Low high-density lipoprotein level is correlated with the severity of COVID-19 patients

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Research

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Abstract

Background

The aim of the present study was to describe the clinical characteristics of patients with different levels of high-density lipoproteins (HDLs) and analyze the correlation between HDL levels and prognosis of coronavirus disease 2019 (COVID-19) patients.

Methods

In the clinical retrospective analysis, a total of 228 adult COVID-19 patients admitted to Public Health Treatment Center of Changsha, China from January 17 to March 14, 2020 were enrolled. Median with interquartile range and Mann-Whitney test were used to depict and analyze the clinical characteristics of patients. The Kaplan-Meier (KM) curve and cox regression were adopted to analyze the association between HDLs and severe events of COVID-19 patients.

Results

Median levels of high-density lipoprotein cholesterol (HDL-C) in adult COVID-19 patients were below normal range. Compared with patients with high HDL-C, patients with low HDL-C showed higher proportion of male (69.6% vs 45.6%, $P = 0.004$), higher levels of C-reactive protein (CRP) (median, 27.83 vs 12.56 mg/L, $P = 0.000$) and alanine aminotransferase (ALT) (median, 21.49 vs 18.81 U/L, $P = 0.044$), as well as higher proportion of severe events (37.0% vs 14.8%, $P = 0.001$). Moreover, they presented a higher risk of developing severe events compared with those with high HDL-C (Log Rank $P < 0.001$, Fig. 1). After adjusting for age, gender and underlying diseases, patients with low HDL-C still had elevated possibility of developing to severe cases than those with high HDL-C (HR 2.852, 95% CI 1.505–5.407, $P = 0.001$).

Conclusions

HDL-C level decreased in COVID-19 adult patients, and low HDL-C in COVID-19 patients was correlated with a higher risk of developing severe events.

Background

The emergence of coronavirus disease 2019 (COVID-19), which was first reported in Wuhan in December 2019 [1, 2, 3, 4, 5], has led to global spread [6, 7]. As of May 6, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 3 million people, and caused more than 200,000 deaths worldwide [8]. Although we have a certain understanding of the characteristics of the disease, the effects of the virus on function and metabolism of human beings remain largely unknown.

High-density lipoproteins (HDLs) are mainly synthesized in the liver and can transport cholesterol from extrahepatic tissues to the liver for metabolism. Although the primary role of HDL is anti-atherosclerosis, many recent studies found other multiple characteristics of HDL, including anti-infection, anti-inflammatory, anti-apoptotic or antioxidant functions [9, 10, 11]. Moreover, HDLs is believed to play a protective role in many infectious diseases. Patients with low levels of HDLs showed an increased risk of infection [12, 13, 14] and a worse outcome [15, 16, 17]. However, lipoprotein levels and the effect of HDLs on prognosis of COVID-19 patients remain unclear. In this study, we presented the clinical characteristics of adult COVID-19 patients with different high-density lipoprotein cholesterol (HDL-C) levels and analyzed the correlation between HDL levels and the risk for developing severe events.

Methods

Study design

All laboratory-confirmed adult COVID-19 patients admitted to Public Health Treatment Center of Changsha, China on admission from January 17 to March 15, 2020, who tested for blood lipid levels were enrolled.

Data Collection

Two of our team carefully collected and reviewed the medical records of enrolled patients, individually. The detailed information on demographic data, underlying comorbidities, symptoms before and during admission, first laboratory and chest computed tomographic (CT) scans results after admission, virus shedding time, length of hospital stay, mortality and severity of illness were recorded.

Definition And Study Endpoints

Criteria for severe cases were developed with reference to relevant guidelines [18] and were consistent with our previous studies [19]. Patients were given severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid tests at least 2 times consecutively after remission of symptom (sampling time interval is more than 1 day), while two consecutive negative results are considered virus cleared [18]; virus shedding duration is defined as the time between symptom onset (the date of diagnosis for asymptomatic cases) and the first negative samples without any positive sample thereafter.

Statistical analysis

We used median with interquartile range to depict all continuous variables, and used Mann-Whitney test to analyze all continuous variables. The $\chi 2$ test or Fisher's exact test was utilized to analyze the categorical variables. The Kaplan-Meier (KM) curve and the Log Rank test were adopted to determine the

correlation between HDLs and the risk for developing severe cases. Multivariate analysis was performed using the cox regression model. All analyses were performed using IBM SPSS version 26 software.

