Relationship Between Blood Lipid Levels and Mortality in Hospitalized COVID-19 Patients

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Abstract

People with comorbid conditions are at increased risk of developing severe/fatal coronavirus disease 2019 (COVID-19). We aimed to investigate the relationship between lipid levels and mortality in patients hospitalized for COVID-19 infection. In this retrospective study, we collected the details of 5274 COVID-19 patients who were diagnosed using the polymerase chain reaction and/or computed tomography and were hospitalized between March and November 2020. Patients (n = 4118) whose blood lipid levels were checked within the first 24 h after hospitalization were included in the study. Multivariable cox proportional hazards regression was used to assess the relationship between lipid variables such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) and death. There was a statistically significant association between LDL-C, HDL-C, and TG levels and the risk of death (P =.002, <.001, and .035, respectively). Low and high LDL-C, low HDL-C, and high TG levels were negatively associated with COVID-19-related mortality. Blood lipid levels may be useful predictors of mortality in COVID-19 patients.

Keywords

lipid levels, COVID-19, mortality, SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic persists worldwide. COVID-19 is mainly caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which involves the respiratory tract and causes acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS).[1] Prevalence of death 6 to 41 days after onset of symptoms is approximately 2.3%.[2,3] Epidemiological data show that although most cases have mild symptoms, patients with severe infections may rapidly progress to acute respiratory disease, multi-organ failure, and sepsis, thus resulting in increased mortality. People with comorbid conditions such as advanced age, cardiovascular diseases, cancer, acute kidney disease, and diabetes mellitus are at increased risk of developing severe and fatal COVID-19.[4,5] Given the limited treatment options, identification of risk factors associated with severe COVID-19 it is important to improve prognosis.[6,7]

It has been reported that metabolic parameters including lipids and lipoproteins vary during bacterial, viral and parasitic infections.[8] In a recent study, it was shown that altered lipid levels are associated with the severity of the disease in patients with COVID-19.[9] Another study reported that low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) are inversely correlated with severity of COVID-19, and there is a correlation between high triglyceride (TG) levels and disease severity.[10,11] In this context, blood lipid levels may predict morbidity and mortality in COVID-19 infection. Therefore, this study aimed to investigate the relationship between lipid levels and mortality in patients hospitalized for COVID-19 infection.

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Materials and Methods

Study Design and Patient Selection

This study is a retrospective study conducted in Erzurum Regional Training and Research Hospital. Data of 5274 patients who were diagnosed with polymerase chain reaction (PCR) and/or computed tomography (CT) and hospitalized between March and November 2020 were scanned. Patients (n = 4118) whose blood lipid levels were checked within the first 24 h after hospitalization were included in the study. This study was performed in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. Patient medical history, drug use history, clinical and demographic characteristics, and hematological and biochemical parameters were recorded.

Definitions

Hypertension (HT) was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or use of any antihypertensive drug.[12] Diabetes mellitus (DM) is defined according to current American Diabetes Association guidelines.[13] Coronary artery disease (CAD) was defined based on invasive or non-invasive imaging.

PCR test: Combined swab samples were obtained from all patients who presented to the emergency department or infection polyclinics in accordance with the specified procedures.[14]

CT: In the COVID-19 guide published by the Ministry of Health, the findings are classified as typical, uncertain, atypical, and negative.[15]

Analysis of Blood Samples

Blood samples were taken from the antecubital vein after a 12-hour fasting by creating a slight venous stasis in the upper arm. Samples were placed in tubes with potassium ethylene diamine tetra-acetic acid (EDTA) for complete blood count. Hemoglobin, hematocrit, platelet, and white blood cell counts were determined by electrical impedance. Biochemical parameters were measured by standard laboratory methods (Beckman Coulter LH 780, Miami, FL, USA). Using the Beckman Coulter AU5800 analytical platform, TC, TG, and HDL-C were measured. LDL-C values were calculated using the Friedewald equation.

Statistics

Median and interquantile range were used for numerical variables, and percent and n were used for categorical values.

Outcome

The primary outcome was time to all-cause death. We used a retrospective cohort study design and followed up patients until death or censoring on 1 Jan 2021.

Main Exposures and Adjustment Variables

Candidate predictors for the primary outcome should be clinically and biologically plausible, and their relationship with all-cause death should be demonstrated in previous studies. We considered all candidate predictors that we included in the model under these principles. We determined the variables, included in the model, according to these principles. Main exposures were LDL-C, HDL-C, and TG. Age, sex, previous statin use, DM, HT, chronic heart failure (CHF), chronic kidney disease (CKD), albumin, neutrophil to lymphocyte ratio (NLR), log D-dimer, and C-reactive protein (CRP) were determined as adjustment variables.

Statistical Modeling

We used the Cox proportional hazards model to examine the relationship between all-cause death and lipid variables (LDL-C, HDL-C, and TG). Continuous variables such as LDL-C, HDL-C, TG, age, NLR, D-dimer, albumin, and CRP are included in the model as flexible smooth parameters using restricted cubic spline (RCS). The RCS transformation allows to model the non-linear relationship between outcome and continuous predictor, and *P* value for nonlinearity is presented to summarize the change between first and third quartile of predictor. We also include the interaction term for LDL-C previous statin use. The association between LDL-C, HDL-C, TG, and all-cause death was quantified by the adjusted hazard ratio with a 95% confidence interval. We retained all candidate predictors in the model and did not remove any of these predictors based on statistical significance. The relative importance of each predictor in the models was estimated with partial χ^2 value for each predictor divided by the model's total χ^2, which estimates the independent contribution of the predictor to the variance of the outcome. We also showed partial effect plot for visualizing the relation of outcome and predictor in an adjusted model. The discrimination of the model was evaluated by calculating the area under curve (AUC).

