Low serum apolipoprotein A 1 is an indicator of severity in patients with coronavirus disease 2019

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Research

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Abstract

Background: Recently, dyslipidaemia was observed in patients with coronavirus disease 2019 (COVID-19), especially in severe cases. This study aimed to explore the predictive value of blood lipid levels for COVID-19 severity.

Methods: All patients with COVID-19 admitted to HwaMei Hospital, University of Chinese Academy of Sciences, from January 23 to April 20, 2020, were included in this retrospective study. General clinical characteristics and laboratory data (including blood lipid parameters) were obtained, and their predictive values for the severity were analysed.

Results: In total, 142 consecutive patients with COVID-19 were included. The non-severe group included 125 cases, and 17 cases were included in the severe group. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A1 (ApoA1) at baseline were significantly lower in the severe group. ApoA1 and interleukin-6 (IL-6) were recognized as independent risk factors for COVID-19 severity. ApoA1 had the highest area under the receiver operator characteristic curve (AUC) among all the single markers (AUC: 0.896, 95% CI: 0.834-0.941). Moreover, the risk model established using ApoA1 and IL-6 enhanced the predictive value (AUC: 0.977, 95% CI: 0.932-0.995). On the other hand, ApoA1 levels were elevated in the severe group during treatment, and there was no significant difference between the severe and non-severe groups during the recovery stage of the disease.

Conclusion: The blood lipid profile in severe COVID-19 patients is quite different from that in non-severe cases. Serum ApoA1 could severe as a good indictor to reflect the severity of COVID-19.

Introduction

The recently emerged pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible coronavirus that has caused an ever-increasing number of Coronavirus Disease 2019 (COVID-19) infections since December 2019 and spread rapidly worldwide. As of May 13, 2020, SARS-CoV-2 has caused 4170424 confirmed cases and 287399 deaths (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). The on-going COVID-19 pandemic has created a significant strain on the medical system globally. Although approximately 80% patients infected with SARS-CoV2 exhibit mild symptoms [1], the remaining severe cases may experience acute respiratory distress, multi-organ failure and loss of life [2]. Therefore, it is necessary to discriminate between severe and mild cases.

Previous studies have found that the development of severe COVID-19 is associated with age and underlying disease, and severe patients are likely to suffer from aberrant inflammation reaction and cytokine storm [1, 3]. Consequently, some clinical characteristics, the inflammation index and cytokine levels have been used as indictors to reflect the severity of COVID-19 by us and others [4, 5]. Recently, emerging evidence suggested that lipid metabolism dysregulation might promote the progression of

COVID-19 as revealed by mass spectrometry (MS)-based proteomics analysis [6-8]. Although MS analysis is not commonly performed, blood lipids are routinely examined using automatic biochemical instruments in clinical laboratories. Thus, blood lipids may be considered as a potential and available indictor of COVID-19 severity.

To determine the predictive value of blood lipids for COVID-19 severity, a retrospective study was performed in Ningbo HwaMei Hospital, University of Chinese Academy of Sciences.

Materials And Methods

Study site and design

This was a single-centre retrospective study performed at HwaMei Hospital, University of Chinese Academy of Sciences, a 2100-bed tertiary general hospital integrating medical treatment, health care, disease prevention, teaching and scientific research. This hospital was the largest designated hospital for COVID-19 during the SARS-CoV-2 epidemic and received most of the patients with COVID-19 from Ningbo, Zhejiang Province, China. The institutional ethics committee approved this study.

Patient selection and data collection

All consecutive patients with confirmed COVID-19 admitted to HwaMei Hospital, University of Chinese Academy of Sciences, from January 23 to April 20, 2020, were enrolled. The diagnosis of COVID-19 and its severity were determined according to the National Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia (6^{th} Trial Version). Patients with confirmed COVID-19 were diagnosed based on a positive SARS-CoV-2 nucleic acid RT-PCR result using specimens derived from throat swab, nasopharynx swab or sputum, and patients were classified as mild, moderate, severe or critical based on clinical manifestations. Mild and moderate patients were included in the non-severe group, while severe and critical patients were included in the severe group. Severe patients exhibited one of the following features: a) shortness of breath with respiration rate (RR) greater than 30 times per minute; b) blood oxygen saturation less than 93% at a state of rest; c) arterial blood oxygen partial pressure/inhaled oxygen concentration less than 300 mmHg; or d) lesion rapidly progressed by more than 50% within one or two days on pulmonary imaging. Critical patients exhibited any of the following features: a) respiratory failure requiring mechanical ventilation for therapy; b) shock; or c) additional organ failure, requiring treatment in the intensive care unit (ICU).

General clinical characteristics, including gender, age, comorbidities, initial symptoms and treatment, and laboratory test data, including peripheral blood cell count, blood coagulation index, biochemical parameters and cytokines, were collected from the electronic medical record (EMR).

