Changes in lipid metabolism in patients with severe COVID-19

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Research

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Abstract

Background: Dyslipidemia plays an important role in the pathogenesis and evolution of critical illness, but limited information exists regarding the lipid metabolism of severe coronavirus disease 2019 (COVID-19) patients. The aim of this study was to investigate role of dyslipidemia in patients with severe COVID-19

Methods: We retrospectively reviewed 216 severe COVID-19 patients with clarified outcomes (discharged or deceased), admitted to the West Court of Union Hospital in Wuhan, China, between February 1 and March 31, 2020. The dynamic changes of lipid profiles and their relationships with disease severity and clinical outcomes were analyzed.

Results: A total of 216 severe COVID-19 patients, including 24 non-survivors and 192 survivors, were included in the final analyses. The levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (Apo-AI) on admission were significantly lower in non-survivors compared to survivors. During hospitalization, low-density lipoprotein cholesterol (LDL-C), total cholesterol(TC), HDL-C and Apo-AI were shown an increasing trend in survivors, but maintained lower levels or shown downward trend in non-survivors. The serum levels of HDL-C and Apo-AI were inversely correlated with C-reactive protein (CRP), length of hospital stay of survivors and disease severity. The receiver operating characteristic (ROC) curve analysis identified a CRP/ HDL-C ratio cut-off value of 62.54 as the predictor for in-hospital mortality (AUC=0.823, Sensitivity=83.3%, Specificity=70.8%). Logistic regression analysis demonstrated that hypertension, neutrophils-to-lymphocytes ratio(NLR), platelet count and high CRP/ HDL-C ratio (>62.54) were independent factors to predict in-hospital mortality.

Conclusions: The results demonstrated that dyslipidemia was associated with the inflammatory response, disease severity and poor prognosis of COVID-19. High CRP/ HDL-C ratio may serve as an independently potential predictor for hospital mortality among patients with severe COVID-19.

Background

In December 2019, a novel pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, and the disease caused by SARS-CoV-2 has been named as the coronavirus disease-2019 (COVID-19) by the World Health Organization(WHO). On March 11, 2020, the World Health Organization (WHO) declared that COVID-19 has evolved into a global pandemic, with a significant impact on the global economy and life security. Until July 15, 2020, the WHO announced that the overall number of confirmed cases of COVID-19 was 12,964,809 worldwide, with 570,288 deaths [1]. Among a total of 72 314 case of COVID-19 reported by the Chinese Center for Disease Control and Prevention, most patients were classified as mild (81%),14% were severe and 5% were critical, and the overall case-fatality rate was 49.0% among critical cases[2]. Although most of mild patients had asymptomatic and/or mild clinical symptoms and good prognosis, some of severe COVID-19 patients, especially those patients with old age and several preexisting comorbidities, could develop to severe

illnesses including acute respiratory distress syndrome, septic shock, multiple organ failure or even death in a short period of time[3, 4]. Therefore, it is meaningful to determine effective indicators to predict the disease severity and clinical outcome, and help to reduce the mortality of severe and critical patients with COVID-19.

Dyslipidemia play an important role in the pathogenesis and evolution of atherosclerosis, and they are always at the forefront of medical research. However, it is not widely known that lipids are an integral part of the pulmonary innate and adaptive immune responses to various pulmonary diseases, including influenza pneumonia, asthma, acute lung injury (ALI), chronic obstructive pulmonary disease, and other lung disorders[5, 6]. In addition, high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (Apo-AI), low-density lipoprotein cholesterol (LDL-C) and other lipid parameters showed significant changes during pulmonary infection and inflammation[7]. HDL display pleiotropic characteristics, including lipopolysaccharide (LPS) and lipoteichoic acid (LTA) neutralization, anti-inflammatory, anti-thrombotic, anti-oxidative, anti-apoptotic and endotheliocyte protective effects [8, 9]. Clinical data demonstrate that HDL concentration decrease rapidly during sepsis, and there is a significant correlation between the low level of HDL and the poor prognosis of sepsis[10]. Experimental studies have also manifested that injection of reconstituted HDL (rHDL) or HDL mimetic peptide can reduce the mortality of sepsis animal models[11–13]. Apo-AI is the major protein component of HDL, and it has anti-inflammatory properties. The decrease of Apo -AI level was reported to be closely associated with poor prognosis in multiple disease states, such as infective endocarditis, systemic inflammatory response syndrome, acute pancreatitis, and sepsis[14–16].Furthermore, administration of Apo-AI mimetic peptides or over-expression of Apo-AI could reduce LPS- or influenza virus-induced lung inflammatory damage[17, 18]. Therefore, changes of lipid metabolism in patients under inflammatory conditions was related to adverse clinical outcomes. During the course of COVID-19, SARS-CoV-2 could induce excessive and uncontrolled cytokine storm in severe and critical patients with COVID-19, which was associated with the disease severity and prognosis of the disease[19]. Thus, elevated cytokines may change lipid profile of patients with COVID-19.