Results

All 228 adult patients diagnosed as COVID-19 by March 15, 2020 and tested for blood lipid levels were included in this study. Regarding the lipoprotein profile, the median level of total cholesterol, triglyceride and low-density lipoprotein cholesterol (LDL-C) were all in the normal range, while only the median level of HDL-C was below normal range [median (IQR), 0.78 (0.66–0.97) mmol/L]. Compared with non-severe patients, severe patients presented lower level of HDL-C (Table 1). Therefore, we further analyzed the effect of HDL-C level on COVID-19.

Table 1
Blood lipid levels of adult COVID-19 patients

	Normal range	**All patients (n = 228)**	**Severe (n = 44)**	**Non-severe (n = 184)**	***P* value**
Total cholesterol, median (IQR), mmol/L	2.33–5.69	3.76 (3.22–4.26)	3.63 (3.04–4.15)	3.81 (3.24–4.34)	0.082
Triglyceride, median (IQR), mmol/L	0.25–1.71	1.08 (0.78–1.44)	1.08 (0.76–1.36)	1.09 (0.79–1.47)	0.382
HDL-C, median (IQR), mmol/L	0.90–1.94	0.78 (0.66–0.97)	0.69 (0.59–0.95)	0.79 (0.69–0.97)	**0.032**
LDL-C, median (IQR), mmol/L	0.60–4.14	2.63 (2.21–3.09)	2.60 (2.19–2.95)	2.65 (2.22–3.10)	0.233
P < 0.05 was considered statistically significant.					
COVID-19: coronavirus disease 2019; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; IQR, Inter-Quartile Range.					

Clinical characteristics of adult COVID-19 patients with different levels of HDL-C were summarized in Table 2. Low HDL-C is defined as below 0.65 mmol/L (25 mg/dl), while high HDL-C is defined as above or equal to 0.65 mmol/L based on previous studies [16, 20]. There were no significant differences in age and underlying diseases between patients with high and low level of HDL-C. Compared with patients with high HDL-C, patients with low HDL-C showed higher proportion of male (69.6% vs 45.6%, $P = 0.004$), lower proportion of headache (2.2% vs 16.5%, $P = 0.011$) and nausea (4.3% vs 15.4%, $P = 0.048$) (Table 2). They also showed higher levels of C-reactive protein (CRP) (median, 27.83 vs 12.56 mg/L, $P = 0.000$) and alanine aminotransferase (ALT) (median, 21.49 vs 18.81 U/L, $P = 0.044$) (Table 3).

Table 2
Baseline Characteristics of COVID-19 patients with different levels of HDL-C

	Low HDL-C (n = 46)	High HDL-C (n = 182)	*P* value
Sex (male/female)	32/14	83/99	**0.004**
Age, median (IQR), y	46.0 (37.8–59.0)	45.0 (35.0–61.0)	0.795
Comorbidity			
Hypertension (n, %)	9 (19.6)	27 (14.8)	0.432
Cardiovascular disease (n, %)	1 (2.2)	8 (4.4)	0.789
Diabetes (n, %)	5 (10.9)	10 (5.5)	0.327
Chronic liver disease (n, %)	5 (10.9)	7 (3.8)	0.124
Symptoms			
Fever (n, %)	38 (82.6)	135 (74.2)	0.232
Pharyngalgia (n, %)	5 (10.9)	29 (15.9)	0.389
Cough (n, %)	41 (89.1)	146 (80.2)	0.160
Expectoration (n, %)	24 (52.2)	81 (44.5)	0.351
Dyspnea (n, %)	20 (43.5)	60 (33.0)	0.182
Hemoptysis (n, %)	3 (6.5)	4 (2.2)	0.298
Chills (n, %)	5 (10.9)	24 (13.2)	0.673
Myalgia (n, %)	6 (13.0)	18 (9.9)	0.724
Fatigue (n, %)	24 (52.2)	82 (45.1)	0.387
Dizziness (n, %)	3 (6.5)	26 (14.3)	0.158
Headache (n, %)	1 (2.2)	30 (16.5)	**0.011**
Diarrhea (n, %)	11 (23.9)	41 (22.5)	0.841
Nausea (n, %)	2 (4.3)	28 (15.4)	**0.048**
Anorexia (n, %)	26 (56.5)	88 (48.4)	0.322

P < 0.05 was considered statistically significant.