Determination of blood lipid

Blood lipids were tested using a fully automatic biochemical analyser (ADVIA2400, Siemens, Germany) according to the manufacturer's instructions (Purebio Biotechnology Co., Ltd, Ningbo, Zhejiang, China). Briefly, total cholesterol was measured using the cholesterol oxidase-p-aminophenazone (CHOD-PAP) method. Triglycerides were assessed using the glycerol phosphate oxidase-p-aminophenazone (GPO-PAP) method. High-density lipoprotein cholesterol (HDL-C) was assessed using the direct-hydrogen peroxide method. Low-density lipoprotein cholesterol (LDL-C) was assessed using the direct-surfactant removal method; apolipoprotein A1 (ApoA1), ApoB and Lipoprotein (a) were assessed using the immunoturbidimetric method.

Statistical analysis

SPSS statistical 16.0 software (IBM, Armonk, NY, USA) and GraphPad PRISM 5.0 software (GraphPad Software, San Diego, CA, USA) were used for statistical analysis. Normally and non-normally distributed continuous data were expressed as the mean ± SD (standard deviation) and medians and interquartile range (IQR), respectively. Categorical variables were reported as numbers (%). The differences between the non-severe and severe groups were assessed using Student's *t*-test and Mann-Whitney U test for normally and non-normally distributed continuous data, respectively, and chi square or Fisher's exact tests were used for categorical variables. Multivariate logistic regression analysis was used to explore independent risk factors for the severity of COVID-19, and receiver operator characteristic (ROC) curves were generated to assess their predictive values. Correlations between different variables were determined by Spearman rank correlation analysis. A *P*-value <0.05 indicates statistical significance.

Results

General clinical characteristics

In total, 142 consecutive patients with confirmed COVID-19 were included in this study. The mean age was 49.10±16.36 years, and 55 (38.73%) patients were men. Hypertension (37, 26.06%), diabetes (12, 8.45%), hepatic disease (10, 7.04%) and chronic lung disease (9, 6.34%) were the most common comorbidities. Fever (84, 59.15%) was the leading initial symptom, followed by cough (61, 42.96%), expectoration (32, 22.54%) and fatigue (27, 19.01%). In addition, 18 cases (12.68%) showed no obvious symptoms upon admission. All included patients received antiviral treatment. Moreover, 88 (61.97%), 53 (37.32%) and 52 (36.62%) patients were treated with gamma globulin, oxygen and antibiotics, respectively.

Among the 142 patients, 125 (88.03%) patients (19 mild and 106 moderate) were classified into the non-severe group, and 17 (11.97%) patients (14 severe and 3 critical) were included in the severe group. Significant differences in age (56.88±11.61 years vs. 48.04±16.66 years, *P*=0.010), body mass index (BMI) (26.13±5.47 kg/m^2 vs. 23.50±3.42 kg/m^2, *P*=0.007), hypertension (9 [52.94%] vs. 28 [22.40%], *P*=0.007) and fever (14 [82.35%] vs. 70 [56.00%], *P*=0.038) were noted between the severe and non-severe groups. Regarding clinical treatment, a greater proportion of patients in the severe group than the non-

severe group received glucocorticoids, antibiotics, oxygen, invasive mechanical ventilation and intensive care unit treatment (Table 1).

Baseline laboratory parameters

The baseline laboratory parameters of patients were obtained within 5 days of admission. Compared with those in the non-severe group, patients in the severe group exhibited increased levels of neutrophil%, fibrinogen, activated partial thromboplastin time (aPTT), C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), interferon-γ (INF-γ), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH), as well as reduced levels of lymphocyte%, lymphocyte count, platelet count, total cholesterol, HDL-C, LDL-C, ApoA1 and albumin (ALB). No significant differences in white blood cell (WBC) count, neutrophil count, red blood cell (RBC) count, haemoglobin, D-dimer, prothrombin time (PT), erythrocyte sedimentation rate (ESR), interleukin-2 (IL-2), interleukin-4 (IL-4), tumour necrosis factor-α (TNF-α), triglyceride, ApoB, lipoprotein (a), total bilirubin (TBil), direct bilirubin (DBIL), alanine aminotransferase (ALT), blood urea nitrogen (BUN), blood uric acid (BUA) or serum creatinine (Scr) were noted between the two groups (Table 2).

Risk factors of COVID-19 severity

Univariate logistic analysis showed that age, BMI, hypertension, neutrophil%, lymphocyte%, lymphocyte count, platelet count, fibrinogen, aPTT, CRP, IL-6, IL-10, HDL-C, ApoA1, ALB, AST and LDH were associated with the severity of COVID-19. However, only IL-6 (odds ratio [OR]: 1.097, 95% confidence interval [CI]: 1.034-1.165, P=0.002) and ApoA1 (OR: 0.865, 95% CI: 0.800-0.935, P<0.001) were recognized as independent risk factors by multivariate logistic analysis (Table 3).

