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Low-density lipoprotein cholesterol levels are associated with poor clinical outcomes in COVID-19

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Abstract *Background and aims:* Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the sole causative agent of coronavirus infectious disease-19 (COVID-19).
Methods and results: We performed a retrospective single-center study of consecutively admitted patients between March 1st and May 15th, 2020, with a definitive diagnosis of SARS-CoV-2 infection. The primary end-point was to evaluate the association of lipid markers with 30-days all-cause mortality in COVID-19.

A total of 654 patients were enrolled, with an estimated 30-day mortality of 22.8% (149 patients). Non-survivors had lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) levels during the entire course of the disease. Both showed a significant inverse correlation with inflammatory markers and a positive correlation with lymphocyte count. In a multivariate analysis, LDL-c $\leq$ 69 mg/dl (hazard ratio [HR] 1.94; 95% confidence interval [CI] 1.14–3.31), C-reactive protein >88 mg/dl (HR 2.44; 95% CI, 1.41–4.23) and lymphopenia <1000 (HR 2.68; 95% CI, 1.91–3.78) at admission were independently associated with 30-day mortality. This association was maintained 7 days after admission. Survivors presented with complete normalization of their lipid profiles on short-term follow-up.
Conclusion: Hypolipidemia in SARS-CoV-2 infection may be secondary to an immune-inflammatory response, with complete recovery in survivors. Low LDL-c serum levels are independently associated with higher 30-day mortality in COVID-19 patients.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AUROC, Area under the receiver operating characteristic curve analysis; CoQ10, Coenzyme Q10; COVID-19, Coronavirus disease 2019; CRP, C-Reactive protein; HDL-c, High-density lipoprotein cholesterol; IL6, Interleukin 6; LDH, Lactate dehydrogenase; LDL-c, Low-density lipoprotein cholesterol; PCT, Procalcitonin; RT-PCR, Reverse transcription-polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TC, Total cholesterol; TG, Triglycerides.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single-stranded RNA virus [1], and it is considered the sole causative agent of Coronavirus disease-2019 (COVID-19). According to the World Health Organization, approximately 2,191,898 patients are currently dead after 101,406,059 confirmed cases worldwide [2]. Initial reports have suggested that SARS-CoV-2 binds to a human angiotensin-converting enzyme-2 receptor to gain intracellular entry [1] after it causes some protein and lipid conformational changes at the edges of cholesterol-rich lipid domains [3].

Cholesterol is a precursor of steroid hormones and bile acids and is an essential constituent of cell membranes that facilitates signal transduction. Besides, membrane cholesterol is a critical component to facilitate viral entry into host cells, and evidence suggests that inflammation can alter circulating levels of lipids [4–7]. Interestingly, COVID19 is associated with a great inflammatory burden and inflammatory markers have been associated with an increased mortality rate [1,8]. Converseverly, studies in SARS-CoV patients showed long-term metabolic dysregulations [9].

This evidence led us to hypothesize that COVID-19 may disrupt cholesterol homeostasis and mirror the lipid changes observed in other inflammatory conditions. Herein, we conducted a retrospective study involving hospitalized SARS-CoV-2 infected patients to evaluate the relationship between COVID-19 and lipid profiles. For this purpose, we also evaluated previous baseline and follow-up lipid profiles, as well as inflammatory profiles.

Methods

Study design and population

We conducted this retrospective single-center study at a Spanish tertiary hospital (Hospital Clínico Universitario de Valladolid, Spain, Valladolid). Between March 1st, 2020, and May 15th, 2020, data from a total of 654 consecutive patients with a definitive diagnosis of SARS-CoV-2 infection confirmed through positive reverse transcriptase-polymerase chain reaction (RT-PCR). Exclusion criteria were age <18 years old, pregnant women, and death in the first 24 h after admission. We retrospectively collected the baseline clinical features, radiologic procedures, and laboratory tests. We also recorded ongoing treatment and clinical outcomes from the electronic medical records. Special attention was given to the accurate recording of the prescribed therapy before admission and during hospital stay according to our institution's protocols and the discretion of the medical team. Follow-up continued through until July 25th, 2020.

The local ethics committees approved the study protocol. Informed consent was waived, given the retrospective and observational nature of the study. The work was carried out by following the guidelines of the Declaration of Helsinki of the World Medical Association.

Outcome measure

The primary endpoint was to investigate any relationship between serum levels of lipid markers in the first hours of admission and all-cause mortality at 30-days. Secondary endpoints included the correlation between lipid and inflammatory markers (1) during hospitalization and (2) after discharge on the first-time follow-up as well as their (3) association with disease prognosis.