All statistical analysis was carried out using R-software v. 3.5.1 (R statistical software, Institute for statistics and mathematics, Vienna, Austria). A 2-sided $P<.05$ was considered statistically significant.

Results

A total of 4118 patients hospitalized for COVID-19 between March 2020 and November 2020 were included in the study (median age: 65 years, interquartile range (IQR): 53–74, 50% were female). Median hospital stay was 8 days (IQR, 5–13 day). During hospitalization, the need for mechanical ventilation developed in 404 patients (9.8%), and 690 patients (16.7%) were followed up in the intensive care unit. Patients were followed up after discharge (up to Jan 2021). Median follow-up was 110 days (73–141 days). Overall, 532 patients (12.9%) died during the in-hospital follow-up period, 85 patients (2.1%) died after discharge (total: 617 patients). In addition, 465 (11.3%) patients were hospitalized again after discharge, while 45 (1.1%) patients were

hospitalized due to re-infection. Tables 1–3 show a summary of baseline characteristics according to LDL-C, HDL-C, and TG quartiles (Table 4).

Multivariable cox proportional hazards regression was used to show the relationship between lipid variables (LDL-C, HDL-C, and TG) and death. In addition to these lipid

Table 1. Summary of Baseline Characteristics by LDL-C Quartiles.

	First	Second	Third	Fourth	p
N	1035	1031	1026	1026	
Total hospital length of stay, days (median [IQR])	8.0 [5.0; 13.0]	8.0 [5.0; 12.0]	8.0 [5.0; 13.0]	8.0 [5.0; 12.0]	.602
Re-hospitalization, n (%)	106 (10.2)	110 (10.7)	112 (10.9)	137 (13.4)	.11
Stay in intensive care, n (%)	259 (25.0)	144 (14.0)	156 (15.2)	131 (12.8)	<.001
Mechanical ventilation, n (%)	178 (17.2)	88 (8.5)	75 (7.3)	63 (6.1)	<.001
30-day mortality, n (%)	215 (20.8)	116 (11.3)	81 (7.9)	78 (7.6)	<.001
Death, n (%)	262 (25.3)	144 (14.0)	112 (10.9)	99 (9.6)	<.001
Out-of-hospital death, n (%)	39 (4.8)	19 (2.1)	17 (1.8)	10 (1.1)	<.001
In-hospital death, n (%)	223 (21.5)	125 (12.1)	95 (9.3)	89 (8.7)	<.001
Reinfection, n (%)	14 (1.4)	10 (1.0)	9 (.9)	8 (.8)	.576
Acetylsalicylic acid use, n (%)	267 (25.8)	205 (20.0)	227 (22.2)	229 (22.4)	.017
P2Y12 inhibitor use, n (%)	94 (9.1)	61 (5.9)	62 (6.0)	54 (5.3)	.002
Statin use, n (%)	162 (15.7)	117 (11.3)	93 (9.1)	98 (9.6)	<.001
Beta-blocker use, n (%)	256 (24.7)	225 (21.8)	201 (19.6)	193 (18.8)	.005
Insulin use, n (%)	112 (10.9)	88 (8.6)	92 (9.0)	95 (9.3)	.312
Oral antidiabetic use, n (%)	184 (17.8)	171 (16.7)	189 (18.5)	197 (19.3)	.467
Ace/Arb use, n (%)	369 (35.7)	365 (35.4)	359 (35.0)	380 (37.0)	.788
Male, n (%)	552 (53.5)	533 (51.7)	506 (49.3)	466 (45.4)	.002
Age, years (median [IQR])	68 [54; 77]	65 [54; 74]	64 [51; 73]	62 [52; 71]	<.001
DM, n (%)	300 (29.0)	268 (26.0)	293 (28.6)	288 (28.1)	.44
HT, n (%)	549 (53.0)	517 (50.1)	514 (50.1)	517 (50.4)	.474
CAD, n (%)	273 (26.4)	219 (21.2)	201 (19.6)	224 (21.8)	.002
CHF, n (%)	83 (8.0)	55 (5.3)	36 (3.5)	42 (4.1)	<.001
COPD, n (%)	178 (17.2)	142 (13.8)	126 (12.3)	114 (11.1)	<.001
CVD, n (%)	27 (2.6)	19 (1.8)	25 (2.4)	17 (1.7)	.377
CKD, n (%)	41 (4.0)	33 (3.2)	22 (2.1)	18 (1.8)	.009
Asthma, n (%)	38 (3.7)	49 (4.8)	35 (3.4)	46 (4.5)	.357
LDH U/L (median [IQR])	327 [249; 445]	306 [242; 386]	295 [237; 378]	284 [230; 358]	<.001
TG mg/dL (median [IQR])	110 [82; 150]	119 [92; 165]	136 [99; 185]	157 [116; 214]	<.001
HDL-C mg/dL (median [IQR])	30 [24; 38]	32 [27; 40]	34 [28; 41]	36 [30; 44]	<.001
LDL-C mg/dL (median [IQR])	54 [44; 61]	77 [72; 82]	96 [92; 102]	126 [117; 142]	<.001
Albumin g/dL (median [IQR])	3.5 [3.1; 3.9]	3.7 [3.3; 4.0]	3.8 [3.4; 4.0]	3.8 [3.5; 4.2]	<.001
Glucose mg/dL (median [IQR])	139 [110; 184]	132 [106; 176]	130 [106; 182]	136 [109; 189]	.054
Creatinine mg/dL (median [IQR])	.94 [.77; 1.27]	.89 [.74; 1.14]	.87 [.73; 1.09]	.86 [.73; 1.06]	<.001
CRP mg/L (median [IQR])	47.4 [18.5; 94.3]	39.1 [16.7; 78.9]	36.7 [11.9; 73.5]	30.1 [11.3; 63.9]	<.001
log D-dimer mg/L (median [IQR])	5.64 [4.52; 6.71]	5.36 [4.44; 6.41]	5.34 [4.41; 6.42]	5.49 [4.43; 6.49]	.006
Ferritin μg/L (median [IQR])	299 [124; 645]	276 [120; 565]	263 [126; 566]	273 [116; 549]	.14
Procalcitonin μg/L (median [IQR])	.24 [.05; .96]	.14 [.03; .59]	.10 [.02; .48]	.08 [.02; .36]	<.001
Hb g/dL (median [IQR])	12.9 [11.4; 14.2]	13.3 [12.0; 14.3]	13.4 [12.3; 14.4]	13.5 [12.4; 14.6]	<.001
LYM 109/L (median [IQR])	1.05 [.69; 1.49]	1.15 [.82; 1.57]	1.29 [.90; 1.73]	1.33 [.96; 1.78]	<.001
NLR (median [IQR])	5.30 [2.73; 10.28]	4.26 [2.45; 7.63]	4.15 [2.24; 7.21]	3.92 [2.35; 6.73]	<.001
NEU 109/L (median [IQR])	5.63 [3.69; 8.52]	5.07 [3.56; 7.37]	5.10 [3.58; 7.33]	5.32 [3.67; 7.27]	.001
WBC 109/L (median [IQR])	7.49 [5.44; 10.44]	7.04 [5.38; 9.33]	7.11 [5.58; 9.35]	7.32 [5.80; 9.39]	.005
PLT 109/L (median [IQR])	212 [167; 270]	230 [182; 287]	238 [191; 291]	251 [203; 305]	<.001
Fibrinogen mg/dL (median [IQR])	451 [363; 535]	448 [369; 538]	441 [362; 538]	454 [367; 544]	.677

