Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Articles

Hypolipidemia is associated with the severity of COVID-19

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KEYWORDS:
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Cholesterol

BACKGROUND: Many patients with coronavirus disease 2019 (COVID-19) suffer multiple organ dysfunctions. However, whether patients develop dyslipidemia is unknown.

OBJECTIVE: In this study, we aimed to investigate the pathological alterations of low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and total cholesterol (TC) in COVID-19 patients and their relationships with the disease severity.

METHODS: A retrospective study was performed to examine serum levels of LDL-c, HDL-c, and TC on 597 COVID-19 patients (mild: 394; severe, 171; critical: 32) who were hospitalized in our center between February 1 and March 3, 2020. Age- and gender-matched normal subjects (n = 50) who had routine laboratory lipid tests between October 1 and November 1, 2019 in our center were included as the control group.

RESULTS: LDL-c and TC levels were significantly lower in COVID-19 patients as compared with normal subjects ($P < .001$). There were significant and gradual decreases in levels of LDL-c (median (IQR) in mg/dL, mild: 91 (76, 104); severe: 86 (69, 102); critical: 69 (48, 81); $P < .02$) and TC (mild: 173 (148, 203); severe: 167 (138, 197); critical: 125 (95, 162); $P < .05$) across all three groups. HDL-c levels only decreased significantly in critical cases as compared with levels in mild and severe cases. LDL-c and TC levels inversely correlated with C-reactive protein and interleukin-6, and positively correlated with the number of lymphocytes in patients.

CONCLUSIONS: Development of hypolipidemia begins in patients with mild symptoms. It progressively becomes worse in an association with the disease severity.

Conflict of interest: The authors do not have any professional and financial affiliations that may be perceived to have biased the presentation.

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Introduction

The pandemic of coronavirus disease 2019 (COVID-19) has become a big threat to global public health system.[1] The disease is believed to be of zoonotic origin.[2,3] Snakes, pangolins, and turtles are speculated to be intermediate host(s).[4] Since the middle of December 2019, person-to-person transmission of COVID-19 has been evident, becoming a strong propagating force driving the spread of virus.[5] The estimated basic reproduction rate (R0) ranges from 2.24 to 3.58.[6] Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is the causative organism for COVID-19.[7] The SARS-COV2 spike (S) protein, composed of subunits S1 and S2, is considered for the virus entering host cells via surface angiotensin-converting enzyme 2 (ACE2).[8,9] The S2 subunits of SARS-COV-2 and SARS-COV are highly conserved with 99% identity; the S1 subunit of SARS-COV-2 has an approximate 70% identity with SARS-COV, but conserves a receptor-binding domain similar to that of SARS-COV, which may result in a high affinity to ACE2.[10,11] COVID-19 patients can be asymptomatic or symptomatic. The incubation period for symptomatic development in COVID-19 is approximately 4 to 7 days.[5] Many patients with coronavirus disease 2019 (COVID-19) suffer multiple organ dysfunctions, suggesting a systemic targeting by the SARS-COV-2. The mortality rate of COVID-19 is estimated to be about 2.3%, with a range from 6 to 41 days from the onset of symptoms to death.[10,11]

The dyslipidemia associated with SARS has been reported, although rarely. There was a report showing a lower level of total cholesterol (TC) in SARS patients as compared with healthy subjects.[12] Altered lipid metabolism was reported in recovered SARS patients 12 years after infection.[13] These reports indicate that patients with coronavirus-related diseases may develop dyslipidemia but have been underrated. We posit that dyslipidemia may occur in COVID-19 patients. In this study, we performed a retrospective investigation of lipid profiles on patients with COVID-19. We found that COVID-19 patients showed hypolipidemia, which positively correlated with the severity of disease.