Following the institution's protocols, a blood sample was drawn on the first 24 h and on the 7th day during hospitalization according to medical criteria. We assessed after overnight fasting total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), and inflammatory markers as well as a complete blood count measurement. Medical records were also used to identify baseline (performed on the last eighteen months before the index event) and follow-up lipid levels, excluding those performed in the hospital, to evaluate potential patterns among COVID-19 patients.

Clinical laboratory tests

We carried out all tests at our certified clinical laboratory (ISO 9001:2015). White blood cells, lymphocyte, and monocyte counts were performed on Sysmex XN-1000® analyzer using the manufacture's reagents (Sysmex Corporation, Japan). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), LDL-c, HDL-c, TC, and TG were tested on Roche Cobas 8100 sampling system analyzer (Module Cobas® c 702, Roche Diagnostics, Switzerland) using manufacture's reagents. The methodology for direct LDL-c, HDL-c, and TC methods are based on a standard homogeneous enzymatic colorimetric assay. We tested interleukin 6 (IL6) on IMMULITE® 2000 immunoassay system using the manufacture's luminescent immunoassay reagents (IMMULITE® 2000 IL6, Siemens Healthcare Diagnostic, Germany). Procalcitonin (PCT) measurement in plasma was performed by electrochemiluminescence immunoassay on a chemistry analyzer (Cobas 6000, Roche Diagnostics) limit of detection, as below 0.02 ng/ml. We measured serum C-reactive protein (CRP) by particle enhanced immunoturbidimetric (e501 Module Analyser, Roche Diagnostics). The limit of detection was set below 0.3 mg/L.

Statistical analysis

We reported categorical variables as absolute values and percentages. Continuous variables were reported as median (interquartile range [IQR]). The normal distribution of continuous variables was verified with the Kolmogorov–Smirnov test and q–q plot. Categorical

variables were compared with the chi-square test and the Fisher exact test when necessary. We compared continuous variables with the Mann–Whitney U test. A Spearman test was performed to analyze the correlation between lipid variables with the rest of the serum markers. We assessed the accuracy of analyzed variables to identify non-survivors patients by using the area under the receiver operating characteristic curve analysis (AUROC). We determined the optimal operating point (OOP) in the AUROC as the one that equaled sensitivity and specificity regarding mortality, and we used it as the cut-off point in the lipid profiles. We analyzed time to 30-day mortality by Kaplan–Meier survival curves and compared using the log-rank test. In a further step, we performed a multivariable Cox-regression analysis with a stepwise forward selection to determine the predictors of 30-day mortality in the global study population. Proportional hazard assumptions were verified by Shoenfeld residual test and check using the log(-log(survival)) plots. Sensitivity subgroup analyses were performed to determine possible differences in LDL-c levels as markers of poor prognosis by age, sex, and plasma lipids. We performed the statistical analyses with the use of R software, version 3.6.1 (R Project for Statistical Computing) and IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp. Differences were statistically significant when the p-value was <0.05.

Results

Baseline and clinical characteristics

The main baseline and clinical characteristics at admission are listed in Table 1. A total of 654 patients were admitted due to COVID-19 with an estimated 30-day fatality rate of 22.8%. Non-survivors were older (82 vs. 66 years old; $p < 0.001$) and had a greater prevalence of hypertension (74.5% vs. 46.7%; $p < 0.001$), diabetes mellitus (31.5% vs 17%; $p < 0.001$), dyslipidemia (52.3% vs. 34.3%; $p < 0.001$) as well as other comorbidities such as chronic kidney disease (19.5% vs. 5.7%; $p < 0.001$) or ischemic heart disease (14.8% vs. 8.1%; $p = 0.016$). In accordance, non-survivors were more commonly treated prior to admission with antihypertensive drugs, oral antidiabetics, antiplatelets, and statins.

Time interval from symptom onset to admission (4 vs. 7 days; $p < 0.001$) and baseline oxygen saturation levels at admission (91% vs 95%; $p < 0.001$) were smaller among non-survivors. They also displayed greater levels parameters of organ damage and inflammation such as creatinine (1.16 vs. 0.81 mg/dL; $p < 0.001$), D-dimer (1394 vs. 664 ng/mL; $p < 0.001$), CRP (128.4 vs. 54.5 mg/L; $p < 0.001$), procalcitonin (0.33 vs. 0.08 ng/mL; $p < 0.001$), LDH (357 vs. 265 U/L; $p < 0.001$) and IL6 (52.1 vs. 18.4 pg/mL; $p < 0.001$) levels. In contrast, non-survivors had lower blood count of haemoglobin (12.4 vs. 13.3 g/dL; $p < 0.001$) lymphocytes (805 vs. 1130 cells/mm^3; $p < 0.001$) and platelets (183 vs. 218 cells/mm^3 x10^3; $p < 0.001$).