Ace/Arb: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, *DM*: diabetes mellitus, *HT*: hypertension, *CAD*: coronary artery disease, *CHF*: chronic heart failure, *COPD*: chronic obstructive pulmonary disease, *CVD*: cerebrovascular disease, *CKD*: chronic kidney disease, *LDH*: lactate dehydrogenase, *TG*: triglyceride, *HDL-C*: high density lipoprotein cholesterol, *LDL-C*: low density lipoprotein cholesterol, *CRP*: C-reactive protein, *Hb*: hemoglobin, *LYM*: lymphocytes, *NLR*: neutrophil to lymphocyte ratio, *NEU*: neutrophils, *WBC*: white blood cells, *PLT*: platelets, *IQR*: interquartile range.

variables, age, sex, previous statin use, DM, HT, CHF, CKD, albumin, NLR, log D-dimer, and CRP were added to the model as adjustment variables. In the analysis using RCS transformation, the relationship of LDL-C and HDL-C with survival time was clearly non-linear (J-shaped) (p for non-linearity .0006 and .0007, respectively), but there was no significant nonlinearity for TG (p for nonlinearity .145). There was a statistically significant association between LDL-C, HDL-C, and TG levels and the risk of death ($P = .002$, <.001, and .035, respectively). Both low (∼<85 mg/dl) and high (∼>150 mg/dl) LDL-C levels were associated with a greater risk of death, whereas only low HDL-C levels (∼<35 mg/dl) were found to be associated with the risk of death. Moreover, TG levels <125 mg/dl were associated with a lower risk of death. The R^2 value of the model was .353 and the AUC value was .897 (Figures 1A–C). As can be seen in Figure 2, 5.9% of the explainable variation in the risk of death could be explained by HDL-C, 3.7% by LDL-C, and 2.1% by TG. Figure 3 shows time-dependent AUC values. Accordingly, while the model discrimination was at an acceptable level (>.7) especially in the first 2 months, it was weak for the last 4 months of follow-up.

Discussion

The present study reports the relationship between HDL-C, LDL-C, and TG levels and mortality caused by COVID-19 in a large population; LDL-C, HDL-C, and TG levels were associated with the risk of mortality. There may be several reasons why blood lipid levels are affected during COVID-19 infection. Evidence supports the hypothesis that both inflammatory conditions and infectious diseases are associated with changes in lipid metabolism.[8] Studies have shown some metabolic changes accompanied by high TG and low HDL-C levels in infection and sepsis.[16,17] In addition, lipid metabolism dysregulation has been demonstrated in patients with sepsis secondary to both community and hospital-acquired pneumonia.[18,19] Also, it has been reported that low serum HDL-C levels at admission is a risk factor for the development of severe sepsis.[20]

Inflammatory cytokines released during viral infection can influence lipid metabolism. Cytokines such as interleukin (IL)-6 and IL-1β can alter liver function and reduce cholesterol transport.[21] Increased free radicals in virus-infected host cells can cause lower LDL-C, HDL-C, and TC levels.[22] Furthermore, vascular permeability may be altered in critically ill patients with COVID-19 so that a number of cholesterol particles infiltrating the extravascular space may form exudates in tissues such as alveolar spaces. These exudative fluids contain high concentrations of protein and cholesterol.[23] Exudative fluids have been demonstrated even in the early phase of lung pathology caused by COVID-19 infection.[24] In addition, it is known that lipid metabolism is required for the replication of various viruses.[25,26]

