Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1059453

Anatolian Curr Med J 2022; 4(2); 162-166

The role of serum lipoprotein levels in predicting independent short-term mortality in COVID-19 patients

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Cite this article as: Aydemir S, Hoşgün D. The role of serum lipoprotein levels in predicting independent short-term mortality in COVID-19 patients. Anatolian Curr Med J 2022; 4(2); 162-166.

ABSTRACT

Background: Plasma lipoprotein levels typically change as a result of systemic inflammation in coronavirus disease (COVID-19). These changes have been reported to be related to the severity and prognosis of the disease. The aim of this study was to evaluate the relationship between serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and cholesterol levels andindependent short-term (28-day) mortality in COVID-19 patients with critical disease.

Material and Method: The retrospective study included patients that had a positive result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on real-time reverse transcriptase polymerase chain reaction (RT-PCR) and were followed up in ICU due to pneumonia and acute hypoxemic respiratory failure between March 2020 and January 2021.

Results: The 123 patients comprised 69 (56.1%) women and 54 (43.9%) men with a mean age of 65.41±13.93 years. Mean hospital and ICU stays were 16.07±9.84 and 8.54±8.24 days, respectively. Short-term (28-day) mortality occurred in 33 (26.8%) patients. Mean serum LDL, HDL, triglyceride, and cholesterol levels were 100.61±36.32, 41.57±10.74, 136.67±85.33, and 164.4±40.73 mg/dL, respectively. Short-term (28-day) mortality established a significant relationship with LDL and HDL levels, whereas no significant relationship was established with cholesterol and triglyceride levels (p=0.001, p=0.001, p=0.332, and p=0.222, respectively). The durations of hospital and ICU stay established a significant relationship with LDL levels (p=0.033 and p=0.002, respectively).

Conclusion: Based on our results, we suggest that monitoring HDL and LDL levels with serial measurements in patients with critical and severe COVID-19 pneumonia may be useful for predicting the prognosis.

Keywords: COVID-19, high-density lipoprotein, low-density lipoprotein,cholesterol, triglyceride, mortality

INTRODUCTION

Lipoproteins are classified into five groups based on their density, including chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). In recent studies, changes in lipid metabolism have been found in cases of infection (1). It has also been reported that HDL play a role in the transport of endotoxins, lipopolysaccharides, and lipotoxins from the liver and that HDL have anti-inflammatory, antioxidant, and immunomodulatory effects (2,3). By contrast, LDL has been shown to facilitate bacterial toxin clearance in sepsis and to play a role in the body's defence against bacterial and viral pathogens. Studies have found that both the HDL and LDL levels decrease in response to gram-negative and positive acute infection and inflammation (3). Additionally, a significant relationship was found between clinical worsening and HDL level in a study conducted on community-acquired pneumonia and a correlation between HDL and acute phase reactants was shown in some other studies. Besides, there are studies aimed at evaluating the prognostic value ofHDL in cases of infection (4).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was named Coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), is a viral pneumonia causing acute respiratory distress syndrome (ARDS) and is mostly diagnosed by nucleic acid amplification tests (NAAT) such as real-time reverse transcriptase polymerase chain reaction (RT-PCR). Approximately 81% of infected symptomatic patients develop mild infection while 14% of them develop severe disease and 5% of them develop critical disease (5). In addition to these conditions, cytokine storm caused by COVID-19, homeostaticchanges,

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Received: 18.01.2022 **Accepted:** 06.02.2022

severe vasculitis, changes in plasma lipoprotein levels caused by complications, and changes in endothelial levels have been reported in COVID-19 cases (5,6). Sorokin et al. (6) reported that the changes in HDL levels are due to their anti-inflammatory and antioxidant effects in COVID-19 patients. Wang et al. (7) evaluated 228 COVID-19 patients retrospectively and found that the severity of the disease correlated with the HDL level. Nevertheless, to our knowledge, the relationship between mortality and plasma lipoproteins and the cut-off values for the concentration of these lipoproteins in COVID-19 patients remain unclear. In this study, we aimed to evaluate the relationship between serum HDL, LDL, triglyceride, and cholesterol levels and independentshort-term (28-day) mortality in COVID-19 patients with critical disease followed up in intensive care unit (ICU).