Specific COVID-19 treatment was more commonly prescribed in survivors with comparable prescription rate in respect to statins (7.4% vs. 7.4%; $p = 0.996$) and corticosteroids (57.2% vs. 63.1%; $p = 0.202$) in the two groups. The incidence of respiratory failure (92.5% vs. 43.3%; $p < 0.001$), nosocomial infection (31.5% vs. 14.9%; $p < 0.001$) and ICU admission (20.3% vs. 8.1%; $p < 0.001$) were more common among non-survivors during hospitalization.

Lipid profile among COVID-19 patients

Lipid profiles were tracked from previous laboratory reports before SARS-CoV-2 infection (when available), at hospital admission, on the 7th day during hospitalization, and until first-time follow-up after discharge. In the overall population (including both groups), serological levels of all the analyzed lipid markers, except TG, displayed a significant decrease at the time of admission concerning the previous baseline values. Besides, baseline serum TC and LDL-c levels were significantly higher in survivors than non-survivors at any time; whereas, HDL-c was comparable at admission but significantly lower in non-survivor before (47.2 vs. 52.6 mg/dL; $p = 0.004$) and in the 7th day (27 vs. 34 mg/dL; $p = 0.011$) after hospital admission.

The results of changes in the concentration of lipid and inflammatory markers over time are summarized in Fig. 1 and Table 2. Overall, non-survivors had a progressive decline of TC, LDL-c, and HDL-c levels in comparison to survivors, who presented with complete recovery to previous baseline lipid levels and CRP (1.7 [1–3.2] mg/L) after a median time to first-time follow-up of 73 days.

Correlation of lipid markers with other inflammatory markers

A Spearman correlation analysis assessed the relationship of lipid parameters with all the gathered analytical parameters. Interestingly, LDL-c and TC levels at admission were inversely correlated with the levels of CRP ($r = -0.217$ and -0.209, respectively; $p < 0.001$), PCT ($r = -0.313$ and -0.229; $p < 0.001$) and IL6 ($r = -0.334$ and -0.301; $p < 0.001$) with a positive correlation with lymphocytes ($r = 0.179$ and 0.191; $p = 0.001$), which was maintained throughout hospitalization and until recovery (see Table S1 in the Supplementary appendix). LDL-c did show a very strong positive correlation with TC ($r = 0.937$; $p < 0.001$) as opposed to HDL-c ($r = 0.201$; $p < 0.001$). We also observed a significant mild correlation of TC ($R = -0.287$; $p < 0.001$) and LDL-c ($R = -0.273$; $p < 0.001$) with age at the time of admission.

AUROC curve analysis and threshold values

We analyzed the diagnostic performance accuracy of lipid profiles to predict 30-day mortality using the area under the receiver operating characteristic curve analysis (AUROC). The best estimated threshold values for LDL-c and TC were those calculated by the optimal operating point (OOP) in the AUROC as the one that equaled

Table 1 Baseline Characteristics and main features during admission in hospitalized patients due to Coronavirus Disease 2019 according to mortality.