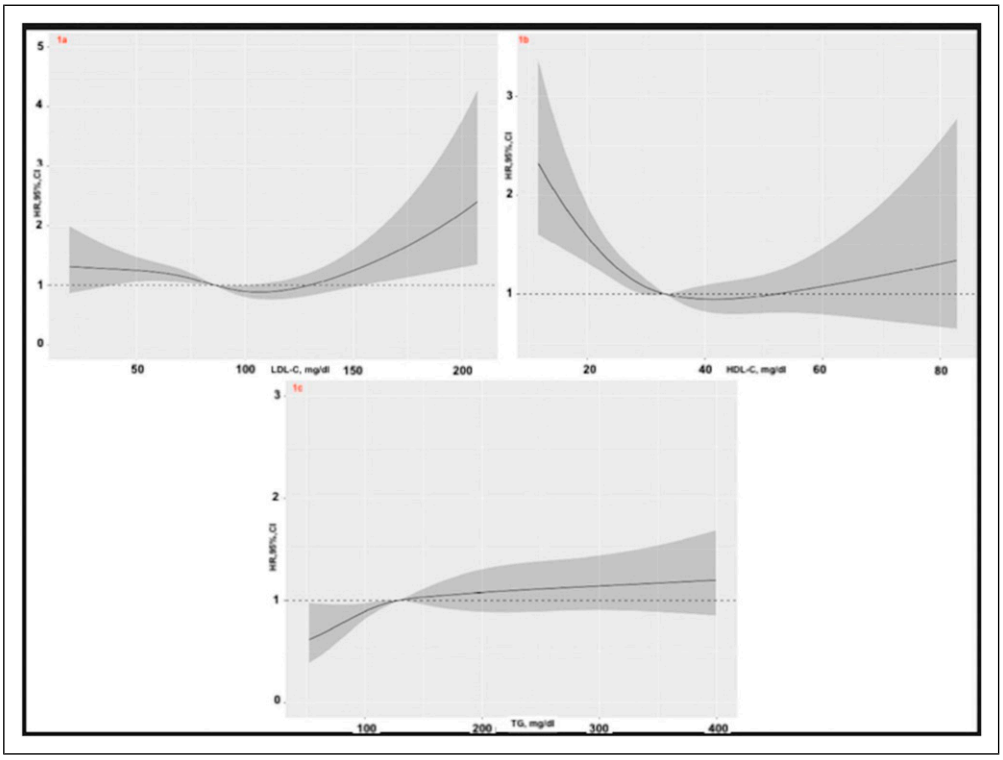

Figure 1. Partial effect plot of LDL-C, HDL-C, and TG. (LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio).

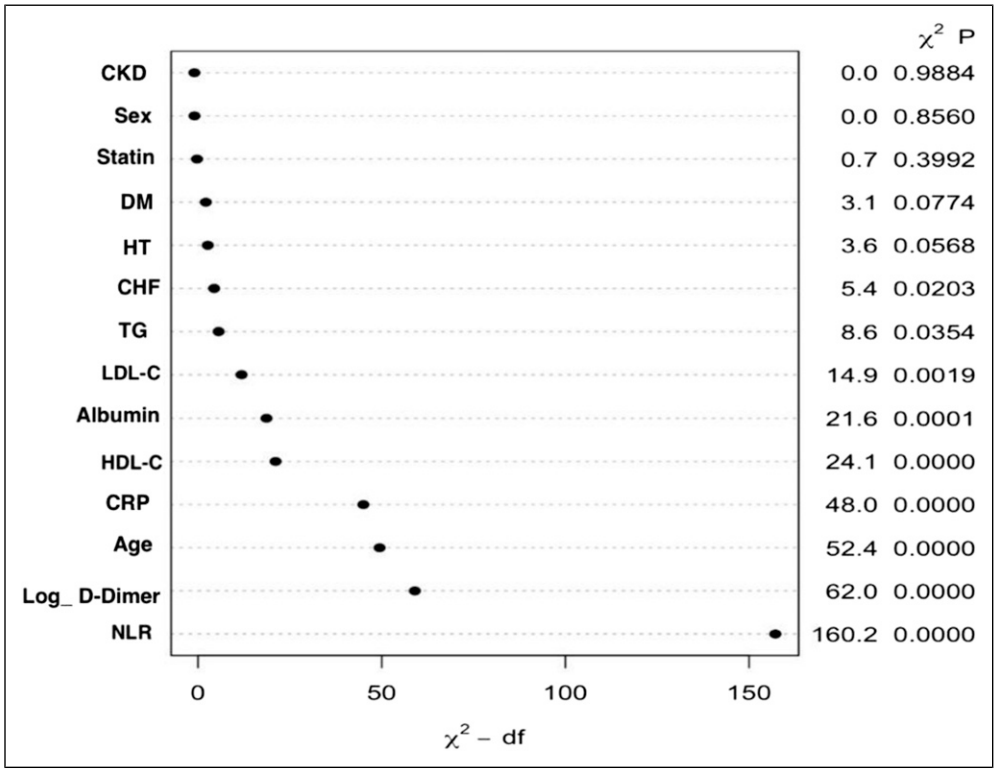

Figure 2. Importance of predictors included in the multivariable Cox proportional hazard model. (CKD: chronic kidney disease, DM: diabetes mellitus, HT: hypertension, CHF: chronic heart failure, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein, NLR: neutrophil to lymphocyte ratio, χ^2 chi square, df: degrees of freedom, *P* value).