COVID-19: coronavirus disease 2019; HDL-C: high density lipoprotein cholesterol; IQR, Inter-Quartile Range.

	Low HDL-C (n = 46)	High HDL-C (n = 182)	*P* value
Vomiting (n, %)	4 (8.7)	21 (11.5)	0.581
Abdominal pain (n, %)	1 (2.2)	6 (3.3)	1.000
Chest CT positive rate (n, %)	46 (100.0)	172 (94.5)	0.221
Chest CT with ground-glass change (n, %)	20 (43.5)	88 (48.4)	0.554
Severe cases (n, %)	17 (37.0)	27 (14.8)	**0.001**
Length of hospital stay, median (IQR), days	13.0 (11.0-22.5)	16.0 (11.0–25.0)	0.712
Virus shedding duration, median (IQR), days	17.0 (13.5–24.0)	18.0 (13.0–26.0)	0.269
Mortality (n, %)	1 (2.2)	1 (0.5)	0.364
$P < 0.05$ was considered statistically significant.			
COVID-19: coronavirus disease 2019; HDL-C: high density lipoprotein cholesterol; IQR, Inter-Quartile Range.			

Table 3
Laboratory findings of adult COVID-19 patients with different levels of HDL-C

	Normal range	Low HDL (n = 46)	High HDL (n = 182)	*P* value
White blood cell count, $x10^9$/L, medium (IQR)	4–10	4.78 (3.82–6.13)	4.58 (3.52–5.66)	0.627
Lymphocyte count, $x10^9$/L, medium (IQR)	0.8-4.0	1.02 (0.72–1.51)	1.17 (0.84–1.59)	0.207
Lymphocyte %, medium (IQR)	20–40	22.35 (17.58–30.10)	27.45 (20.05-33.00)	0.050
Alanine aminotransferase, U/L, medium (IQR)	0–42	21.49 (16.13–30.28)	18.81 (13.81–26.61)	**0.044**
Aspartate aminotransferase, U/L, medium (IQR)	0–37	25.87 (19.53–34.01)	23.76 (19.25–28.77)	0.109
Total bilirubin, μmol/L, medium (IQR)	3.4–20.5	11.16 (8.16–15.35)	10.87 (8.68–16.36)	0.769
C reactive protein, mg/L, medium (IQR)	0–8	27.83 (14.68–44.74)	12.56 (3.29–26.88)	**0.000**
Erythrocyte sedimentation rate, mm/h, medium (IQR)	0–15	52.00 (22.00-67.75)	39.50 (22.0-68.25)	0.538
Procalcitonin, ≥ 0.05 ng/mL, No. (%)	≤ 0.05	17 (37.0%)	46 (25.3%)	0.113
Creatinine, μmol/L, medium (IQR)	21.5–104	53.70 (43.61–65.02)	50.85 (41.22–64.02)	0.209
Creatine kinase, U/L, medium (IQR)	10–190	83.35 (57.05-148.63)	69.75 (46.30-114.45)	0.116

P < 0.05 was considered statistically significant.

COVID-19: coronavirus disease 2019; HDL-C: high density lipoprotein cholesterol; IQR, Inter-Quartile Range.

	Normal range	Low HDL (n = 46)	High HDL (n = 182)	*P* value
Creatine kinase-MB, U/L, medium (IQR)	0–24	9.35 (5.33–12.50)	9.57 (6.40-12.92)	0.624
P < 0.05 was considered statistically significant.				
COVID-19: coronavirus disease 2019; HDL-C: high density lipoprotein cholesterol; IQR, Inter-Quartile Range.				

In terms of outcome indicators, patients with low HDL-C showed higher proportion of severe cases (37.0% vs 14.8%, *P* = 0.001) (Table 2). However, there were no significant differences in mortality, length of hospital stays and virus shedding time between the two groups.

Moreover, patients with low HDL-C showed a higher risk of developing severe events compared with those with high HDL-C (Log Rank *P* < 0.001, Fig. 1). After adjusting for age, gender and underlying diseases, patients with low HDL-C still had elevated possibility of developing to severe cases than those with high HDL-C (HR 2.852, 95% CI 1.505–5.407, *P* = 0.001) (Table 4).