Variable	All population N = 654	Survivors N = 505 (77.2)	Non-survivors N = 149 (22.8)	p-value
Demographics				
Female sex	278 (42.5)	223 (44.6)	55 (36.9)	0.116
Age (years)	70 [58–81]	66 [55–76]	82 [72–87]	<**0.001**
Cancer	117 (17.9)	81 (16)	36 (24.2)	**0.023**
CKD[a]	58 (8.9)	29 (5.7)	29 (19.5)	<**0.001**
Diabetes	133 (20.3)	86 (17)	47 (31.5)	<**0.001**
Dyslipidemia	251 (38.4)	173 (34.3)	78 (52.3)	<**0.001**
Hypertension	347 (53.1)	236 (46.7)	111 (74.5)	<**0.001**
Hypothyroidism	81 (12.4)	51 (10.1)	22 (13.4)	0.252
IHD	63 (9.6)	41 (8.1)	22 (14.8)	**0.016**
Obesity	62 (9.5)	47 (9.3)	15 (10.1)	0.781
Prior pulmonary disease	143 (21.9)	106 (21)	37 (24.8)	0.319
Prior rheumatic disease	48 (7.3)	34 (6.7%)	14 (9.4)	0.273
Prior stroke/TIA	41 (6.3)	29 (5.9%)	12 (8.1)	0.306
Treatment prior to admission				
Antiplatelets	106 (16.2)	70 (13.9)	36 (24.3)	**0.002**
ACEI/ARB	266 (40.7)	182 (36)	84 (56.8)	<**0.001**
Levothyroxine	71 (10.9)	52 (10.3)	19 (12.8)	0.383
Oral anticoagulation	79 (12.1)	40 (8.3)	37 (25)	<**0.001**
Oral antidiabetics	106 (16.2)	73 (14.5)	33 (22.3)	**0.023**
Statins	210 (32.2)	151 (29.9)	59 (39.9)	**0.022**
Main findings at admission				
Time from onset (days)	7 [3–10]	7 [4–10]	4 [2–7]	<**0.001**
Pathological Chest X-ray	597 (91.8)	462 (91.8)	135 (91.8)	0.996
Positive RT-PCR[b]	638 (97.6)	489 (96.8)	149 (100)	**0.030**
Basal O^2 saturation	94 [91–96]	95 [92–97]	91 [86–94]	<**0.001**
Sat:FiO^2	447 [433–457]	452 [438–462]	433 [409–448]	<**0.001**
Laboratory findings at admission				
Haemoglobin (g/dL)	13.1 [12–14.4]	13.3 [12.2–14.5]	12.4 [11–14]	<**0.001**
CK (μmol/L)	80 [49–134]	78 [49–123]	101 [53–221]	**0.016**
C-Reactive protein (mg/L)	67.7 [26.75–134.05]	54.5 [21–105.6]	128.4 [72.2–191.5]	<**0.001**
Creatinine (mg/dL)	0.87 [0.7–1.15]	0.81 [0.7–1.02]	1.16 [0.88–1.63]	<**0.001**
D-Dimer (ng/mL)	756 [449–1386]	664 [414–1134]	1394 [747–2576]	<**0.001**
Ferritin (ng/mL)	609 [294–1134]	605 [290–1100]	640 [302–1298]	0.205
ALT (U/L)	24 [17–43]	25 [17–44]	22 [15–37]	**0.004**
AST (U/L)	36 [24–52]	34 [24–49]	41 [25–60]	**0.022**
Interleukin-6 (pg/mL)	20.9 [10–47]	18.4 [9.3–40.5]	52.1 [22.5–115]	<**0.001**
LDH (U/L)	283 [215–359]	265 [206–331]	357 [303–460]	<**0.001**
Lymphocytes (cells/mm^3)	1050 [720–1470]	1130 [820–1570]	805 [580–1215]	<**0.001**
Neutrophils (cells/mm^3)	4600 [3020–6830]	4260 [2840–5920]	6125 [4035–9805]	<**0.001**
Platelets (cells/mm^3x10^3)	213 [163–274]	218 [169–284]	183 [137–260]	<**0.001**
Procalcitonin (ng/ml)	0.11 [0.06–0.29]	0.08 [0.05–0.16]	0.33 [0.13–0.82]	<**0.001**
Troponin (pg/mL)	15.04 [7.91–22.28]	9.3 [7–17.2]	33.6 [16–148.1]	<**0.001**
Specific COVID-19 treatment				
Azithromycin	588 (94.2)	470 (95.3)	118 (90.1)	**0.022**
Betaferon	244 (39.1)	182 (36.9)	62 (47.3)	**0.03**
Hydroxychloroquine	605 (97)	483 (98)	122 (93.1)	**0.008**
Lopinavir/Ritonavir	590 (94.4)	473 (95.7)	117 (89.3)	**0.004**
Non-specific COVID-19 treatment				
Antibiotics	551 (84.4)	424 (84.1)	127 (85.2)	0.743
Anticoagulation[c]	545 (83.8)	434 (86.3)	111 (75.5)	**0.002**
Corticosteroids/Glucocorticoids	383 (58.6)	289 (57.2)	94 (63.1)	0.202
Statins	48 (7.4)	37 (7.4)	11 (7.4)	0.996
Main in-hospital outcomes				
LOS (days)	9 [5–15]	10 [6–16]	7 [4–14]	<**0.001**
ICU admission	71 (10.9)	41 (8.1)	30 (20.3)	<**0.001**
Mechanical ventilation	77 (9.7)	33 (6.6)	34 (22.1)	<**0.001**
Nosocomial infection	122 (18.7)	75 (14.9)	47 (31.5)	<**0.001**
Respiratory failure[d]	354 (54.5)	218 (43.3)	136 (92.5)	<**0.001**

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitors; ALT: alanine aminotransferase; ARB: angiotensin receptor blocker; AST: aspartate aminotransferase CKD: Chronic kidney disease; ICU: Intensive care unit; IHD: Ischemic heart disease; LDH: Lactate dehydrogenase; LOS: Length of stay; RT-PCR: Reverse transcription-polymerase chain reaction.

Values are reported as median (IQR) or n (%). Significant values ($p < 0.05$) are bold.