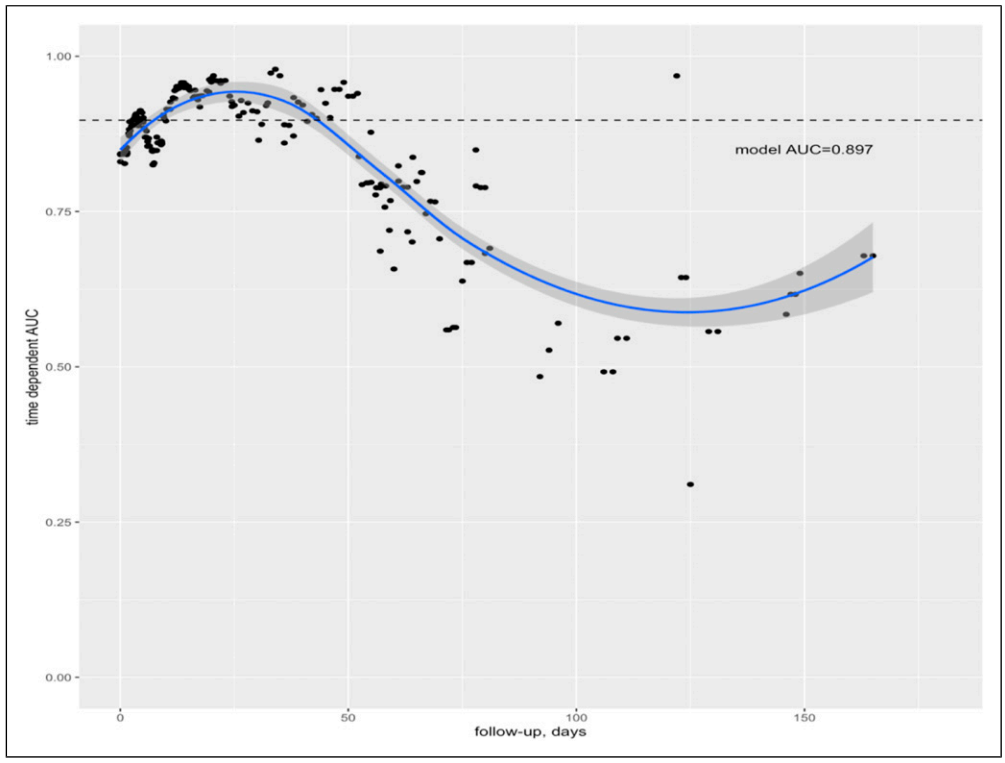

Figure 3. Time-dependent AUC of multivariable Cox proportional hazard model. While the model discrimination was at an acceptable level (>.7) especially in the first 2 months, it was weak for the last 4 months of follow-up. (*AUC*: area under curve).

Table 2. Summary of Baseline Characteristics by HDL-C Quartiles.