Methods

Study design and patients

This retrospective study was carried out at the Cancer Center, Union Hospital of Tongji Medical College, Wuhan, and was approved by the Institutional Review Board at the Union Hospital. The requirement for informed consent was waved by the Institutional Review Board committee. A total of 597 COVID-19 patients admitted to the hospital between February 1 and March 3, 2020, were included in this study. Electronic data regarding epidemiological, demographic, clinical symptoms and diagnosis, laboratory tests, and treatments were extracted. All patients were tested SARS-COV-2 positive on nasopharyngeal swabs using a real-time reverse transcription polymerase chain reaction.[11] Pneumonia was diagnosed according to the guidelines from Chinese Thoracic Society and Chinese Medicine Association. Based on the severity of symptoms and Chinese Center for Disease Control guidelines, COVID-19 can be classified into three categories.[1,2,11] Detailed clinical diagnostic criteria and guideline are listed in Table 1. Patients were classified into three severity categories by two independent physicians based on their symptoms on admission, for example, mild (n = 394), severe (n = 171), and critical (n = 32) cases. Any disagreements were subjected to adjudications from a third independent physician. Age- and gender-matched normal healthy subjects (n = 50, age: 62 (53, 69)) who had routine laboratory lipid tests between October 1 and November 1, 2019, in our center were included in this study as the control group. De-identified electronic data including only age, gender, and values of lipid profiles were extracted. One additional data set from normal subjects (n = 1574, age: 40 (32, 52)) representing adult population of Wuhan with lipid tests in 2019 at our hospital was also extracted. A CONSORT flow diagram is shown in Figure 1.

Clinical laboratory tests

All tests were carried out at our certified clinical laboratory under standard procedures and practices that fully complied with regulations and guidelines of the Chinese Food and Drug Administration and Center for Disease Control. White blood cells, lymphocyte, and monocyte counts were performed on Beckman LH750 analyzer using manufacture's reagents (Beckman Coulter, Brea, CA). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), TC, and triglycerides were tested on Beckman AU5800 chemistry analyzer using manufacture's reagents (Beckman Coulter, Brea, CA). Methodology for direct LDL-c, HDL-c, and TC methods is a standard homogeneous assay from Beckman Coulter (Cat# OSR6283, OSR6587, and OSR6616). Interleukin-6 (IL-6) was tested on Abbott i2000 using manufacture's chemiluminescent immunoassay reagents (Abbott, Chicago, IL). T cell subpopulations were analyzed using Beckman FC500 flow cytometry and manufacture's reagents (Beckman Coulter, Brea, CA). C-reactive protein (CRP) was performed using the BC-5390 reagent (MINDRAY, Shenzhen, Guangzhou, China). The clinical laboratory data included in this study were from the blood samples drawn fasting on admission.

Statistical analysis

Statistical analyses were performed with the SPSS software (IBM, Armonk, NY). Data were presented as

Table 1 Demographic and clinical characteristics of COVID-19 patients

Characteristics	Normal subjects	COVID-19 patients			
Category (N)	50	Mild (394)	Severe (171)	Critical (32)	*P*
Age, y	62 (53, 69)	64 (53, 69)	69 (64, 77)	69 (61, 83)	<.05
Male	27 (54%)	189 (48%)	100 (58%)	16 (50%)	
Female	23 (46%)	215 (52%)	71 (42%)	16 (50%)	
Clinical diagnostic criteria[1,2,11]		Onset of symptoms: fever, cough, fatigue, headache, diarrhea, and so forth, with or without mild pneumonia	Dyspnea, acute respiratory stress, decrease in blood oxygen saturation, lung infiltrates, multiple peripheral ground-glass opacities on both lungs	Respiratory or multiple organ failure and septic shock	
Comorbidities					
2-DM		48 (12%)	20 (12%)	6 (19%)	n.s.
Hypertension		96 (24%)	74 (43%)	10 (31%)	<.01
CVD		15 (4%)	21 (12%)	6 (19%)	<.05
Onset symptoms					
Fever		234 (59%)	91 (53%)	29 (90%)	
Cough		143 (36%)	59 (35%)	26 (80%)	
Fatigue		52 (13%)	14 (8%)	14 (44%)	
Shortness of breath		5 (1%)	26 (15%)	21 (70%)	
Diarrhea		8 (2%)	5 (3%)	0 (0%)	
Life-support treatment					
Oxygen		173 (44%)	164 (96%)	32 (100%)	
Ventilation		0 (0)	0 (0)	17 (53%)	
HLOS (d)		14 (9, 21)	26 (17, 29)	36 (30, 42)	<.05

CVD, cardiovascular disease; 2-DM, type 2 diabetes mellitus; HLOS, hospital length of stay.
Data were median (IQR) or n (%). n.s., no significance.