Recently, studies have found that levels of LDL-C and TC in COVID-19 patients are decreased[20, 21]. Nevertheless, these studies largely focused on the levels of total cholesterol(TC), triglycerides (TG), HDL cholesterol(HDL-C) and LDL cholesterol(LDL-C). Little is known about lipoprotein and apolipoprotein levels and the dynamic change of lipid. More importantly, whether these changes and lipid profiles at admission can help to predict the clinical outcome of the COVID-19 patients remains unclear. C-reactive protein (CRP) is a common inflammatory marker, which increases in most patients with COVID-19 and is closely related to the severity of the disease[22]. And HDL and Apo-AI display pleiotropic properties including anti-oxidant and anti-inflammatory functions[9].Therefore, the ratio of CRP/HDL-C or CRP/ Apo-AI may reflect the balance between pro-inflammatory and anti-inflammatory process. In this retrospective study, we aim to evaluate whether dysregulation of lipid profiles, new markers (CRP/HDL-C and CRP/ Apo-AI) and the dynamic changes in lipid profiles serve as prognostic indicator in patients with severe COVID-19.

Materials And Methods

Study design and participants

This was a retrospective, single-center, observational study among patients with severe COVID-19 who was admitted to the West Court of Union Hospital of Huazhong University of Science and Technology during the management by national medical team from February 1 to March 31, 2020. All the participants were diagnosed with COVID-19 based on the WHO interim guidance. Classification of clinical types of COVID-19 were based on Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) published by National Health Commission & National Administration of Traditional Chinese Medicine of China[23]. Patients with severe COVID-19 met any of the following criteria: respiratory rate ≥ 30 breaths per minute; finger of oxygen saturation $\leq 93\%$ at rest; $\text{PaO}_2 / \text{FiO}_2 \leq 300$ mmHg. We excluded patients who received parenteral nutrition containing lipids at the time of blood sampling, patients who were immunocompromised, patients with a known severe hepatic dysfunction, patients with familial or genetic disorders of lipid metabolism, and patients without lipid profiles detection on admission. By the time of March 31, 2020, a total of 216 severe COVID-19 patients with the clarified clinical outcome (died or recovered) were recruited in this study, and a flow diagram is showed in Fig. 1. The study was approved by the Ethics Committee of Union Hospital of Huazhong University of Science and Technology and ethics board of Xiangya Hospital, Central South University (No. 202003049). Written informed consent was waived by the Ethics Commission of the designated hospital due to the emerging infectious diseases.

Data Collection

The clinical records and laboratory data of each patient was obtained from the electronic medical system. A group of experienced respiratory clinicians reviewed and refined the data. The demographic data, comorbidities, clinical symptoms and signs and clinical outcomes (death or recovery) were extracted from their electronic medical records. Laboratory results on admission, including blood routine, liver function, kidney function, coagulation function, C-reactive protein, were collected and evaluated. The dynamic changes of lipid and apolipoprotein levels for severe COVID-19 patients during hospitalization (day 1, $n = 216$), day 5–7 ($n = 121$) and day 15–17 ($n = 130$) were collected as well. All laboratory data were tested in the same laboratory with the same standard. Furthermore, disease severity was also evaluated by the National Early Warning Score 2[24] (NEWS 2) and Sequential Organ Failure Assessment (SOFA) score.

Statistical analysis

Categorical variables were presented as numbers (percentages, %), and compared by Chi-square test or Fisher's exact test. Continuous variables with normal distribution were shown as mean $\pm$ standard deviation and compared with the Student t test, otherwise, continuous variables with skewed distribution

were presented with medians [interquartile range (IQR)], and compared with Mann-Whitney U test. Correlations between variables were analyzed with Spearman's coefficients. Receiver operating characteristic (ROC) curve analyses were performed to determine the cutoff values, sensitivity, and specificity of potential mediators (Apo-AI, HDL-C, CRP/ HDL-C ratio and CRP/ Apo-AI ratio) for predicting in-hospital mortality. Meanwhile, the best Youden index (sensitivity + specificity - 1) was obtained to calculate appropriate cut-off point of potential mediators (CRP/ HDL-C ratio and CRP/ Apo-AI ratio) to predict in-hospital death. In addition, risk factors were evaluated by univariate analysis, and variables with statistical significance in univariate analysis were selected in the multivariate analysis by using a multiple logistic stepwise regression to calculate independent risk factors to predict in-hospital mortality. For all analyses, $P < 0.05$ (two-tailed) was considered statistically significant. Graphpad Prism 8.0 (Graphpad Software, La Jolla, CA, USA) and SPSS 22.0 softwares (SPSS Inc., Chicago, IL, USA) were used for statistical graphs and analyses.

Results

Demographics and baseline clinical characteristics of severe COVID-19 patients

A total of 216 severe COVID-19 patients were included in the final analysis based on the selection criteria (Fig. 1). The demographics and baseline clinical characteristics of severe COVID-19 patients are summarized in Table 1. Twenty-four patients died during hospitalization and 192 were discharged from hospital. The mean age of the 216 patients was 61.3 years, and 139 (64.4%) were men. Hypertension is the most common comorbidity, followed by diabetes, coronary heart disease, chronic obstructive lung disease and malignancy. Compared with the survivor group, the non-survivor had higher prevalence of hypertension (66.7% vs 41.7%, $P = 0.02$). The respiration rate and temperature were significantly higher in non-survivors compared to survivors. However, there was no significant difference between the two groups in high respiratory rate (> 24 breaths per min) and fever (temperature ≥ 37.3 °C). Compared with the survivors, the non-survivors had greater disease severity as evidenced by higher SOFA score and NEWS 2 score ($P < 0.0001$), accompanied with significantly higher white blood cell and neutrophil count, NLR, CRP, procalcitonin, lactate dehydrogenase, total bilirubin, urea nitrogen, hypersensitive troponin I and D-dimer, and lower lymphocyte, albumin and platelet count compared to survivors (Table 2).