Table 4
Multivariate Cox regression analysis for severe events of adult COVID-19 patients

Variables	HR	95% CI	*P value*
Low HDL-C	2.852	1.505–5.407	**0.001**
Gender	1.346	0.715–2.533	0.357
Age	1.030	1.006–1.054	**0.014**
Hypertension	1.969	0.935–4.148	0.075
Cardiovascular disease	1.608	0.574–4.504	0.366
Diabetes	0.627	0.211–1.862	0.400
* means statistically significant.			
HR: Adjusted hazard ratios; COVID-19: coronavirus disease 2019; HDL-C: high density lipoprotein cholesterol.			

Discussion

This observational study first revealed the blood lipids status of adult COVID-19 patients, found that low HDL-C was associated with poor outcomes of adult COVID-19 patients, and provided a basis for HDL-C to predict COVID-19 prognosis and even become a potential therapeutic target for COVID-19.

In this study, HDL-C levels of adult COVID-19 patients were lower than normal at admission, which was similar to previous researches. Several studies showed infected patients, especially those with sepsis, always had a significant drop in HDL levels [10, 12, 15, 20, 21, 22], but the reason for the decline in HDL level remained unexplained. However, several hypotheses are considered to be possible, including a decrease in HDL synthesis, overconsumption or redistribution of HDL particles from intravascular to the extravascular space [10, 23].

Previous studies also showed septic patients with low HDL-C level showed higher mortality and other adverse clinical outcomes [15, 22]. Several studies have found significant increases in mortality in sepsis patients with an HDL level below 25 mg/dl (0.65 mmol/L) [16, 20], so we compared the clinical characteristics and prognosis of COVID-19 patients with an HDL level above and below 25 mg/dl (0.65 mmol/L). In this study, patients with low HDL-C level showed higher proportion of severe events, while further regression analysis also revealed that low HDL-C was an independent risk factor for severe events in COVID-19. Therefore, HDL-C may play a protective role in COVID-19, while COVID-19 patients with reduced HDL-C need to be given timely monitoring and treatment as soon as possible to improve the outcomes.

Excessive inflammation is one of the important features of COVID-19 patients, especially in severe and died patients [24, 25, 26, 27], usually manifested by a marked increase in inflammatory factors, such as CRP and interleukins [3, 28]. HDL-C is believed to have an inhibitory effect on inflammation [29, 30, 31]. In this study, patients with low HDL-C showed a higher level of CRP, which suggested that HDL-C may inhibit the inflammatory response and thus play a protective role in COVID-19 patients.

The protective effect of HDL-C in bacterial infection is relatively definite. Numerous studies have found that HDL-C can bind and neutralize the biological toxicity of lipopolysaccharide (LPS) and lipoteichoic acid (LTA) [32, 33, 34]. In different experimental septic models, infusion of reconstituted HDL reduced inflammation, decreased bacterial count, attenuated organ injury and improved survival [10, 35, 36], which greatly encouraged the application of HDL in sepsis treatment in the future. However, the role of HDL-C in viral infection remains unclear. We found in this study that HDL-C decreased in COVID-19 patients, and HDL-C level was negatively correlated with severity of illness, which suggests that HDL-C may be a potential therapeutic target for COVID-19, but the specific mechanism is still unclear, and further research is still needed.

Our study has some limitations. First, we cannot obtain the basic HDL-C data before symptom onset, so it is uncertain whether the decrease in HDL-C level occurred after infection with SAR-CoV-2. Second, previous studies showed that HDLs decrease significantly in the early stage of sepsis, but the time from the symptom onset to the detection of HDLs is different, which may cause some bias in the analysis of the relationship between HDLs and COVID-19. Third, we have not got the HDL-C data on the recovery period, and the correlation between the dynamic changes of HDL-C and the outcome of COVID-19 may be more valuable.

Conclusion

In summary, we presented for the first time the blood lipid status of COVID-19 patients. We found low HDL-C was associated with higher proportion of severe events in COVID-19. Moreover, low HDL-C seemed to be an independent risk factor for developing severe events.

Declarations

Ethics approval and consent to participate

This case series was subject to approval by the institutional ethics board of the second Xiangya Hospital of Central South University (No. 2020001).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Public Health Treatment Center of Changsha but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Public Health Treatment Center of Changsha.

Competing interests

All authors had no conflict of interest.