	First	Second	Third	Fourth	p
N	1030	1029	1029	1030	
Total hospital length of stay, days (median [IQR])	7.0 [5.0; 11.0]	8.0 [5.0; 13.0]	8.0 [5.0; 13.0]	9.0 [6.0; 14.0]	<.001
Re-hospitalization, n (%)	117 (11.4)	127 (12.3)	114 (11.1)	107 (10.4)	.567
Stay in intensive care, n (%)	110 (10.7)	165 (16.0)	194 (18.9)	221 (21.5)	<.001
Mechanical ventilation, n (%)	43 (4.2)	96 (9.3)	113 (11.0)	152 (14.8)	<.001
30-day mortality, n (%)	82 (8.0)	130 (12.6)	142 (13.8)	136 (13.2)	<.001
Death, n (%)	110 (10.7)	154 (15.0)	168 (16.3)	185 (18.0)	<.001
Out-of-hospital death, n (%)	28 (3.0)	23 (2.6)	20 (2.3)	14 (1.6)	.307
In-hospital death, n (%)	82 (8.0)	131 (12.7)	148 (14.4)	171 (16.6)	<.001
Reinfection, n (%)	11 (1.1)	12 (1.2)	5 (.5)	13 (1.3)	.282
Acetylsalicylic acid use, n (%)	210 (20.4)	242 (23.6)	245 (23.8)	231 (22.6)	.227
P2Y12 inhibitor use, n (%)	67 (6.5)	72 (7.0)	68 (6.6)	64 (6.2)	.913
Statin use, n (%)	86 (8.3)	116 (11.3)	142 (13.8)	126 (12.2)	.001
Beta-blocker use, n (%)	215 (20.9)	218 (21.2)	227 (22.1)	215 (20.9)	.901
Insulin use, n (%)	59 (5.7)	85 (8.3)	101 (9.9)	142 (13.9)	<.001
Oral antidiabetic use, n (%)	123 (12.0)	165 (16.1)	212 (20.7)	241 (23.5)	<.001
Ace/Arb use, n (%)	334 (32.4)	357 (34.7)	384 (37.3)	398 (38.6)	.016
Male, n (%)	511 (49.7)	539 (52.4)	518 (50.3)	489 (47.6)	.175
Age, years (median [IQR])	66 [52; 76]	66 [55; 75]	65 [54; 74]	61 [50; 70]	<.001
DM, n (%)	189 (18.3)	268 (26.0)	312 (30.3)	380 (36.9)	<.001
HT, n (%)	503 (48.8)	524 (50.9)	545 (53.0)	525 (51.0)	.319
CAD, n (%)	207 (20.1)	239 (23.2)	250 (24.3)	221 (21.5)	.103
CHF, n (%)	58 (5.6)	54 (5.2)	64 (6.2)	40 (3.9)	.106
COPD, n (%)	179 (17.4)	154 (15.0)	128 (12.4)	99 (9.6)	<.001
CVD, n (%)	25 (2.4)	23 (2.2)	20 (1.9)	20 (1.9)	.841
CKD, n (%)	23 (2.2)	24 (2.3)	33 (3.2)	34 (3.3)	.303
Asthma, n (%)	37 (3.6)	45 (4.4)	33 (3.2)	53 (5.1)	.119
LDH U/L (median [IQR])	283 [224; 360]	302 [245; 389]	311 [251; 401]	306 [239; 418]	<.001
TG mg/dL (median [IQR])	79 [67; 87]	111 [103; 120]	151 [139; 164]	229 [201; 283]	<.001
HDL-C mg/dL (median [IQR])	37 [30; 45]	33 [28; 40]	32 [27; 40]	31 [25; 38]	<.001
LDL-C mg/dL (median [IQR])	76 [59; 95]	83 [65; 102]	91 [71; 113]	98 [78; 122]	<.001
Albumin g/dL (median [IQR])	3.7 [3.4; 4.0]	3.7 [3.3; 4.0]	3.7 [3.3; 4.0]	3.8 [3.3; 4.1]	.034
Glucose mg/dL (median [IQR])	119 [100; 150]	129 [106; 173]	139 [112; 188]	159 [119; 229]	<.001
Creatinine mg/dL (median [IQR])	.83 [.70; 1.06]	.89 [.74; 1.11]	.92 [.76; 1.19]	.92 [.76; 1.21]	<.001
CRP mg/L (median [IQR])	32.7 [11.4; 66.5]	37.9 [14.9; 74.7]	41.7 [15.7; 83.2]	41.9 [13.5; 84.6]	<.001
log D-dimer mg/L (median [IQR])	5.36 [4.40; 6.40]	5.39 [4.47; 6.49]	5.56 [4.47; 6.58]	5.49 [4.44; 6.62]	.115
Ferritin μg/L (median [IQR])	181 [69; 380]	268 [132; 560]	300 [152; 651]	376 [155; 742]	<.001
Procalcitonin μg/L (median [IQR])	.09 [.03; .48]	.11 [.03; .48]	.15 [.03; .61]	.15 [.03; .75]	<.001
Hb g/dL (median [IQR])	13.2 [12.0; 14.3]	13.4 [12.1; 14.5]	13.2 [11.9; 14.4]	13.3 [12.0; 14.4]	.039
LYM 10⁹/L (median [IQR])	1.15 [.82; 1.53]	1.17 [.81; 1.59]	1.22 [.82; 1.69]	1.29 [.90; 1.78]	<.001
NLR (median [IQR])	4.08 [2.33; 7.45]	4.19 [2.40; 7.69]	4.35 [2.41; 8.22]	4.62 [2.49; 8.21]	.039
NEU 10⁹/L (median [IQR])	4.75 [3.27; 6.91]	4.99 [3.47; 7.34]	5.36 [3.69; 7.71]	5.76 [4.11; 8.34]	<.001
WBC 10⁹/L (median [IQR])	6.68 [5.20; 8.91]	7.05 [5.37; 9.24]	7.33 [5.65; 9.59]	7.83 [6.15; 10.37]	<.001
PLT 10⁹/L (median [IQR])	222 [178; 277]	228 [184; 288]	235 [184; 291]	248 [192; 305]	<.001
Fibrinogen mg/dL (median [IQR])	425 [347; 512]	449 [363; 538]	455 [375; 558]	461 [376; 550]	<.001

Ace/Arb: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, *DM*: diabetes mellitus, *HT*: hypertension, *CAD*: coronary artery disease, *CHF*: chronic heart failure, *COPD*: chronic obstructive pulmonary disease, *CVD*: cerebrovascular disease, *CKD*: chronic kidney disease, *LDH*: lactate dehydrogenase, *TG*: triglyceride, *HDL-C*: high density lipoprotein cholesterol, *LDL-C*: low density lipoprotein cholesterol, *CRP*: C-reactive protein, *Hb*: hemoglobin, *LYM*: lymphocytes, *NLR*: neutrophil to lymphocyte ratio, *NEU*: neutrophils, *WBC*: white blood cells, *PLT*: platelets, *IQR*: interquartile range.

During inflammation, there are also changes in the activity of lipoprotein lipase (LPL).[27] Proteins such as tumor necrosis factor (TNF), IL-1, IL-11, and interferon-γ are released by activated macrophages.[27,28] These inflammatory cytokines, which are greatly increased during COVID-19, can directly interact with regulatory proteins such as LPL or apolipoprotein (apo) CII and reduce LPL activity.[29] Thus, the conversion of TG-rich lipoproteins to LDL-C is reduced, leading

Table 3. Summary of baseline characteristics by TG quartiles.