Table 1
Baseline Characteristics of Patients with severe COVID-19

Variable	Total (n = 216)	Non-survivor (n = 24)	Survivor (n = 192)	p Value
Age(years), mean $\pm$ SD	61.3 $\pm$ 11.2	64.3 $\pm$ 8.5	60.9 $\pm$ 11.5	0.083
Male, n [%]	139(64.4%)	17(70.8%)	122(63.5%)	0.482
Comorbidities, n				
Hypertension	96(44.4%)	16(66.7%)	80(41.7%)	0.020
Diabetes	50(23.1%)	4(16.7%)	46(24.0%)	0.425
Coronary heart disease	29(13.4%)	6(25.0%)	23(12.0%)	0.148
Chronic obstructive lung disease	19(8.8%)	4(16.7%)	15(7.8%)	0.288
Malignancy	11(5.1%)	3(12.5%)	8(4.2%)	0.208
Vital signs				
Respiration rate, median (IQR),(times per min)	22(20–25)	24.5(22–30)	22(20–25)	0.048
Respiratory rate > 24 breaths per min, no. (%)	78(36.1%)	12(50.0%)	66(34.4%)	0.133
Pulse, mean $\pm$ SD, (bpm)	91.7 $\pm$ 16.4	93.1 $\pm$ 16.5	91.5 $\pm$ 16.4	0.661
MAP, median (IQR), (mmHg)	94.7(89.1-104.2)	94.3(87.3-105.3)	94.7(89.3-104.2)	0.979
T, median (IQR), (°C)	36.75(36.3–37.3)	37.25(36.5-38.15)	36.7(36.3–37.3)	0.031
Fever (temperature $\geq$ 37.3 °C), no. (%)	56(25.9%)	10(41.7%)	46(24.0%)	0.062
Disease severity scores				
SOFA score	2(1.25-3.0)	3.5(3-4.75)	2(1–2)	$\leq$ 0.0001
NEWS2 score	7(6–8)	8.5(8–10)	7(5–8)	$\leq$ 0.0001
Data are presented as mean $\pm$ standard deviation (SD), medians (IQR) and n (%). P values were calculated by Student t test, Mann–Whitney U test, Chi-square test or Fisher's exact test, as appropriate. P values indicate differences between non-survivors and survivors. Abbreviations : IQR, interquartile range; MAP, mean arterial pressure; NEWS 2 score, National Early Warning Score 2 score ; SOFA score ,Sequential Organ Failure Assessment score.				

Table 2
Laboratory findings of patients with different outcomes

Laboratory findings	Total (n = 216)	Non-survivor (n = 24)	Survivor (n = 192)	p Value
Blood Routine				
White blood cell count, $\times 10^9/L$	5.99(4.40–8.04)	8.82(5.67–11.7)	5.56(4.39–7.48)	0.001
Platelet count, $\times 10^9/L$	218(168.25–305)	147.50(98.25–212.75)	234(174.50–307.75)	≤ 0.0001
Neutrophil count, $\times 10^9/L$	4.21(2.94–6.68)	7.86(4.82–9.76)	3.95(2.90–5.76)	≤ 0.0001
Lymphocyte count, $\times 10^9/L$	1.01(0.69–1.30)	0.57(0.47–0.72)	1.04(0.77–1.35)	≤ 0.0001
NLR	4.21(2.47–7.99)	11.93(7.59–22.48)	3.80(2.25–6.82)	≤ 0.0001
Hemoglobin, g/L	125.20 $\pm$ 17.60	126.90 $\pm$ 20.50	125.00 $\pm$ 17.30	0.610
Blood Biochemistry				
Aspartate aminotransferase, U/L	30(22–42)	33.50(27.25–54.50)	29(22–41)	0.107
Alanine aminotransferase, U/L	30(20–48)	27(16–47.45)	31(21–48)	0.439
Lactate dehydrogenase, U/L	258.50(202–368.25)	460.5(323.75–622.50)	252(198–347)	≤ 0.0001
Total bilirubin, $\mu\text{mol/L}$	11.20(8.83–15.38)	14.05(9.40–25.70)	11.05(8.70–15.03)	0.043
Albumin, g/L	30.51 $\pm$ 5.63	26.70 $\pm$ 4.54	30.98 $\pm$ 5.58	≤ 0.0001
Urea nitrogen, mmol/L	4.96(3.87–6.95)	7.80(4.28–9.48)	4.80(3.71–6.57)	0.001
Creatinine, $\mu\text{mol/L}$	66.75(58.18–81.05)	74.60(65.80–95.35)	65.75(57.88–80.03)	0.056
Myocardial Injury Markers				
Creatine kinase, U/L	73.50(44–128.75)	114(49.75–300.75)	72(42.25–117.75)	0.025
Hypersensitive troponin I, ng/L	5.70(2.80–10.88)	23.20(10.75–552.05)	4.15(2.40–8.58)	≤ 0.0001
Inflammatory Markers				
C-reactive protein, mg/L	28.87(4.41–74.38)	83.01(59.68–122.39)	22.09(4.03–59.23)	≤ 0.0001