[a] Chronic kidney disease was defined as a glomerular filtration rate of <60 ml/min or need for dialysis.

[b] At hospital admission.

[c] Includes prophylactic, intermediate and complete anticoagulation doses.

[d] Defined as $pO^2 < 60$ mmHg, SO_2 <92% or need for non-invasive or mechanical ventilation.

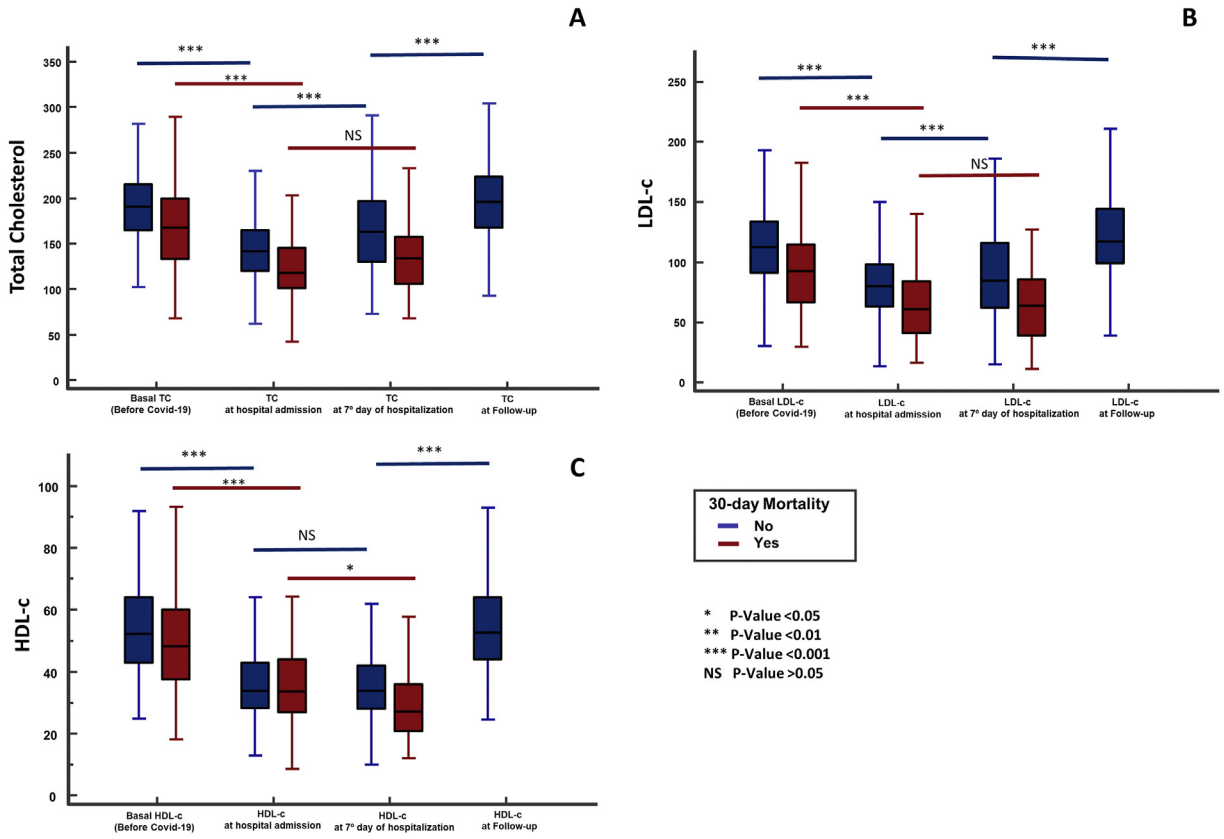

Figure 1 Temporal changes in lipid profile levels in COVID-19 patients according to the clinical course of the disease: A) Total cholesterol; B) LDL-c; C) HDL-c. The horizontal lines represent the median value in each group. HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; TC: Total cholesterol.

sensitivity and specificity regarding mortality. These cut offs were 69 mg/dl on admission and 75 mg/dl in the 7th day of hospitalization for LDL-c. For TC estimated cut-off were 132 mg/dL and 147 mg/dL (see Fig. S1). Threshold values for LDL-c and TC were also calculated from the quartiles, but had a worse balance between sensitivity and specificity, so they were not selected for multivariate analysis.

Association between mortality and lipid profile

Independent predictors of mortality were estimated through a Cox uni- and multivariate regression analysis. The variables included in the multivariate model were those with a p-value <0.05 on the univariate analysis (age, hypertension, diabetes, dyslipidemia, ischemic heart disease, chronic renal disease, angiotensin receptor antagonist, angiotensin-converting enzyme inhibitors, statins, lymphopenia, CRP, antiviral treatment, anticoagulation, total cholesterol, and LDL-c).