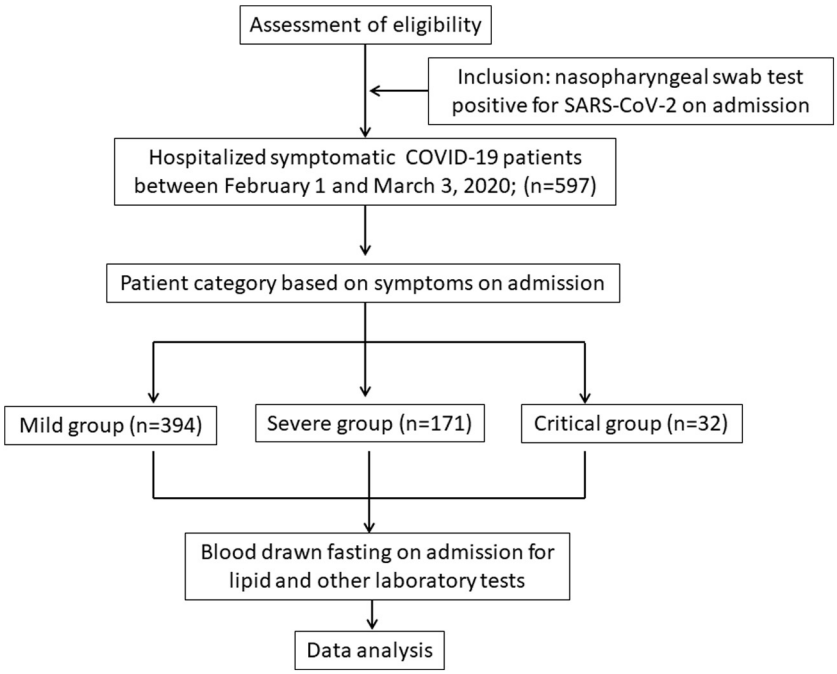

Figure 1 A CONSORT flow diagram for inclusion of the COVID-19 patients in this study.

median (interquartile range, IQR), or "median ± 95% confidence interval (CI)". Kruskal-Wallis test was used to compare variables among multiple groups and a Mann-Whitney *U*-test was used to compare differences between two groups. A Pearson correlation analysis was used to calculate the correlation coefficient. $P < .05$ was considered as statistical significance.

Results

Demographic and clinical characteristics of COVID-19 patients

A total of 597 COVID-19 cases were included in this study: 394 mild, 171 severe, and 32 critical cases. The age for all patients was 66 (59, 72) (median (IQR)) years. The ages for the critical and severe cases were 69 (61, 83) and 69 (64, 77), respectively; the patients in these groups were significantly older than those with mild cases (64 (53, 69)) ($P < .05$) (Table 1). Male cases represented 51% (n = 305) and female cases 49% (n = 292) of the sample. There were more female patients than male patients in the mild group (52% vs 48%). The main onset symptoms included fever, cough, fatigue, and shortness of breath, which occurred in 59%, 38%, 13%, and 9% of total patients, respectively (Table 1). Thirteen patients did not survive with a fatality rate of 2.2%. The ratios of comorbidities, life-support treatments, and hospital length of stay among patients in each category were listed in Table 1. The age- and gender-matched normal control subjects had a median age of 62 years with 54% male and 46% female, which was not significant as compared with the COVID-19 patient group (Table 1, $P = .064$).

Clinical laboratory results showed that lymphocytes and $CD8^+$ T cell subpopulation decreased significantly in patients across all three categories (Table 2). Levels of white blood cells and CRP increased gradually and significantly during the disease progression (Table 2). IL-6 levels increased dramatically in all subgroups of patients with a peak in severe cases (Table 2). Changes in number of monocytes and levels of ALT, AST, ALP, and gamma-glutamyl transferase were not in evidence (Table 2).

