60	54
TG	0.542	0.45	–	0.42–0.66	–	–
LDL-C	0.704	**<0.00***	≤81.50	0.61–0.80	69	70
HDL-C	0.576	0.17	–	0.47–0.68	–	–

TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – High –density lipoprotein cholesterol

Discussion

Although there is much new information about the severity and mortality of COVID-19, the relationship of lipid disorders in patients with the severity, mortality, and duration of hospitalization remains unclear. Therefore, this study aims to emphasize the relationship between the lipid profiles of COVID-19 patients and their clinical outcomes. The main findings we have obtained were as follows: (1) CRP, PCT, D-Dimer levels were found to be high, while Albumin, TC, HDL-c, and LDL-c levels were found to be low in critical type patients; (2) CRP, PCT, and D-Dimer levels were higher in the patients who were intubated compared to those who were not intubated. Albumin and HDL levels were low; (3) DH was found to have a significantly negative relationship with TC and HDL-c, and (4) Sensitivity of LDL-c in predicting mortality was found to be 69 % and specificity 70 %. It was observed that patients with low LDL-c levels had higher mortality rates.

Excessive cytokine activation in COVID-19 patients appears to contribute to multi-organ failure. As a result, severe complications such as sepsis and septic shock can occur in critical COVID-19 patients (12, 13).

There is also a negative correlation between HDL-c ($r = -0.45$; $p < 0.001$) levels, which is a common diagnostic tool in determining the severity of sepsis (SOFA) (14).

HDL-c has direct anti-inflammatory effects by neutralizing lipopolysaccharides (LPS). As a result of these effects, it plays a vital role in host defense against viral and bacterial infections (15).

Pro-inflammatory cytokines, such as increased CRP during infections, may also directly inhibit the activity of the apolipoprotein synthesis enzyme, leading to a decrease in the synthesis of HDL-c (16).

In our study, severe and critical groups were examined in terms of CRP levels. CRP levels of the patients in the critical group were significantly higher (Tab. 1). Moreover, a negative correlation was observed between CRP and HDL-c in the whole study population (Tab. 3). Serum HDL-c levels were lower in critically ill patients compared to mild to moderate cases. One of the reasons for this is that pro-inflammatory cytokines that increase during infections reduce the synthesis of HDL-c.

In a recent study, it was emphasized that lipid disorders might be a critical pathway in COVID-19 pathogenicity (17).

Another study found that severe COVID-19 patients had low serum TC, LDL-c, and HDL-c levels. Besides, in the same study, it was observed that the severe group of COVID-19 patients were malnourished (10).

Low TC and LDL-c levels are indicators of malnutrition since the basic substrate required for cholesterol synthesis is provided from nutrition (18).

For example, it was shown that early enteral feeding accelerates the recovery of TC levels (19).

For all these reasons, we think that hypocholesterolemia may reflect malnutrition in severe COVID-19 patients.

A study revealed a negative correlation between TC and LDL-c levels and DH in patients with COVID-19 pneumonia at the time of admission to the hospital. The same study also showed that low cholesterol levels cause long DH, which contributes negatively to recovery (11).

Our study determined that DH has a significantly negative relationship with TC and HDL-c. According to this relationship, patients with low TC and HDL-c levels stayed in the hospital for a longer time.

In our study, the performance of the lipid profile to predict 28-day mortality in COVID-19 patients was also evaluated. Our results revealed that LDL-c could be a valuable marker in predicting

mortality (Tab. 4). When the literature was investigated, in a study examining the relationship between lipid profile and in-hospital death, the performance of low HDL/apoA-1 levels in predicting mortality was found as HDL-c, sensitivity 73 %, specificity 81 % AUC 0.75 (0.61–0.88); apoA-1, sensitivity 67 %, specificity 83 % AUC 0.74 (0.61–0.88), respectively (10).

Our study and previous studies show that there is a significant relationship between lipid profile and mortality.

Consequently, we think that dyslipidemia seen in viral infections has several possible mechanisms. The first cause is that COVID-19 can cause acute liver damage. As a result, LDL-c synthesis may be reduced. However, there was no relationship between AST, ALT levels, and lipid profile in our study. Therefore, it cannot be said that the main reason for the decrease in LDL-c levels changes in liver function.

The second cause is that lipids are highly vulnerable to disintegration by free radicals, which are elevated in viral infections (20). However, to determine the validity of this possibility, it is necessary to look at the levels of oxidized LDL-c in the patient's blood.

The third cause is that exudate-type fluid is observed in the early phase of the lung pathology of COVID-19 (21).

It was shown that exudative fluid containing high cholesterol levels is caused by the vascular permeability associated with the infection (22). COVID-19 infection can alter vascular permeability, causing cholesterol molecules to leak into alveolar spaces to form exudate.

The fourth cause is that pro-inflammatory cytokines such as CRP, which are increased during infections, directly inhibit the activity of the apolipoprotein synthesis enzyme, causing a decrease in HDL-c synthesis (16).

Conclusion

MONDO international study showed that lipid levels are inversely correlated with infection-related deaths (23). Therefore, it should be kept in mind that hypocholesterolemia may be an indicator of impending danger. Besides, we think that more research to be performed on lipids is necessary to have sufficient information about the molecular mechanism underlying COVID-19. Thus, we have come a long way in the prevention and treatment of COVID-19.

In conclusion, our study examined COVID-19 in terms of lipid metabolism and offers a different perspective on the disease.

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