Laboratory findings	Total (n = 216)	Non-survivor (n = 24)	Survivor (n = 192)	<i>p</i> Value
Blood Coagulation				
D-dimer, µg/mL	0.71(0.33–1.99)	6.50(0.83-8)	0.66(0.31–1.55)	⊠0.0001
Prothrombin time, s	13.10(12.50–14.00)	14.20(13.10-15.15)	13.10(12.40–13.70)	⊠0.0001
International normalized ratio	1.01(0.95–1.11)	1.14(1.01–1.29)	1.01(0.95–1.08)	⊠0.0001
Bacterial Infection Marker				
Procalcitonin, ng/mL	0.07(0.05–0.15)	0.20(0.14–0.41)	0.07(0.05–0.12)	⊠0.0001
Lipids				
TC, mmol/L	4.09 ± 0.92	3.86 ± 0.88	4.12 ± 0.92	0.195
TG, mmol/L	1.35(1.04–1.84)	1.21(1.06–1.72)	1.37(1.01–1.86)	0.701
HDL-C, mmol/L	0.89(0.76–1.03)	0.79(0.64–0.92)	0.89(0.76–1.05)	0.006
LDL-C, mmol/L	2.43 ± 0.75	2.34 ± 0.82	2.44 ± 0.75	0.554
Apo-AI ,g/L	0.80 ± 0.19	0.68 ± 0.14	0.81 ± 0.19	0.001
Apo-B ,g/L	0.99 ± 0.25	1.01 ± 0.28	0.98 ± 0.25	0.572
LP-A,mg/dL	13.65(5.90-24.53)	16.45(8.63–36.98)	12.75(5.73–23.83)	0.135
CRP/ HDL-C ratio	31.47(4.90-91.21)	128.11(71.74-175.31)	22.94(4.32–75.36)	⊠0.0001
CRP/ Apo-AI ratio	37.11(5.39-102.07)	143.90(76.02-200.75)	27.58(4.59–87.77)	⊠0.0001
<p>Data are presented as mean ± standard deviation (SD) and medians (IQR). P values were calculated by Student t test, Mann–Whitney U test, as appropriate. P values indicate differences between non-survivors and survivors.</p> <p>Abbreviations : NLR,neutrophils-to-lymphocytes ratio; TC, total cholesterol; TG, triglycerides;HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo-AI, apolipoprotein AI; Apo-B, apolipoprotein B; LP-A, lipoprotein A; CRP,C-reactive protein.</p>				

Lipid Levels In Patients With Severe Covid-19

Lipid profiles were analyzed on admission (day 1), on day 5–7 and day 15–17 after admission (Fig. 2). On admission, the serum levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (Apo-AI) were significantly lower in non-survivors, whereas there was no difference in total

cholesterol(TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), Apo-B and lipoprotein A (LP-A) (Table 2). Furthermore, HDL-C and Apo-AI levels were significantly lower in non-survivors at all time points (Fig. 2). The LDL-C and TC concentration was significantly lower in non-survivors on day 5–7 ($p < 0.05$) and day 15–17($p < 0.001$). During day 1 to day 15–17, low-density lipoprotein cholesterol (LDL-C), total cholesterol(TC), HDL-C and Apo-AI were shown an increasing trend in survivors, but maintained lower levels or shown downward trend in non-survivors(Fig. 2).

Relationship between lipid profiles and CRP levels, disease severity

The levels of HDL-C and Apo-AI were significantly higher in survivors, while the levels of C-reactive protein were higher in non-survivors($P=0.0001$)(Table 1).Both HDL and Apo-AI were inversely correlated with SOFA score, NEWS2 score, length of hospital stay of survivors and CRP level (Table 3). Of these, Apo-AI had the strongest inverse correlation with length of stay of survivors ($R= -0.562$, $p < 0.001$) and CRP ($R= -0.570$, $p < 0.001$). The ratios (CRP/HDL-C or CRP/ Apo-AI) may serve as new markers to reflect the balance between pro-inflammatory and anti-inflammatory factors. Surprisingly, the ratios of CRP/HDL-C and CRP/ Apo-AI were significantly higher in non-survivors(Table 2). Additionally, CRP/HDL-C and CRP/ Apo-AI had the strongest negative correlation with SOFA score, length of hospital stay of survivors and CRP(Table 3).