Serum hypolipidemia in COVID-19 patients

LDL-c, HDL-c, and TC levels were significantly lower in COVID-19 patients as compared with the levels in normal subjects (median (IQR) in mg/dL; LDL-c, 88 (74, 102) vs 110 (96, 147), $P < .001$; HDL-c, 49 (41, 58) vs 52 (40, 65), $P < .05$; TC, 169 (143, 199) vs 184 (166, 221); $P < .001$). There were significant and gradual decreases in levels of LDL-c ($P < .02$) and TC ($P < .05$) in patients across all three categories (Fig. 2, Table 2). HDL-c levels decreased significantly in critical cases as compared with levels in mild and severe cases ($P < .05$) (Fig. 2, Table 2). Triglycerides levels in COVID-19 patients were significantly higher than the levels in normal subjects ($P < .01$), but significantly decreased in critical cases as compared with mild and severe cases ($P < .01$, Table 2). The age- and gender-matched normal control group (n = 50; age: 62 (53, 69)) showed almost the same median values of LDL-c, HDL-c, and TC, but slightly narrow

Table 2 Main clinical laboratory profiles of COVID-19 patients

Laboratory testing	Reference ranges	COVID-19 patients			*P*
		Mild (394)	Severe (171)	Critical (32)	
LDL-c	*110 (96, 147) mg/dL	91 (76, 104)	86 (69, 102)	69 (48, 81)	<.02
HDL-c	*52 (40, 65) mg/dL	50 (42, 59)	50 (41, 59)	36 (29, 43)	<.05
TC	*184 (166, 221) mg/dL	173 (148, 203)	167 (138, 197)	125 (95, 162)	<.05
TG	*111 (86, 176) mg/dL	150 (124, 213)	142 (89, 189)	115 (88, 186)	<.01
WBC	3.5–9.5 ($\times 10^9$/L)	5.5 (4.5, 6.5)	5.6 (4.5, 7.5)	7.5 (4.7, 12.6)	<.001
LY	*2.1 (1.7, 2.5) ($\times 10^9$/L)	1.5 (1.1, 1.8)	1.3 (0.9, 1.8)	0.8 (0.4, 1.3)	<.001
MO	0.1–0.6 ($\times 10^9$/L)	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)	0.6 (0.3, 0.8)	n.s.
IL-6	0.1–2.9 pg/mL	12.8 (5.2, 33.0)	27.9 (8.6, 80.1)	18.6 (11.0, 37.9)	<.05
$CD3^+$ T	58–84 (%)	78 (69, 83)	74 (66, 79)	70 (65, 80)	<.05
$CD4^+$ T	25–51 (%)	49 (43, 55)	44 (35, 53)	58 (31, 63)	<.05
$CD8^+$ T	14–39 (%)	24 (20, 30)	23 (18, 30)	13 (5, 17)	<.001
CD4/CD8	0.41–2.72	2.0 (1.7, 2.6)	2.0 (1.5, 2.8)	7.9 (3.2, 11.2)	<.001
ALT	5–35 U/L	32 (21, 52)	32 (20, 51)	37 (15, 48)	n.s.
AST	8–40 U/L	27 (22, 36)	28 (21, 40)	33 (23, 45)	n.s.
ALP	40–150 U/L	87 (73, 104)	88 (71, 106)	88 (78, 116)	n.s.
GGT	7–32 U/L	29 (19, 42)	31 (18, 56)	31 (20, 68)	n.s.
CRP	<4 mg/L	3.1 (1.3, 6.6)	5.1 (1.6, 25.3)	27 (6.8, 105.1)	<.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c; low-density lipoprotein cholesterol; WBC, white blood cells; LY, lymphocyte; MO, monocyte; TC, total cholesterol; TG, triglycerides; IL-6, interleukin-6; n.s., no significance.

*Data were measured from the age and gender-matched normal subjects (n = 50). Kruskal-Wallis test was used to compare variables among groups (mild, severe and critical).

IQRs, as compared with that from adult healthy population (n = 1574, age: 40 (32, 52)) (Fig. 2).

Relationships of lymphocyte, CRP, and IL-6 with LDL-c

CRP levels inversely correlated with the levels of LDL-c (R = −0.290, $P < .001$, Fig. 3A), TC (R = −0.332, $P < .001$, Fig. 3B), and HDL-c (R = −0.351, $P < .001$, Fig. 3C). The number of lymphocytes positively correlated with the levels of LDL-c (R = 0.236, $P < .001$, Fig. 3D), TC (R = 0.277, $P < .001$, Fig. 3E), and HDL-c (R = 0.158, $P < .001$, Fig. 3F) in COVID-19 patients. The IL-6 levels showed an inverse correlation with LDL-c (R = −0.176, $P = .032$, Fig. 3G) and TC (R = 0.170, $P = .038$, Fig. 3H), but no significant association with HDL-c.