	First	Second	Third	Fourth	p
n	1029	1031	1029	1028	
Total hospital length of stay, days (median [IQR])	9.0 [5.0; 13.0]	8.0 [5.0; 12.0]	8.0 [5.0; 12.0]	8.0 [5.0; 12.0]	.359
Re-hospitalization, n (%)	97 (9.4)	109 (10.6)	100 (9.7)	159 (15.5)	<.001
Stay in intensive care, n (%)	286 (27.8)	159 (15.4)	130 (12.6)	114 (11.1)	<.001
Mechanical ventilation, n (%)	205 (19.9)	89 (8.6)	60 (5.8)	49 (4.8)	<.001
30-day mortality, n (%)	228 (22.2)	108 (10.5)	80 (7.8)	73 (7.1)	<.001
Death, n (%)	273 (26.5)	132 (12.8)	102 (9.9)	109 (10.6)	<.001
Out-of-hospital death, n (%)	31 (3.9)	14 (1.5)	16 (1.7)	24 (2.5)	.004
In-hospital death, n (%)	242 (23.5)	118 (11.4)	86 (8.4)	85 (8.3)	<.001
Reinfection, n (%)	3 (.3)	11 (1.1)	5 (.5)	22 (2.1)	<.001
Acetylsalicylic acid use, n (%)	240 (23.5)	235 (22.9)	226 (22.0)	227 (22.1)	.852
P2Y12 inhibitor use, n (%)	68 (6.6)	75 (7.3)	75 (7.3)	53 (5.2)	.169
Statin use, n (%)	136 (13.2)	123 (11.9)	107 (10.4)	104 (10.1)	.096
Beta-blocker use, n (%)	236 (22.9)	232 (22.5)	208 (20.2)	199 (19.4)	.134
Insulin use, n (%)	120 (11.7)	104 (10.1)	81 (7.9)	81 (7.9)	.006
Oral antidiabetic use, n (%)	185 (18.1)	196 (19.1)	201 (19.6)	159 (15.5)	.085
Ace/Arb use, n (%)	361 (35.1)	380 (36.9)	373 (36.2)	359 (34.9)	.761
Male, n (%)	704 (68.5)	567 (55.0)	471 (45.8)	314 (30.5)	<.001
Age, years (median [IQR])	65 [53; 74]	65 [54; 74]	64 [53; 74]	64 [51; 74]	.218
DM, n (%)	314 (30.5)	307 (29.8)	281 (27.3)	246 (23.9)	.004
HT, n (%)	509 (49.5)	547 (53.1)	532 (51.7)	508 (49.4)	.269
CAD, n (%)	259 (25.2)	245 (23.8)	214 (20.8)	199 (19.4)	.005
CHF, n (%)	72 (7.0)	51 (4.9)	48 (4.7)	45 (4.4)	.032
COPD, n (%)	123 (12.0)	146 (14.2)	135 (13.1)	156 (15.2)	.17
CVD, n (%)	18 (1.7)	29 (2.8)	21 (2.0)	20 (1.9)	.359
CKD, n (%)	27 (2.6)	29 (2.8)	26 (2.5)	32 (3.1)	.858
Asthma, n (%)	39 (3.8)	36 (3.5)	44 (4.3)	49 (4.8)	.48
LDH U/L (median [IQR])	355 [273; 486]	305 [244; 384]	289 [232; 363]	273 [221; 339]	<.001
TG mg/dL (median [IQR])	146 [109; 205]	135 [101; 184]	123 [92; 166]	115 [84; 165]	<.001
HDL-C mg/dL (median [IQR])	23 [20; 25]	30 [29; 32]	36 [35; 38]	47 [44; 54]	<.001
LDL-C mg/dL (median [IQR])	76 [57; 95]	86 [68; 108]	91 [72; 112]	94 [74; 120]	<.001
Albumin g/dL (median [IQR])	3.5 [3.1; 3.8]	3.7 [3.4; 4.0]	3.8 [3.4; 4.1]	3.8 [3.5; 4.1]	<.001
Glucose mg/dL (median [IQR])	142 [112; 197]	134 [108; 184]	132 [107; 181]	128 [104; 169]	<.001
Creatinine mg/dL (median [IQR])	.98 [.80; 1.30]	.91 [.77; 1.15]	.86 [.73; 1.08]	.81 [.68; 1.03]	<.001
CRP mg/L (median [IQR])	59.3 [27.1; 103.9]	38.6 [16.1; 75.1]	32.7 [12.2; 65.7]	24.9 [6.8; 58.5]	<.001
log D-dimer mg/L (median [IQR])	5.66 [4.58; 6.71]	5.37 [4.38; 6.51]	5.41 [4.41; 6.42]	5.43 [4.43; 6.45]	.001
Ferritin μg/L (median [IQR])	416 [211; 857]	300 [143; 572]	261 [118; 527]	179 [68; 371]	<.001
Procalcitonin μg/L (median [IQR])	.27 [.06; 1.09]	.12 [.03; .51]	.09 [.02; .43]	.08 [.02; .44]	<.001
Hb g/dL (median [IQR])	13.3 [11.7; 14.5]	13.5 [12.1; 14.5]	13.4 [12.1; 14.4]	13.0 [12.1; 14.1]	<.001
LYM 10⁹/L(median [IQR])	1.08 [.72; 1.58]	1.19 [.84; 1.66]	1.22 [.87; 1.64]	1.28 [.91; 1.72]	<.001
NLR (median [IQR])	5.22 [2.67; 10.36]	4.14 [2.33; 7.48]	4.10 [2.43; 7.19]	4.04 [2.28; 7.00]	<.001
NEU 10⁹/L(median [IQR])	5.78 [3.84; 8.68]	5.00 [3.56; 7.46]	5.00 [3.50; 7.15]	5.22 [3.62; 7.29]	<.001
WBC 10⁹/L(median [IQR])	7.79 [5.80; 10.53]	7.05 [5.50; 9.52]	7.00 [5.42; 9.08]	7.18 [5.57; 9.35]	<.001
PLT 10⁹/L(median [IQR])	221 [173; 288]	231 [182; 290]	236 [186; 287]	241 [195; 291]	<.001
Fibrinogen mg/dL (median [IQR])	466 [388; 561]	456 [375; 548]	443 [370; 526]	420 [341; 522]	<.001

Ace/Arb: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, *DM*: diabetes mellitus, *HT*: hypertension, *CAD*: coronary artery disease, *CHF*: chronic heart failure, *COPD*: chronic obstructive pulmonary disease, *CVD*: cerebrovascular disease, *CKD*: chronic kidney disease, *LDH*: lactate dehydrogenase, *TG*: triglyceride, *HDL-C*: high-density lipoprotein cholesterol, *LDL-C*: low-density lipoprotein cholesterol, *CRP*: C-reactive protein, *Hb*: hemoglobin, *LYM*: lymphocytes, *NLR*: neutrophil to lymphocyte ratio, *NEU*: neutrophils, *WBC*: white blood cells, *PLT*: platelets, *IQR*: interquartile range.