MATERIAL AND METHOD

The retrospective study included patients that had a positive SARS-CoV-2 RT-PCR result and were followed up in ICU due to pneumonia and acute hypoxemic respiratory failure between March 2020 and January 2021. Laboratory results, discharge reports, and short-term (28-day) mortality rates were retrieved from the electronic database and intensive care observation forms after obtaining an approval from the scientific research and ethics committee of the Keçiören Training and Research hospital of Health General Directorate of Health Services (Date: 01/11/2021, Decision No: 2012-KAEK-15/2444). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Inclusion criteria were as follows: HDL, LDL, triglyceride, and cholesterol levels measured in the first hour of ICU admission, age over 18 years, a positive SARS-CoV-2 RT-PCR result, pneumonia and hypoxemic respiratory failure due to COVID-19 (hypoxia or pulmonary involvement in excess of 50% on imaging, tachypnea [respiratory rate>30/min], partial arterial oxygen pressure [PaO_2]/ fraction of inspiration O_2 (FiO_2) ≤300 mmHg) (8,9). Patients with an active infection except for COVID-19, active malignancy, connective tissue disease and vasculitis, use of drugs that could affect HDL, LDL, triglyceride, and cholesterol levels, patients aged under 18 years, and pregnant women were excluded from the study (**Figure 1**). HDL, LDL, triglyceride, and cholesterol concentrations were assessed using a Beckman AU5800 biochemical detector (Beckman Coulter, Inc., Brea, CA, USA) with the turbidimetric method. The reference range for HDL, LDL, triglyceride, and cholesterol concentrations was 40-60, 0-130, 50-200, and 50-200 mg/dL, respectively.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (Statistical Package for the Social Sciences). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as percentages (%). Pearson Chi-square and Fisher's exact test statistics were used compared categorical variables. Normal distribution of data was tested using Shapiro Wilk tests. In groups with normal distribution, binary comparisons were performed using Student's t-tests. In groups with nonnormal distribution, binary comparisons were performed using Mann-Whitney U test.A p value of <0.05 was considered significant. Multiple logistic regression analysis was used with all of the prespecified factors with a p <0.25 in the univariate analysis. Statistical significance in the multivariate analysis was accepted at p <0.05.

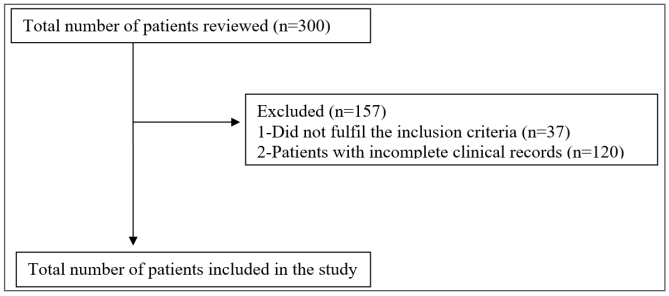

Figure 1. Flow-chart of the study

RESULTS

The 123 patients comprised 69 (56.1%) women and 54 (43.9%) men with a mean age of 65.61±14.05 years. Mean hospital and ICU stays were 16.03±9.81 and 9.28±12.48 days, respectively. Short-term (28-day) mortality occurred in 33 (26.8%) patients. All the patients had hypoxemic respiratory failure and 26 (21.13%) of them were receivinginvasive mechanical ventilation (IMV), 18 (14.64%) were receiving non-invasive mechanical ventilation (NIMV), 56 (45.53%) were receiving high-flow nasal oxygen (HFNO), and 72 (58.54%) were receiving supplementary oxygen support with a reservoir oxygen mask. **Table 1** presents the demographic, clinical characteristics and respiratory support therapies of the patients.The rate of hospital stay (days) ,age, SOFA and APACHE II scores were significantly higher in mortality patients compared to non-mortality patients (p<0.05). ICU stay (days) and gender were found to be insignificant factors affecting 28-day mortality (p=0.394 and p=0.496, respectively).

Mean serum LDL, HDL, triglyceride, and cholesterol levels were 99.298±38.08, 39.6±12.23, 136.59±89.54, and 164.69±48.72 mg/dL, respectively. Short-term (28-day) mortality established a significant relationship with LDL, HDL, cholesterol and triglyceride levels (p=0.001, p=0.008, p=0.016, and p=0.012, respectively) (**Table 2**).