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Authors' contributions

GW was involved in study design, interpreting data, creating tables and figures, and writing of the manuscript. YZ was involved in interpreting data, statistical analysis, and designed the research, supervised the work. QZ, HD, CW, FW, BY, JL, SW, YW, GW and SZ were all involved in data collection, data interpretation and critical revisions of the manuscript.

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Figures

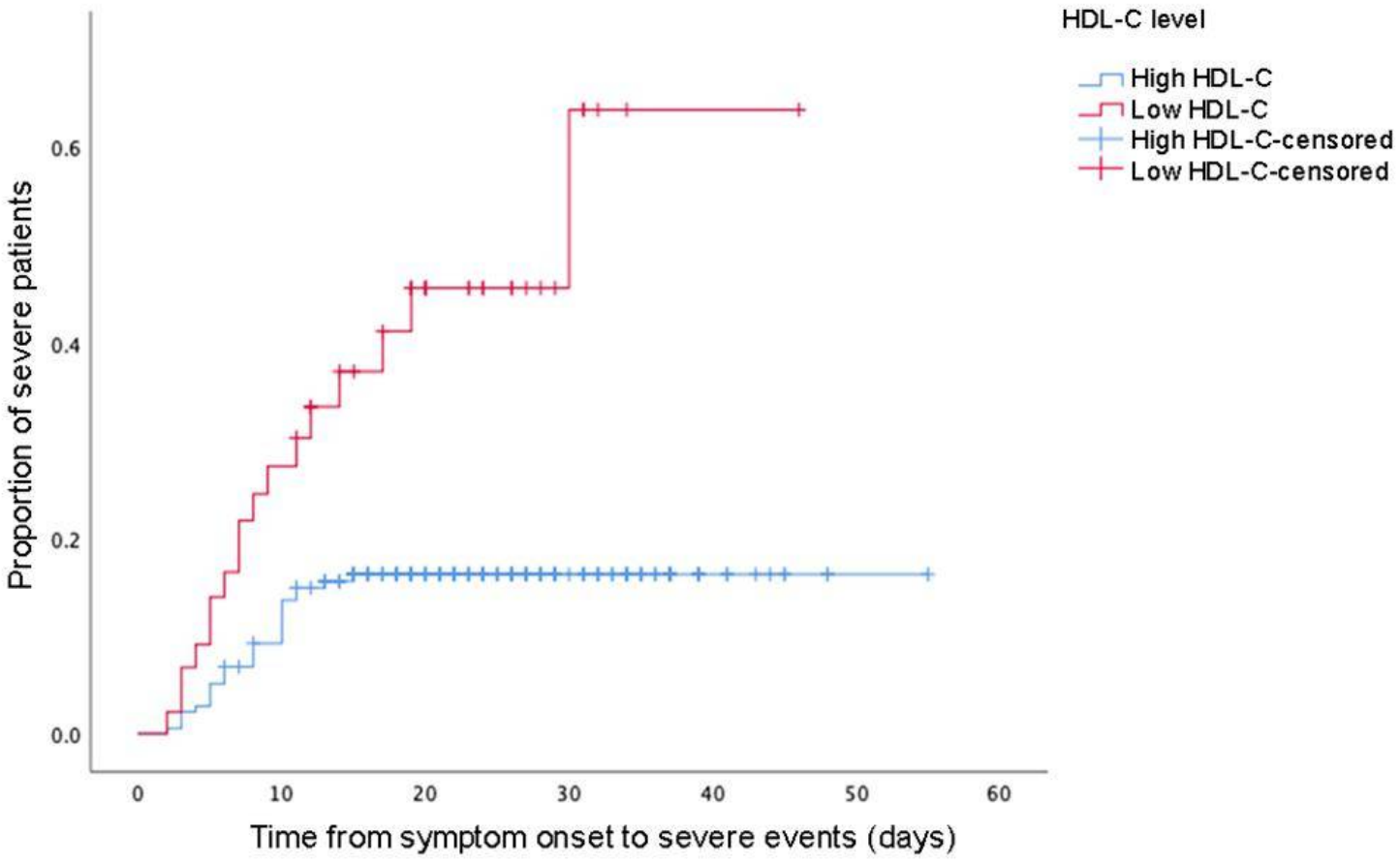

Figure 1

The time-dependent risk of developing severe event in COVID-19 patients with low and high levels of HDL-C using Kaplan-Meier curve. Abbreviations: COVID-19: coronavirus disease 2019; HDL-C: high-density lipoprotein cholesterol.