Table 3
Correlation between the lipid levels, CRP, length of hospital stay of survivors and the disease severity scores

	Statistics	SOFA score	NEWS2 score	Length of hospital stay of survivors	CRP
TC	<i>R</i>	-0.137	0.017	-0.165	-0.123
	<i>P</i>	0.044	0.801	0.022	0.071
TG	<i>R</i>	-0.013	0.128	-0.068	-0.137
	<i>P</i>	0.845	0.060	0.352	0.045
HDL-C	<i>R</i>	-0.270	-0.182	-0.345	-0.297
	<i>P</i>	0.001	0.007	0.001	0.001
LDL-C	<i>R</i>	-0.075	0.009	-0.044	0.014
	<i>P</i>	0.271	0.900	0.545	0.835
Apo-AI	<i>R</i>	-0.420	-0.228	-0.562	-0.570
	<i>P</i>	0.001	0.001	0.001	0.001
Apo-B	<i>R</i>	0.062	0.147	0.074	0.137
	<i>P</i>	0.368	0.030	0.310	0.044
LP-A	<i>R</i>	0.165	0.089	0.078	0.198
	<i>P</i>	0.015	0.193	0.284	0.003
CRP/ HDL-C ratio	<i>R</i>	0.519	0.403	0.573	0.981
	<i>P</i>	0.001	0.001	0.001	0.001
CRP/ Apo-AI ratio	<i>R</i>	0.516	0.396	0.568	0.989
	<i>P</i>	0.001	0.001	0.001	0.001
Correlations between variables were analyzed with Spearman's coefficients. Abbreviations : TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo-AI, apolipoprotein AI; Apo-B, apolipoprotein B; LP-A, lipoprotein A; CRP, C-reactive protein. NEWS 2 score, National Early Warning Score 2 score ; SOFA score ,Sequential Organ Failure Assessment score.					

Table 4

ROC Curve of HDL-C, APO-AI, CRP/ HDL-C ratio and CRP/ Apo-AI ratio to predict in-hospital mortality.

Parameter	AUC (95% CI)	SE	P-value
APO-AI	0.295(0.196–0.394)	0.051	0.001
HDL-C	0.328(0.224–0.431)	0.053	0.006
CRP/ HDL-C ratio	0.823(0.737–0.910)	0.044	0.0001
CRP/ APO-AI ratio	0.811(0.726–0.895)	0.043	0.0001
Abbreviations : HDL-C, high-density lipoprotein cholesterol; Apo-AI, apolipoprotein AI; CRP,C-reactive protein; AUC, area under the ROC curve ;SE, standard error.			

CRP/ HDL-C ratio may serve as a new marker to predict adverse clinical outcome

In order to evaluate the prognostic value and determine the best cut-off of CRP/ HDL-C ratio for predicting in-hospital mortality among COVID-19 patients, receiver operation characteristic (ROC) curves were performed (Fig. 3). The area under the ROC curve (AUC) was 0.295(95% CI:0.196–0.394, $P = 0.001$) for Apo-AI, 0.328(95% CI:0.224–0.431, $P = 0.006$) for HDL-C, 0.823(95% CI:0.737–0.910, $P = 0.0001$) for CRP/ HDL-C ratio, 0.811(95% CI:0.726–0.895, $P = 0.0001$) for CRP/ Apo-AI ratio (Table 3). The best cut-off points of CRP/ HDL-C ratio for predicting in-hospital mortality was 62.543 with the best Youden index, the sensitivity of 83.3%, the specificity of 70.8% and the accuracy of 72.2% (Fig. 3). Similarly, the best cut-off points of CRP/Apo-AI ratio was 84.264 for predicting in-hospital death, with the sensitivity for 75.0%, the specificity for 75.0% and the accuracy for 75.0%. Then, we defined the high CRP/ HDL-C ratio (≥ 62.543) and the high CRP/ Apo-AI ratio (≥ 84.264).

In univariate analysis, we exclude the variables that are calculated from other variables to prevent the occurrence of collinearity, such as disease severity scores, or those variables of the same type with different indicators and strong correlation [16]. Finally, parameters including hypertension, respiration rate, temperature, platelet count, NLR, lactate dehydrogenase, total bilirubin, albumin, urea nitrogen, creatine kinase, D-dimer, procalcitonin, high CRP/ HDL-C ratio (≥ 62.543) and high CRP/ Apo-AI ratio (≥ 84.264) were entered into the multivariate logistic regression model. In the final model, hypertension, NLR, platelet count and high CRP/ HDL-C ratio were independent factors to predict in-hospital mortality (Table 5). The clinical characteristics and outcomes of patients were divided into two groups by low and high CRP/ HDL-C ratio (high CRP/ HDL-C ratio ≥ 62.543 and low CRP/ HDL-C ratio < 62.543 , Table 6) according to the cut-off value calculated by the ROC curve (Figure. 3). The rate of hospital mortality, the proportion of COVID-19 with critical subtype, SOFA score and NEWS2 score were significantly higher in high CRP/ HDL-C ratio group than in the group with a low CRP/ HDL-C ratio. Moreover, patients in high CRP/ HDL-C ratio group were older with more men, accompanied with higher levels of white blood cell count, neutrophil, lymphocyte, NLR, aspartate aminotransferase, lactate dehydrogenase, total bilirubin, albumin, urea

nitrogen, hypersensitive troponin I, C-reactive protein, D-dimer, prothrombin time, international normalized ratio and procalcitonin than the patients in low CRP/ HDL-C ratio group (Table 6).

Table 5
Logistic regression of the final model.