Multivariate adjusted models showed that age ([hazard ratio [HR] 1.08; 95% confidence interval [CI], 1.05–1.11]; $p < 0.001$), lymphopenia <1000 cells/ml (HR 2.68; 95% CI, 1.91–3.78; $p < 0.001$), LDL-c <69 mg/dL (HR 1.94; 95% CI, 1.14–3.31; $p = 0.014$) and CRP >88 mg/dL (HR 2.44; 95% CI, 1.41–4.23; $p = 0.001$) at admission were independent variables associated with a greater risk of 30-day mortality. However, statins were not independently associated with mortality. A sensitivity subgroup analysis was performed to identify potential differences at the time of admission for LDL-c (See Fig. S2). Overall, when we repeated the multivariate analysis including analytics values on 7th day of admission, the results remained consistent. In fact, age, presence of lymphopenia, CRP levels> 33 mg/dL and LDL-c levels <75 mg/dL determined on the 7th day of admission, were the only variables associated with 30-day mortality (See Table 3).

The unadjusted survival Kaplan–Meier curves for 30-day global mortality were performed and shown in Fig. 2. Those patients with LDL-c levels <69 mg/dl at the time of admission and <75 mg/dl on the 7th day showed a 20% higher 30-day mortality rate than the rest of the patients. On the other hand, it was observed that the lower the LDL-c levels, the higher the mortality on day 30, represented by Kaplan–Meier curves (Suppl. Figure 3).

Discussion

Lipoproteins play a vital role in innate immunity and perform different functions against infection: receptor

Table 2 Lipid and inflammatory profile of patients with Coronavirus Disease 2019 in the global study population and according to mortality during the full course of the disease.

Variable	All population N = 654	Survivors N = 505 (77.2)	Non-survivors N = 149 (22.8)	p-value
Lipid laboratory profile before admission				
Total cholesterol (mg/dL)	187.5 [155–214]	191 [164.5–215]	167.5 [133–200]	<**0.001**
HDL-c (mg/dL)	51.6 [41.7–62.1]	52.6 [43–64]	47.2 [37.5–60]	**0.004**
LDL-c (mg/dL)	108.4 [84.6–129.6]	113.2 [91.3–134.3]	93 [66.4–112.6]	<**0.001**
Triglycerides (mg/dL)	109.5 [82.0–146.0]	108 [79–146]	116.5 [91–145]	0.122
TC/HDL-c	3.5 [2.9–4.3]	3.5 [3–4.3]	3.5 [2.8–4]	0.328
Lipid laboratory profile at admission				
Total cholesterol (mg/dL)	137 [117–163]	142 [120–165]	121 [101.5–146.5]	<**0.001**
HDL-c (mg/dL)	34 [28–43]	34 [28.3–43]	33.5 [27–44]	0.278
LDL-c (mg/dL)	77 [59–97]	80 [63–98]	61.1 [41–84.2]	<**0.001**
Triglycerides (mg/dL)	118 [91–163]	119 [92–163]	114 [86.5–157]	0.240
TC/HDL-c	3.9 [3.11–4.84]	3.9 [3.2–4.9]	3.39 [2.9–4.6]	**0.012**
Lipid laboratory profile during 7th day of hospitalization				
Total cholesterol (mg/dL)	157 [126–192]	163 [130.5–197]	134 [106.5–158]	<**0.001**
HDL-c (mg/dL)	33 [26.5–41.6]	34 [28–41.8]	27 [19.1–37]	**0.011**
LDL-c (mg/dL)	79.7 [55–107.5]	85.7 [62–115.5]	56.4 [39.3–75.1]	**0.001**
Triglycerides (mg/dL)	184 [130–257]	189 [132–261.5]	161.5 [124–226]	0.057
TC/HDL-c	4.54 [3.73–5.95]	4.5 [3.7–5.9]	4.4 [3.6–6.1]	0.965
Lipid laboratory profile during follow-up[a]				
Total cholesterol (mg/dL)	196 [168–223.5]	196 [168–223.5]	NA	NA
HDL-c (mg/dL)	52.8 [44.1–64]	52.8 [44.1–64]	NA	NA
LDL-c (mg/dL)	117.3 [99.3–144.7]	117.3 [99.3–144.7]	NA	NA
Triglycerides (mg/dL)	111 [83–156]	111 [83–156]	NA	NA
TC/HDL-c	3.7 [3.2–4.3]	3.7 [3.2–4.3]	NA	NA