Table 1. Demographic, clinical characteristics

Variables	Mortality Ort.± SD-Median (Min-Max)			P value
	Alln=123	No=90	Yes=33	
Age (year)	65.41±13.935	62.79±14.080	72.58±10.799	<0.001
Gender (Male /Female)	69/54	51/39	18/15	0.496
SOFA	5 [2-12]	4[2-12]	8 [2-12]	<0.001
APACHE II	18 [5-38]	15 [5-31]	24 [10-38]	<0.001
Comorbidity	88 (71.5%)	64 (71.1%)	24 (72.7%)	0.860
Cardiovascular diseases (n %)	27 (22.0%)	18 (20.0%)	9 (27.3%)	0.388
Hypertension (n %)	52 (42.3%)	38 (42.2%)	14 (42.4%)	0.984
Diabetes Mellitus (n %)	33 (26.8%)	27 (30.0%)	6 (18.2%)	0.190
Asthma (n %)	5 (4.1%)	4 (4.4%)	1 (3.0%)	0.725
Congestive heart failure (n %)	8 (6.5%)	5 (5.6%)	3 (9.1%)	0.481
Malignancy (n %)	7 (5.7%)	3 (3.3%)	4 (12.1%)	0.062
Neurological Disease (n %)	11 (8.9%)	8 (8.9%)	3 (9.1%)	0.972
IMV	26 (21.1%)	8 (8.9%)	18 (54.5%)	<0.001
NIMV	18 (14.6%)	9 (10%)	9 (27.3%)	0.016
HFNO	56 (45.5%)	41 (33.3%)	15 (45.5%)	0.969
Reservoir Oxygen Mask	72 (58.5%)	59 (65.5%)	13 (39.4%)	0.012
Hospital stay (days)	13 [2-46]	15[5-46]	11 [2-30]	0.009
ICU stay (days)	5 [1-46]	4[1-36]	2 [2-46]	0.394
LDL (mg/dL)	95 [16-210.4]	103.8 [16.8-210.4]	80 [16-141]	<0.001
HDL (mg/dL)	39.06±11.808	40.74±12.292	34.45±9.028	0.008
Cholesterol (mg/dL)	157 [56-341]	162 [56-341]	144 [56-246]	0.012
Triglyceride (mg/dL)	114 [35-585]	107.5 [35-517]	124 [81-585]	0.016

APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, HT: Hypertension, CKD: Chronic kidney disease, SD: Standard deviation, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, HFNO: High-flow nasal oxygen

Table 2. Logistic regression analysis

	Univariate analyze					Multivariate analyze (backward wald 5. step)				
	Wald	p	OR	95% CI for EXP(B)		Wald	p	OR	95% CI for EXP(B)	
				Lower	Upper				Lower	Upper
Age	10.145	0.001	.061	1.023	1.100	4.049	0.044	0.892	0.799	0.997
APACHE II	18.216	<0.001	1.167	1.087	1.253	9.253	0.002	1.927	1.263	2.940
SOFA	22.101	<0.001	1.544	1.288	1.851					
IMV	24.527	<0.001	12.450	4.589	33.775					
NIMV	5.468	0.019	3.417	1.220	9.569					
Reservoir Oxygen Mask	6.207	0.013	0.353	0.155	0.801					
LOS hospital (days)	7.829	0.005	0.922	0.871	0.976	10.556	0.001	0.714	0.583	0.875
LDL (mg/dL)	11.846	0.001	0.976	0.963	0.990	8.443	0.004	0.923	0.875	0.974
HDL (mg/dL)	2.356	0.125	0.973	0.939	1.008					
Cholesterol (mg/dL)	6.093	0.014	0.987	0.978	0.997					
Triglyceride (mg/dL)	2.913	0.088	1.004	0.999	1.009	4.716	0.030	1.015	1.001	1.028

OR: odds ratio. Multinominal logistic regression (Hosmer ve Lemeshow p>0.05), APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation

DISCUSSION

The results indicated that serum HDL and LDL levels were significantly associated with 28-day mortality in COVID-19 patients followed up in ICU due to pneumonia, whereas no significant relationship was found between 28-day mortality and triglyceride and cholesterol levels. Moreover, although a significant relationship was found between the durations of hospital and ICU stay and LDL levels, no significant relationship was established with cholesterol, triglyceride, and HDL levels.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a high infection and has different manifestations in every infected individual. Although it typically leads to a mild-to-moderate infection in most cases and recovers within seven days, it can result in severe pneumonia and ARDS in some cases (8). Althoughthe hospital and ICU admission rates differ across studies, approximately 20% of the patients are hospitalized and 25% of them are admitted to ICU. Global mortality rates rangebetween 4.8-11% depending on the elderly population and developing countries. However,

the mortality rate in ICU patients is over 60% (8,9).