Discussion

In this study, we performed a retrospective analysis of lipid profiles on COVID-19 patients. This is the first report with clinical laboratory lipid data on such a large patient population. Our data demonstrate that patients with COVID-19 develop hypolipidemia as early as when they have mild symptoms. The reduced levels of LDL-c positively correlate with levels of CRP, and inversely correlate with lymphocytic numbers and IL-6 levels. These are three critical factors associated with the disease severity in patients. Our findings provide the first insight into a pathological evolution of lipidology in COVID-19 in patients; this will not only aid in understanding the mechanism of disease's dyslipidemia, but will also help in assessing progression of and prognosis of the disease.

So far, there is no consensus regarding the value of serum TC to define hypolipidemia.[14] In this study, we use the mean of TC (174 mg/dL) from the normal control subjects as the cutoff value to describe this condition in COVID-19 patients. This will provide a direct comparison of lipid levels in COVID-19 patients to the normal subjects with age and gender matched. Furthermore, some reports have used high levels up to 189 mg/dL to define hypolipidemia.[15,16] Hypolipidemia is a rare condition and it can be caused by a genetic alteration or secondary factors. In this study, the decreased levels of lipids are most likely a result from complicated biological and pathological processes caused by SARS-COV-2 infection. Our current data show that a reduction of lipid levels in patients with COVID-19 has an association with the severity of the symptoms. Therefore, the hypolipidemia in COVID-19 patients shall raise an urgent awareness to physicians who are now in the frontline fighting against this pandemic.

Inflammation caused by viral infection may result in dyslipidemia in patients. For example, patients with HIV have altered lipid profiles, such as a decrease in HDL-c and an increase in LDL-c levels[17,18]; patients infected with dengue virus may show a decrease in serum LDL-c levels[19]; and hepatitis B patients in the cirrhosis phase