Parameter	β Coefficient	Standard error	Odds ratios (95%CI)	<i>p</i>
Hypertension	1.752	0.788	5.764(1.231–26.994)	0.026
NLR	0.105	0.048	1.111(1.010–1.221)	0.030
Platelet count	-0.012	0.005	0.988(0.979–0.998)	0.023
High CRP/ HDL-C ratio ^a	3.025	1.283	20.587(1.667–254.330)	0.018
Abbreviations :NLR,neutrophils-to-lymphocytes ratio;HDL-C, high-density lipoprotein cholesterol; CRP,C-reactive protein.				
^a CRP/ HDL-C ratio higher than 62.543.				

Table 6

Patients' demographic data and baseline clinical characteristics grouped according to CRP/ HDL-C ratio.

Variable	^a High CRP/ HDL-C ratio (n = 76)	^b Low CRP/ HDL-C ratio (n = 140)	<i>p</i> Value
Age(years)	63.45 ± 10.63	60.13 ± 11.36	0.037
Male	56(73.68%)	83(59.29%)	0.035
Respiration rate	23(22.00-25.75)	22(20–25)	0.017
T, °C	36.95(36.30–37.90)	36.60(36.33–37.08)	0.068
Hospital mortality	20(26.32%)	4(2.86%)	0.0001
Progress to critical COVID-19	27(35.53%)	5(3.57%)	0.0001
SOFA score	3(2–3)	2(1–2)	0.0001
NEWS2 score	8(7–9)	6(5–8)	0.0001
White blood cell count, ×10 ⁹ /L	6.92(4.75–9.32)	5.52(4.34–6.99)	0.003
Platelet count, ×10 ⁹ /L	205.50(153.75–281.50)	229.00(170.75–310.00)	0.115
Neutrophil count, ×10 ⁹ /L	5.62(3.38–8.39)	3.81(2.70–5.05)	0.0001
Lymphocyte count, ×10 ⁹ /L	0.70(0.50–0.95)	1.17(0.88–1.53)	0.0001
NLR	8.18(4.54–13.75)	3.05(1.96–5.23)	0.0001
Hemoglobin, g/L	127.76 ± 17.74	123.78 ± 17.50	0.113
Aspartate aminotransferase, U/L	36.00(26.25–52.50)	27.00(21.00-35.75)	0.0001
Alanine aminotransferase, U/L	28.50(20.25–53.75)	31.00(19.25–45.75)	0.475
Lactate dehydrogenase, U/L	376.00(294.25-467.25)	224.50(193.25–301.00)	0.0001
Total bilirubin, μmol/L	13.10(9.93–18.20)	10.70(8.23–14.48)	0.001
Albumin, g/L	27.04 ± 4.16	32.39 ± 5.43	0.0001
Urea nitrogen, mmol/L	5.84(4.06–8.58)	4.76(3.81–6.11)	0.014
Creatinine, μmol/L	69.80(61.15–81.50)	64.75(56.23–80.93)	0.086
Creatine kinase, U/L	83.50(45.00-157.50)	70.00(43.25-117.75)	0.190

Variable	^a High CRP/ HDL-C ratio (n = 76)	^b Low CRP/ HDL-C ratio (n = 140)	<i>p</i> Value
Hypersensitive troponin I, ng/L	8.40(4.15–22.10)	3.70(2.20–7.48)	0.0001
C-reactive protein, mg/L	87.64(70.20-120.13)	8.73(2.61–26.66)	0.0001
D-dimer, µg/mL	1.37(0.47–6.58)	0.63(0.27–1.25)	0.0001
Prothrombin time, s	13.75(12.90–14.50)	12.90(12.40–13.40)	0.0001
International normalized ratio	1.08(0.99–1.16)	1.00(0.95–1.06)	0.0001
Procalcitonin, ng/mL	0.14(0.09–0.28)	0.06(0.04–0.09)	0.0001
<p>Data are presented as mean ± standard deviation (SD), medians (IQR) and n (%). P values were calculated by Student t test, Mann–Whitney U test, Chi-square test or Fisher's exact test, as appropriate. P values indicate differences between high CRP/ HDL-C ratio group and low CRP/ HDL-C ratio group. Abbreviations : NLR,neutrophils-to-lymphocytes ratio; HDL-C, high-density lipoprotein cholesterol; CRP,C-reactive protein; NEWS 2 score, National Early Warning Score 2 score ; SOFA score ,Sequential Organ Failure Assessment score.</p> <p>^a CRP/ HDL-C ratio higher than 62.543</p> <p>^b CRP/ HDL-C ratio lower than 62.543</p>			

Discussion

In this study, we found the dyslipidemia in patients with severe COVID-19, and demonstrated that low levels of HDL-C and Apo-AI at admission were significantly associated with high levels of CRP, prolonged hospital stay, increased disease severity. Additionally, the analysis of the longitudinal changes of lipid profiles showed that non-survival COVID-19 patients persistent had hypolipidemia including TC, HDL-C, LDL-C, Apo-AI than the survival patients during the early period of hospitalization. Furthermore, hypertension, NLR, platelet count and high CRP/ HDL-C ratio (≥62.543) could serve as independent factors to predict in-hospital mortality, especially, higher CRP/ HDL-C ratio was closely associated with increased hospital mortality.