In our study, we evaluated COVID-19 pneumonia cases with severe and critical diseasewhorequired ICU care due to hypoxemic respiratory failure. Ourindependent short-term (28-day) mortality rate was found to be 26.8%,whichwas lowerthan those reported in the literature (8,9). This lower rate could be attributed to the longerdurations of hospital and ICU stay in our patients and to our IMV rate (21.13%).In our study age, hospital stay(days) , APACHE II and SOFA scores were found to be significant predictors of independent short-term mortality. These findings of our study were consistent with those reported in the literature (5,7,8). ICU stay (days) and gender were found to be insignifcant predictors of mortality. Therefor our results were thought to be incompatible with the literature (5,7,8).

Lipids and metabolites are major molecules in plasma and their concentrationsmay changein case of infection in the presence of pathophysiological and critical disease (9). Lipids have been shown to play a pathophysiological role in viral infections, fusion of virus membrane with host cell membrane, viral replication, and viral endocytosis and exocytosis. Therefore, lipoproteins are considered to have vital functions in the life cycle of viruses (10,11). HDL have been shown to have anti-inflammatory, antioxidant, immunomodulatory, and antithrombotic effects in virus-related infections (2,4,6). The natural and adaptive immune response against the SARS-CoV-2 plays a role.A cytokine storm termed 'secondary hemophagocytic, lymphohistiocytosis' occurs as a result of exaggerated production of proinflammatory cytokines andthe induction of the activation of proinflammatory macrophages and granulocytes (9). In COVID-19 patients, this cytokine storm leads to immune-mediated inflammatory dyslipoproteinemia, resulting in low HDL and LDL levels and increased triglyceride levels (6). Sorokin et al. (6) showed that the HDL levels decreased in COVID-19 patients due to the anti-inflammatory and antioxidant effectsof HDL and as a result of pulmonary inflammation. The authors also showed that the severity of the disease, including hypoxic pneumonia, reached its peak on the third day of disease onset, the changes in lipid levels were parallel with increases in C-reactive protein (CRP), and these changes were accompanied by lymphocytopeniain COVID-19 patients (6). Cao et al. (11) reported that LDL and total cholesterol levels decreased in COVID-19 patients.In our study, the relationship between plasma lipoproteins and short-term (28-day) mortality was evaluated in COVID-19 pneumonia patients followed up in ICU. Due to the retrospective nature of our study, only the HDL, LDL, cholesterol, and triglyceride levels measured during ICU admission were evaluated and thus, as in other studies, serial measurements could not be performed. Moreover, the effect of disease severity on the changes in serum lipid levels could not be evaluated.

To our knowledge, there are few studies on the relationship between serum lipoproteins and disease severity and mortality in COVID-19. In a prospective study, Tanakeet al. (12) evaluated 48 COVID-19 patients followed up in ICU and reported that the HDL and LDL levels were relatively lower in severe COVID-19 patients.In a retrospective study, Qin et al. (13) evaluated 248 COVID-19 patients and showed that the triglyceride and LDL levels were negatively correlated with the duration of hospitalization. In our study, in a similar way to Tanaka et al. (12), a significant relationship was found between the HDL and LDL levels and 28-day mortality. However, no significant relationship was found between the triglyceride and cholesterol levels and short-term mortality, which could be attributed to the effect of changes in liver functions caused by hemodilution, capillary leakage syndrome, and the medical treatments we used in the treatment of COVID-19 on the triglyceride and cholesterol biosynthesis and their levels (10, 11, and 12). In our study, only LDL was found to be significantlyassociated with the durations of hospital and ICU stay. However, a clear evaluation on this issue could not be made due to the limited number of data and studies on the relationship between plasma lipoproteins andthe durations of hospital and ICU stay in COVID-19 patients. Therefore, we suggest that further multi-center, prospective, randomized controlled studies with largerpatient series are needed.

Our study was limited since it was designed as a retrospective single-center study. Moreover, serum HDL, LDL, cholesterol, and triglyceride levels were not measured prior to hospital admission and no serial measurements were performed, and no comparison could be performed between the measurements performed on admission and inflammatory markers.

CONCLUSION

Based on our results, we has been considered that monitoring HDL and LDL levels with serial measurements in patients with critical and severe COVID-19 pneumonia may be useful for predicting the prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval from the scientific research and ethics committee of the Keçiören Training and Research hospital of Health General Directorate of Health Services (Date: 01/11/2021, Decision No: 2012-KAEK-15/2444).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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