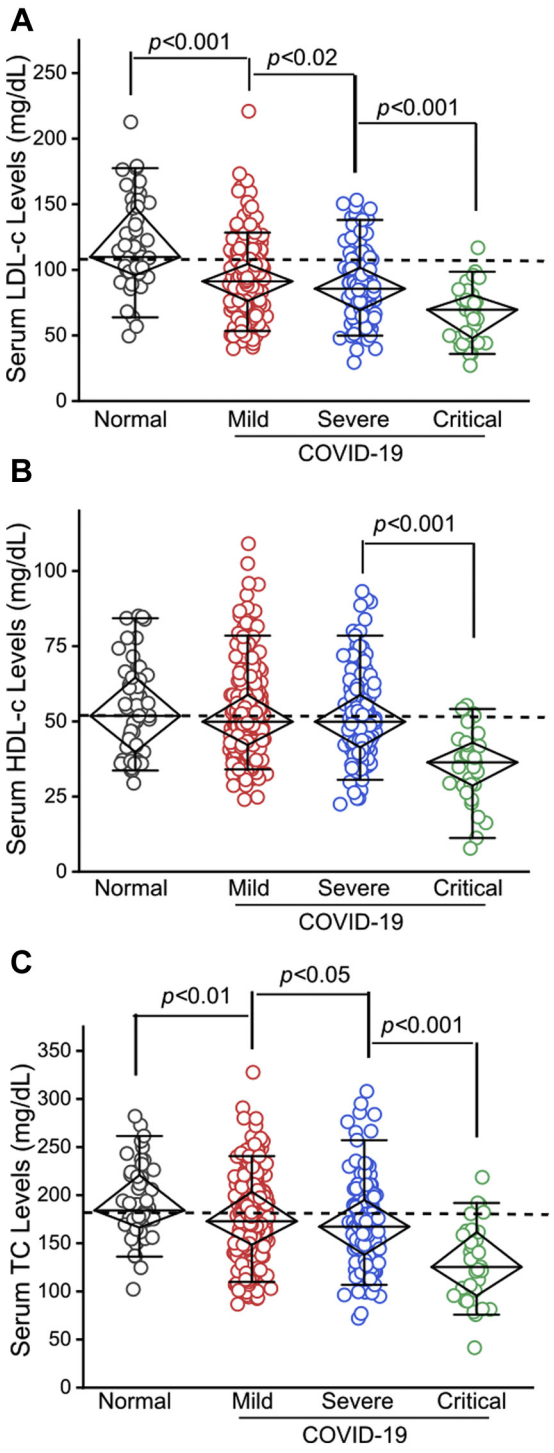

Figure 2 COVID-19 patients show hypolipidemia. Serum LDL-c (A), HDL-c (B), and TC (C) levels are presented from COVID-19 patients in normal subjects (n = 50, age- and gender-matched, Table 1) and patients with mild (n = 394), severe (n = 171), or critical (n = 32) COVID-19, respectively. Whiskers are presented as median ± 95% (CI) with the diamond boxed range of IQR in the plots. A Mann-Whitney *U*-test was used to compare differences between two groups. The dotted lines indicate the median values of LDL-c (109 (92, 128)), HDL-c (52 (41, 65)) and TC (182 (158, 206)) that were measured from normal adult population in Wuhan city, Hubei province (n = 1574, age: 40 (32, 52)), in 2019 at our hospital. HDL-c, high-density lipoprotein cholesterol; LDL-c; low-density lipoprotein cholesterol; TC, total cholesterol.

have lower levels of HDL-c and LDL-c.[20] In this study, we found decreased levels of LDL-c in patients. There are several possible explanations for this dyslipidemia. First, SARS-COV-2 may damage liver function and thereby reduce LDL-c biosynthesis. Serum levels of ALT, AST, and ALP increased moderately in about half of all patients, indicating mild liver-function damage. Therefore, changes in liver function are most likely not the major contributor to the reduced LDL-c levels. Second, acute inflammation induced by SARS-COV-2 alters lipid metabolism. It has been reported that proinflammatory cytokines such as TNF-α, IL-6, and IL-1β modulate lipid metabolism by altering liver function and diminishing cholesterol efflux and transport.[21] We found that IL-6 was dramatically elevated in 96% of all patients. This strongly suggests that proinflammatory cytokines such as IL-6 are a major contributor to the lipid abnormality in patients. Third, lipids are highly vulnerable to degradation by free radicals, whose levels are generally elevated in host cells with a viral infection.[22] A measurement of oxidized LDL-c in patient's serum will be needed to determine this possibility. Fourth, SARS-COV-2 infection may alter vascular permeability, causing a leakage of cholesterol molecules into tissues, such as alveolar spaces, to form exudate. For example, exudates are observed in the early phase of COVID-19 lung pathology.[23] Intra-alveolar exudates have been found in lung autopsies from SARS patients as well as in cynomolgus macaques infected with SARS-COV.[24–26] Exudative fluids, containing high levels of protein (>2.9 g/dL) and cholesterol (>45 mg/dL), are caused by inflammation-related vascular permeability.[27,28] Therefore, one possible mechanism underlying our data is that during the disease progression, severer inflammation and worse vascular permeability are, more plasma cholesterol and lipids leak into alveolar space, and less LDL-c and cholesterol remain in the plasma. We also posit that the dyslipidemia plays an important role in pathological development of COVID-19, which mechanism needs an urgent investigation.

There are several limitations of this study. First, the time from the onset of symptoms to the time of serum sample collection when patients were admitted to the hospital was varying among patients. Therefore, the data might represent heterogeneous stages of the disease course. Second, many patients might had been treated with various remedies at home, such as Chinese traditional medicine, before on admission. Whether and how these factors interfered with our data are unknown. Third, in a small cohort study, we have shown that LDL-c levels can be a predictor for disease progression.[29] However, monitoring the dynamics of lipid profiles before and during the entire disease course in a large cohort of COVID-19 patients will be needed for better characterization of this hypolipidemia, which will be our future research goal.

Collectively, our data demonstrate that the development of hypolipidemia can start in patients with mild symptoms. The degree of hypolipidemia positively correlates with the disease severity.