Table 4. Relationship between LDL-C, HDL-C and TG levels and risk of death.

Lipids	Hazard Ratio, 95% CI
LDL-C, mg/dl	p for nonlinearity = .0006
50	1.40 (1.12–1.74)
100	Ref
150	1.39 (1.11–1.75)
200	2.47 (1.43–4.28)
HDL-C, mg/dl	p for nonlinearity = .0007
20	1.67 (1.31–2.13)
30	1.13 (.92–1.39)
40	Ref
50	1.04 (.92–1.17)
60	1.14 (.84–1.54)
TG, mg/dl	p for nonlinearity = .145
50	.68 (.44–1.03)
100	Ref
150	1.16 (1.02–1.32)
200	1.21 (.96–1.52)
300	1.28 (1.00–1.65)

LDL-C: low-density lipoprotein cholesterol, *HDL-C*: high-density lipoprotein cholesterol, *TG*: triglycerides, *CI*: confidence interval

to high TG and low HDL-C levels. This may be the reason for the high TG levels in our study.

Recent studies have shown that an increased CRP level can be used to predict the severity of COVID-19 infection.[30,31] Proinflammatory cytokines such as IL-6 and CRP inhibit apolipoprotein synthesis enzyme activity, resulting in decreased apo A-1 and HDL production.[32] In a study, LDL-C and HDL-C levels were found to be inversely proportional to CRP levels.[9] In addition, in another COVID-19 study, high CRP and procalcitonin levels, which may suggest secondary coinfection, were found in patients with low LDL-C, low HDL-C, and high TG levels, and coinfection was reported to be a risk factor for poor prognosis of COVID-19.[33] In our study, higher CRP and procalcitonin levels were observed in patients with low LDL-C, low HDL-C, and high TG levels with higher mortality. This increase in mortality can be explained by coinfection.

In studies including patients admitted to the intensive care unit with a diagnosis of COVID-19, the need for intubation and mechanical ventilation was found to be approximately 79–88% and mortality 24–53%.[34-37] Admission to the intensive care unit is a poor prognostic indicator for COVID-19.[37] In another study, the proportion of patients who were admitted to the intensive care unit and needed mechanical ventilation increased with the decrease in LDL-C levels.[38] Similarly, patients with low LDL-C, low HDL-C, and high TG levels in our study had a higher rate of hospitalization in the intensive care unit and need mechanical ventilation.

In our study, LDL-C levels of ∼>150 mg/dl were associated with increased mortality. The severe inflammatory reaction process in COVID-19 patients is always accompanied by oxidative stress.[39] Oxidative stress is manifested by overproduction of oxidative stress products and oxidized LDL particles.[40] In the case of hypercholesterolemia, most of the LDL is converted to oxidized LDL by the presence of high levels of free radicals.[41] Oxidized LDL contributes to atherosclerotic plaque formation and progression by several mechanisms, including induction of endothelial cell activation and dysfunction, macrophage foam cell formation, and smooth muscle cell migration and proliferation.[42] In our study, the increase in mortality in high LDL-C levels may have been caused by atherosclerotic heart disease contributed by oxidized LDL.

Lactate dehydrogenase (LDH) levels in patients with COVID-19 were reported to be significantly higher in patients who died than in survivors.[43] Also, leukopenia, liver dysfunction, ferritin and hypoalbuminemia were found as potential markers for disease severity.[44] In our study, LDH was found to be higher in patients with low LDL-C and low HDL-C levels. At the same time, these patients had higher ferritin levels and lower albumin levels.

A decrease in platelet count was found in patients who died due to severe COVID-19 infection.[45] D-dimer is significantly elevated in patients who died from COVID-19 infection. The literature has shown that high D-dimer is associated with increased disease severity.[46,47] Both decreased platelet count and D-dimer elevation were associated with poor prognosis. In our study, lower platelet count and higher D-dimer were detected in patients with low LDL-C, low HDL-C and high TG levels. The fact that potential markers, which are at a similar level with the literature, are seen in patients with low LDL-C and HDL-C with higher mortality emphasizes that these lipid levels are predictive of mortality. In contrast, leukopenia was not observed at low lipid levels in our study.

In our study, statin use differed significantly between the groups. Statin use was highest in the group with the lowest LDL-C. In addition to anti-inflammatory effects, statins have pleiotropic effects and studies have suggested that they may be protective against ARDS.[48,49] In our study, it was observed that mortality was high in patients using statins. This may be due to the higher incidence of CAD, a mortality predictor, in the group with low LDL-C levels. More studies evaluating the anti-inflammatory properties of statins in COVID-19 patients are needed.

Limitations

The present study is retrospectively designed; prospective, large-scale, long-term studies should yield more accurate results. LPL activity and lipoprotein a levels were not measured. In addition, the results could not be generalized to all COVID-19 patients in the general population because the present study was based on hospitalized patients. Data of

myocardial infarction or arrhythmias was not available in our study.

Conclusion

Low and high LDL-C, low HDL-C, and high TG levels were negatively associated with COVID-19-related mortality. Blood lipid levels may be useful as predictors of mortality in COVID-19 patients. Whether modifying these levels results in better outcome should be investigated.

Author Contribution

S. Aydin, E. Aksakal, F. Aydinyilmaz, S. Aydemir, K. Kalkan, I. Sarac, and I. Tanboga made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. S. Aydin, O. Gulcu, U. Aksu, and R Dogan contributed to drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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