Abbreviations: HDL-c: High-density lipoprotein cholesterol: LDL-c: Low-density lipoprotein cholesterol; NA: Not applicable; TC: Total cholesterol: TG Triglycerides.
Values are reported as median (IQR) or n (%). Significant values ($p < 0.05$) are bold.
[a] Only in survivors.

blocking, lysis, chemotaxis, and neutralization of bacterial endotoxins. Lipids are essential for the replication and pathogenicity of enveloped viruses [10,11]. The main findings of this research are: (1) The observed dyslipidemia and mortality in COVID-19 patients was mainly driven by a stronger inflammatory response; (2) inflammatory markers inversely correlated with lipid levels, with complete resolution among survivors during short-term follow-up after the resolution of inflammation; and (3) low LDL-c levels might be a potential prognostic marker in COVID-19 and septic patients.

The mechanism underlying the observed altered cholesterol homeostasis is likely multifactorial and complex. Serum ALT, AST, and LDH levels were moderately increased in non-surviving patients, indicating mild liver-function impairment, which could be a contributing factor by disrupting uptake and biosynthesis of lipoproteins [12]. Nonetheless, a specific type of viral infections can lead to alteration of lipid metabolism in the acute and chronic phases as a response to an ongoing inflammatory state [6,7].

Although COVID-19 pathophysiology is not fully understood, COVID-19 severity and death are associated with a hyperinflammatory state due to a dysregulated immune system [8,13]. The clinical profile of the patients included in this study shows a similar trend, with systemic inflammation being a major contributor to mortality, but also SARS-CoV-2-mediated dyslipidemia. We observed a paradoxical lipid metabolism with a U-shaped curve of lipid levels among survivors with similar findings previously described in inflammatory diseases [14]. There are a number of possible explanations from an immunological point of view.

HDL-c might become pro-inflammatory under specific conditions that increase reactive oxygen species and

Table 3 Multivariate Cox regression analysis for evaluating the risk of 30-day mortality in the COVID-19 study population.

Variable	Multivariate	
	HR (95% CI)	p value
At admission		
Age	1.08 (1.05–1.11)	<**0.001**
CRP > 88 mg/dL	2.44 (1.41–4.23)	**0.001**
LDL-c < 69 mg/dL	1.94 (1.14–3.31)	**0.014**
Lymphocytes < 1000 cells/mm^3	2.68 (1.91–3.78)	<**0.001**
7th day		
Age	1.06 (1.03–1.1)	<**0.001**
CRP > 33 mg/dL	3.91 (1.9–8.06)	<**0.001**
LDL-c < 75 mg/dL	2.12 (1.06–4.23)	**0.033**
Lymphocytes < 1000 cells/mm^3	3.97 (1.87–8.4)	<**0.001**

CI: Confidence interval; CRP: C-Reactive protein; LDL-c: Low-density lipoprotein cholesterol; HR: Hazard ratio.
Significant values ($p < 0.05$) are bold.

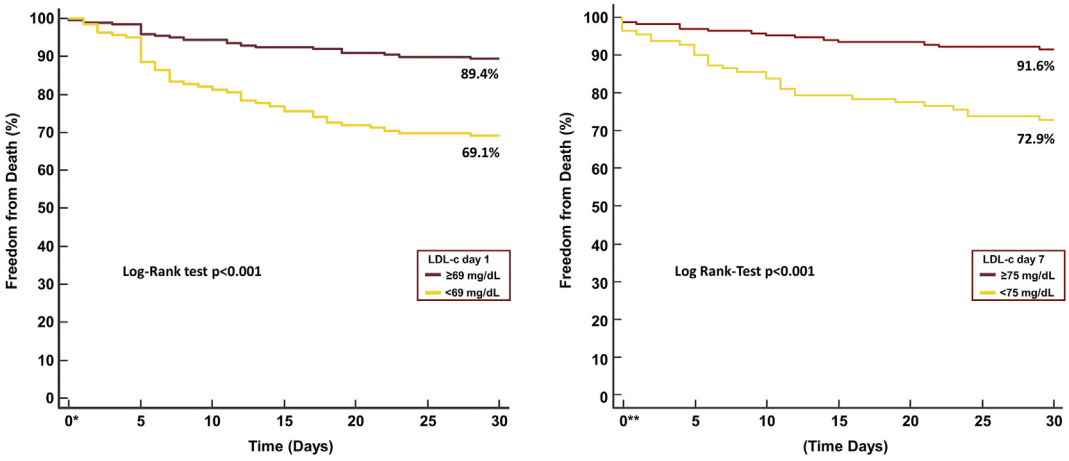

Figure 2 Kaplan–Meier estimates of mortality in the total COVID-19 population according to LDL-c A) at admission and B) at the 7th day of hospitalization based on their optimal cut-off point. * Time scale takes place between day 0 (day of admission) to 30 ** Day 0 represents the seventh day of admission.

myeloperoxidase activity. It can also modify their levels and Apoprotein-AI concentration; hence, altered reverse cholesterol transport [4,15]. LDL-c can be oxidized when its HDL-c counterpart loses its antioxidative properties, or if oxidized phospholipids accumulate. They are identified as damaged-associated molecular patterns (DAMPs) by scavenger receptors, activate the inflammasome [4] and the immune system [13]. Low LDL-c levels may also be the consequence of an increased vascular leakage in the lung parenchyma as a result of endothelial damage [12,13].