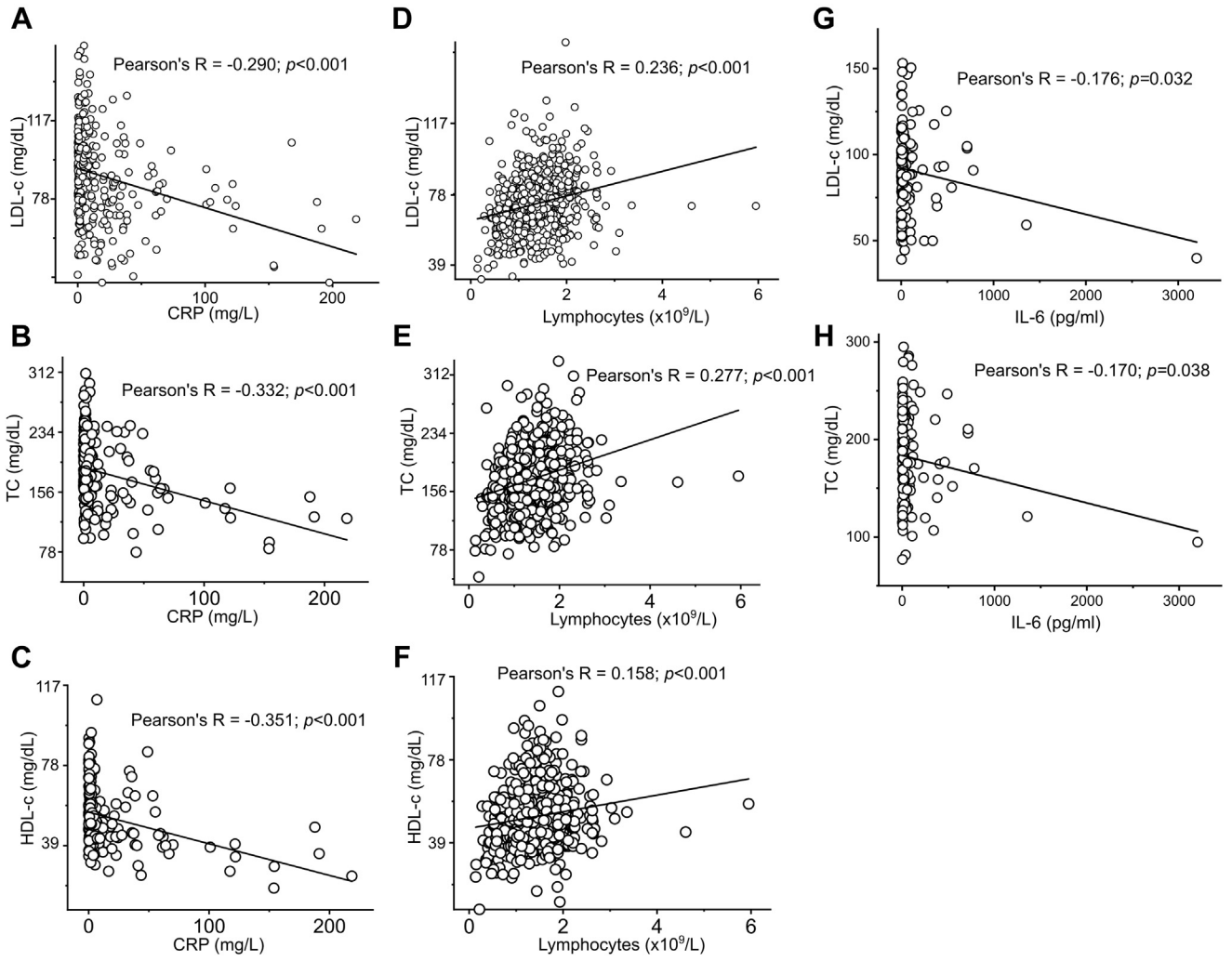

Figure 3 Correlations of CRP levels (A–C), lymphocytic numbers (D–F), or IL-6 levels (G, H) and levels of LDL-c, TC, or HDL-c in COVID-19 patients. A Pearson correlation analysis was used. CRP, C-reactive protein; HDL-c, high-density lipoprotein cholesterol; LDL-c; low-density lipoprotein cholesterol; IL-6, interleukin-6; TC, total cholesterol.

Acknowledgments

Authors' contributions: HW and WT supervised and designed the study. WX, JS, YL, JW, and HW performed the tests and collected the data. WX, JS, and XC contributed to the data analysis. HW and WT contributed to the manuscript writing and data interpretation.

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