Acute inflammation caused by viral infection may result in dyslipidemia in patients, and the lipid metabolism is known to play an important role in host immune response. Clinical observations have displayed that patients with acute Epstein-Barr virus(EBV) infection had lower levels of Apo-AI, HDL-C, TC, Apo B, LDL-C and LP-A compared with their controls[25]. Another study showed that cytomegalovirus(CMV) infection was associated with lower HDL-C in normal-weight females[26]. Compared with other febrile patients, dengue-positive patients had lower HDL-C and LDL-C levels[27]. In addition, SARS patients had lower levels of Apo-AI compared to their normal controls from the results of plasma proteomics [28]. Similarly, our study showed that non-survivors with severe COVID-19 showed lower HDL-C and Apo-AI concentrations at admission compared to those survivors. Additionally, the

analysis of longitudinal changes of lipid profiles demonstrated that LDL-C, HDL-C, TC and Apo-AI remained persistent at low levels, or even further gradually decreased during disease progression in non-survivors, while in survivors, although initially decreased, aforementioned lipid profiles were shown to increase steadily during recovery. Several

possible hypotheses might explain the dynamic changes during the course of COVID-19. Firstly, Liver plays an critical role in lipid metabolism, and liver dysfunction caused by SARS-CoV2 infection or potential drugs will affect lipid synthesis. It was reported that 14%-53% of patients with COVID-19 had hepatic dysfunction, especially in those severe and critical patients[29]. Therefore, the synthesis of apolipoproteins and lipoproteins would be affected by hepatic dysfunction of patients with severe COVID-19. Secondly, acute inflammation caused by SARS-CoV-2 might alter lipid metabolism as well. Severe and critical patients with COVID-19 were commonly accompanied with largely excessive release of pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, IFN - γ and TNF- α , as the disease progressed over time and gradually got worse[30]. It was shown that tumor necrosis TNF- α , IL-1 β , and IL-6 could decrease synthesis and/or secretion of apolipoproteins in hepatic cell lines in dose-dependent way [31]. Additionally, severe inflammatory response could also cause capillary leakage, thus resulting in the leakage of lipoproteins and apolipoproteins particles from intravascular to extravascular compartment [32]. In our study, we found that HDL-C and Apo-AI were closely associated with inflammatory marker of CRP, which might partially explain the hypolipidemia was associated with inflammatory response in severe COVID-19 patients. Finally, a very recent study has showed that a rare missense variant in cholesteryl ester transfer protein gene (CETP, rs1800777-A) that was associated with marked reduction in HDL-C levels and adverse clinical outcome during sepsis[33]. COVID-19 patients who carry the A allele may have lower HDL level and worse prognosis compared with non-carriers[33]. Therefore, the genetic variation of CETP gene is a key regulator of HDL-C levels and clinical prognosis during sepsis. At present, the genetic variation of CETP gene in patients with COVID-19 has not been reported, and it may be a promising research direction in the treatment and evaluation of prognosis among patients with COVID-19.

Since COVID-19 is a global pandemic with a high mortality rate, it will be helpful to determine several early markers to predict the disease severity and prognosis of COVID-19. Previous studies showed that low levels of Apo-AI and HDL-C have been used as prognostic biomarkers in patients with pneumonia, sepsis and other infections. An observational study indicated that a low level of Apo-AI was an indicator for poor prognosis in cirrhotic patients with severe sepsis[16]. Similarly, gradually-declined HDL-C level from day 1 to day 7 after admission could serve as a poor prognostic indicator among patients with severe community-acquired pneumonia[34]. Consistently, our data suggested that both HDL-C and Apo-AI levels were inversely correlated with disease severity scored (SOFA score and NEWS2 score), length of stay of survivors and inflammatory marker of CRP in patients with severe COVID-19. Additionally, our data also reported the low power of HDL-C and Apo-AI levels at admission to predict the in-hospital mortality. HDL and Apo-AI display pleiotropic properties including antioxidant and anti-inflammatory functions[9]. CRP is a common inflammatory marker. Thus, the ratio of CRP/HDL-C or CRP/ Apo-AI may reflect the balance between pro-inflammatory and anti-inflammatory factors. It is noteworthy that severe

COVID-19 patients usually have an imbalance between anti-inflammatory and pro-inflammatory processes. Clinical and experimental studies have shown that patients with severe COVID-19 may exhibit features of systemic hyper-inflammation and inflammatory cytokine storm, which releases pro-inflammatory cytokines excessively and uncontrollably including IL-6 and TNF- α [19, 35]. And clinical reports showed that anti-inflammation therapies (such as glucocorticoids, immunosuppressants and inflammatory cytokines antagonists), which may help in preventing further injury in severe and critical COVID-19 patients, is an effective treatment to improve the clinical outcome[36]. Similarly, we found that the ratios of CRP/HDL-C and CRP/Apo-AI were significantly higher in survival COVID-19 patients compared to those non-survivors, and these ratios had strong negative correlation with SOFA score, length of stay of survivors and CRP. Moreover, high CRP/ HDL-C ratio (62.543) was proved to be independent factor to predict in-hospital mortality among patients with severe COVID-19. Based on these findings, high CRP/ HDL-C ratio not only shows the imbalance of inflammation in patients with severe COVID-19, but also correlate with deteriorating disease severity and worsening prognosis, and might be serve as a potential indicator for poor outcome among COVID-19.