Finally, an increased concentration of pro-inflammatory cytokines may be responsible for a drastic decrease in plasma LDL-c levels during the acute-phase response. Direct effects of cytokines might explain the altered lipid concentrations [14] by up-regulating ox-LDL uptake or overriding suppression of LDL-c receptor through the expression of scavenger receptors. These changes observed with inflammation can increase the odds of cardiovascular disease through the formation of foam cells and endothelial damage [15,16].

Sepsis is defined as the presence of infection with a detrimental host response with organ damage [17]. Low HDL-c levels have been associated before with an increased risk of sepsis [18,19] and adverse outcomes [20–23]. In fact, Maile et al. [24] or Guirgis et al. [25] also suggested that low baseline LDL-c levels are associated with an increased risk of mortality and sepsis, respectively. By analogy, similar findings should be identified in SARS-CoV-2 patients.

In particular, low HDL-c levels in SARS-CoV-2 patients have been associated with disease severity [26,27], but our results are in agreement with those recently published in which low LDL-c levels were associated with COVID-19 severity [12,28]. However, we also observed an association with an increased risk of mortality with low LDL-c levels after the adjusted multivariate analyses. In contrast, a recent work by Walley et al. proposed that low LDL-c levels are merely an indicator of the disease severity in septic patients, without a contributing role to mortality [29].

The observed associated mortality in this cohort of COVID-19 patients may be explained by other mechanism. In this sense, LDL-c transports a large percentage of plasma Coenzyme Q10 (CoQ10), which has a significant antioxidant capacity, avoiding peroxidative damage to the cellular membranes [30,31]. Low LDL-c levels can cause a decrease in plasma CoQ10 levels, which can lead to endothelial dysfunction, organ damage and death, as observed in COVID-19 patients [32]. Furthermore, the incidence of severe COVID-19 among elderly has been the greatest. Aging is associated with increased circulating levels of ox-LDL; thus, it could trigger a vicious cycle due to higher basal levels [33]. All these mechanisms justify that patients with low LDL-c levels have a reduced defensive, energetic and metabolic reaction capacities to be able to properly manage a situation of aggression and organ stress such as COVID-19.

Overall, low LDL-c levels may reflect a pro-inflammatory phenotype of severe SARS-CoV-2 infection, but they may also induce multiple systemic reactions through a complex interplay. Therefore, in the appropriate scenario, we might hypothetically consider low LDL-c levels as a plausible candidate as a routine risk marker during admission and disease progression. Nevertheless, we did not explore role of statins given the lack of association with mortality despite their pleiotropic properties [34]. Additionally, we cannot rule out a catabolic state or high immune cell turnover as a cause of low LDL-c levels in COVID-19 patients. The presence in our study of a statistically significant positive correlation between LDL-c levels and blood lymphocyte count, the latter being an independent variable associated with 30-day mortality together with LDL-c in multivariate regression analysis, can support this theory.

Our work presents certain limitations. These observations should be considered hypothesis-generating only due to the intrinsic retrospective nature of the present work. Moreover, the data were subject to selection bias, and the generalizability of the results may be reduced by the fact that we did not evaluate outpatients. We could not measure apoproteins or oxidized forms of main lipoproteins, which may play a detrimental role in the pathogenesis of COVID-19. Finally, for better characterization of this abnormal cholesterol homeostasis, our findings should be validated in a large prospective multicentric cohort of COVID-19 patients monitoring the dynamics of lipid profiles.

In conclusion, several contributing factors can explain low cholesterol levels in COVID-19, but our results suggest an etiology-dependent mechanism. Reversal of inflammation in COVID-19 patients contributes to resolution of low LDL-c. In addition, LDL-c could be used as a complementary marker in septic patients for better risk stratification. Upcoming studies that determine to what extent resolution of inflammation or changes in lipid levels may impact short-to-long term metabolic disturbances and cardiovascular outcomes are warranted.

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Ethics of protocol

According to the Declaration of Helsinki, the local ethics committee approved this study.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.06.016.

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