HDL and its major protein, Apo-AI, display pleiotropic protective functions, which include anti-infectious, anti-inflammatory, anti-oxidative, anti-thrombotic and Anti-diabetic properties[9]. An increasing number of evidences showed that HDL, particularly its major protein, Apo-AI, played protective effects in a variety of lung disease, including ALI, ARDS, chronic obstructive pulmonary disease(COPD), asthma, pulmonary fibrosis and viral pneumonia[6]. However, there are no clinical and experimental studies on the protective effect of HDL and Apo-AI in COVID-19. In severe and critical COVID-19 patients, clinical outcome can be significantly worsened by excessive release of pro-inflammatory cytokines[30]. HDL and Apo-AI may help in preventing inflammatory injury and improving the clinical outcome with anti-inflammatory and anti-oxidative properties. Then, a systematic review and meta-analysis showed that bacterial co-infection occurred in 7% of hospitalized COVID-19 patients and 14% of ICU patients, and the bacterial co-infection would lead to a higher mortality of COVID-19 [37]. Studies showed that HDL was capable to bind and neutralize Gram-negative LPS and Gram-positive lipoteichoic acid (LTA), thus reducing LTA and LPS-induced inflammatory injury[38, 39], thus providing the conception that HDL-based therapies might be promising in severe COVID-19 patients with bacterial co-infection. Diabetes was a common comorbidity in patients with COVID-19, and associated with greater disease severity and higher mortality of COVID-19[40], especially in those population with poorly-controlled glycemia [41]. Several experimental studies have demonstrated that HDL particles displayed anti-diabetic properties by improving insulin sensitivity and β cell insulin secretion[9, 42, 43]. The evidence suggested that HDL or Apo-AI might improve glycemic control and promote a better prognosis in severe COVID-19 patients. Although no clinical and experimental studies were conducted to determine the role of HDL and Apo-AI-based therapy in COVID-19, it would be a promising direction in searching novel treatment for severe patients with COVID-19.

Our study was subject to a few limitations that should not go unnoticed. Firstly, this study was a retrospective study with a relatively small sample size, large cohort study would be required to further confirm our conclusion. Secondly, asymptomatic patients and those with mild symptoms were not be enrolled, thus the conclusions drew by the study might not be applicable to asymptomatic and mild

patients. Thirdly, a large number of factors could affect the lipid metabolism in COVID-19, the specific mechanism about the dyslipidemia could not be concluded, and would be required further powerful investigation.

Conclusion

In conclusion, our study demonstrated that dyslipidemia was associated with the inflammatory response, disease severity and poor prognosis of COVID-19. High CRP/ HDL-C ratio may serve as an independently potential predictor for hospital mortality among patients with COVID-19. The hypolipidemia in COVID-19 patients would raise an urgent awareness to clinical physicians in the frontline to fight against this global pandemic. Whether HDL-based therapies have a potential therapeutic effects on patients with severe COVID-19 deserves further exploration.

Abbreviations

COVID-19, coronavirus disease 2019 ;NLR, neutrophils-to-lymphocytes ratio; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo-AI, apolipoprotein AI; Apo-B, apolipoprotein B; LP-A, lipoprotein A; CRP, C-reactive protein; MAP, mean arterial pressure; NEWS 2 score, National Early Warning Score 2 score ; SOFA score ,Sequential Organ Failure Assessment score ;IQR, interquartile range; AUC, area under the ROC curve ;SE, standard error.

Declarations

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Author Contributions

Y.L. and P.P. conceived and designed the research. Y.L. and Y.Z. drafted the manuscript. M.D., J.Z., Y.C., B.L., F.L., L.C, D.H.,Y.F,Y.Z. and W.L. collected the data. Y.L., H.L., M.S., and X.C. analyzed the data. Y.L., B.L and S.L. prepared the figures and tables. M.D. and Y.Z. edited and revised the manuscript. P.P. and X.C. approved the final version of manuscript. All authors read and approved the final manuscript.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author (Pinhua Pan, Phone: +86-0731- 89753287, E-mail: pinhuapan668@csu.edu.cn) on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Union Hospital of Huazhong University of Science and Technology and ethics board of Xiangya Hospital, Central South University (No. 202003049). Written informed consent was waived by the Ethics Commission of the designated hospital due to the emerging infectious diseases.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

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Figures

Figure 1

Flow diagram of study population.

Figure 2

Presentation of total cholesterol(TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol(LDL-C), apolipoprotein AI (Apo-AI) and lipoprotein A (LP-A) levels (means $\pm$ SEM) for survivors and non-survivors on admission (day 1, n = 216), day 5-7 (n = 121) and day 15-17 (n = 130). *p<0.05, **p<0.01, ***p<0.001 survivors vs. non-survivors.

Figure 3

The CRP/Apo-AI ratio and CRP/HDL-C ratio for in-hospital mortality of severe COVID-19 by receiver operating characteristic (ROC) curves. The best cut-off points for predicting in-hospital death was 84.264 for CRP/Apo-AI ratio, with the sensitivity for 75.0%, the specificity for 75.0%, the accuracy for 75.0%. The best cut-off points of CRP/ HDL-C ratio for predicting in-hospital mortality was 62.543, the sensitivity of 83.3%, the specificity of 70.8% and the accuracy of 72.2%.