A risk model was established using ApoA1 and IL-6. To predict the severity of COVID-19, the area under ROC curves (AUCs) for ApoA1, IL-6 and the risk model were 0.896 (95% CI: 0.834-0.941), 0.855 (95% CI: 0.786-0.908) and 0.977 (95% CI: 0.932-0.995), respectively (Figure 1, Table 4).

Correlation analyses showed that ApoA1 positively correlated with lymphocyte count (r=0.257, P=0.002), HDL-C (r=0.681, P<0.001) and ALB (r=0.412, P<0.001) but negatively correlated with fibrinogen (r=0.227, P=0.001), CRP (r=-0.337, P<0.001) and AST (r=-0.240, P=0.004). No correlations were found between ApoA1 and age, hypertension, neutrophil count, platelet count, IL-6, IL-10 and ALT (Figure 2).

Dynamic changes in ApoA1

Baseline ApoA1 levels in the severe group were significantly reduced compared with those in the non-severe group (P<0.001). ApoA1 levels in the severe group were increased during treatment (P<0.001); however, this trend was not observed in the non-severe group (P=0.223). In the recovery stage of COVID-19, no significant difference was noted between the two groups (P=0.560) (Figure 3).

Discussion

In this study, blood lipids in severe patients with COVID-19 differed from those in the non-severe patients. Specifically, baseline total cholesterol, HDL-C, LDL-C and ApoA1 levels in the severe group were considerably reduced compared with those in the non-severe group, whereas triglyceride, ApoB and lipoprotein (a) exhibited no significant differences between the two groups. Additionally, ApoA1 was recognized as an independent risk factor of disease severity using multivariate logistic analysis. Furthermore, ApoA1 had the highest AUC among all the single markers of COVID-19 severity, and the combination of ApoA1 and IL-6 yielded an increased AUC. On the other hand, the dynamic increase in ApoA1 in severe patients was parallel to disease improvement.

Previous studies have reported that lipid metabolism impairment may be involved in the pathogenesis of sepsis secondary to pneumonia and influenza [9-11]. Similarly, recent studies observed dyslipidaemia in patients infected with SARS-CoV-2, especially in the severe cases, using MS analysis, [6-8], indicating that blood lipids might serve as a marker of COVID-19 severity. Among the altered lipids, ApoA1 was significantly decreased.

ApoA1, a major protein component of the HDL complex, is involved in “reverse cholesterol transport” by transporting excess cholesterol from peripheral cells back to the liver for excretion. In addition, ApoA1 also has an anti-inflammatory role [12]. In acute inflammatory disease, serum amyloid A (SAA), an acute phase protein, displaces ApoA1 from the HDL complex; then, free ApoA1 is easily eliminated by the kidney, resulting in low levels in the peripheral blood [13]. On the other hand, liver is susceptible to attack by SARS-CoV-2, especially in severe cases [14]; therefore, reduced synthesis by the injured liver may also play a role.

Previous studies have revealed that serum ApoA1 is associated with the outcome of patients with sepsis and acute respiratory distress syndrome induced by pneumonia as well as critically ill patients [15-18]. A recent study reported that low ApoA1 levels are associated with COVID-19 severity, with an AUC of 0.728 for predicting its severity [19]. This study confirmed its role in distinguishing severe cases; however, the predictability of ApoA1 in this study was even higher than that noted in the former study, with an AUC as high as 0.896 (95% CI: 0.834-0.941), and ApoA1 levels were recognized as a risk factor of COVID-19 severity. The difference may be related to the different patients included. This study enrolled all clinical types, including mild, moderate, severe and critical cases, whereas the former study excluded critical patients. Moreover, although the sample size in this study was larger, the number of patients in the severe group (17, 11.97%) was smaller than that in the former study (25, 25.77%). Additionally, the former study was performed in Wuhan, the area most affected by the COVID-19 outbreak in China; therefore, the laboratory examination was potentially delayed. Thus, different time points for baseline detection may also play a role.

IL-6 plays a key role in the development of COVID-19, and its predictive value has been revealed previously by us and others [4, 5]. In this study, IL-6 and ApoA1 were identified as independent risk factors. Additionally, no significant correlation was noted between IL-6 and ApoA1. Due to their

complementarity, the risk model established by these two markers exhibited the highest predictive value, with an AUC of 0.977 (95% CI: 0.932-0.995).

ApoA1 and its mimetic peptide D-amino acids (D-4F) exhibit therapeutic potential in treating cancer, influenza, sepsis and a variety of lung diseases, such as acute respiratory distress syndrome (ARDS), mainly due to its anti-inflammatory, anti-oxidant and anti-apoptotic properties [12, 20-23]. In addition, it is noteworthy that ApoA1 inhibits IL-6 release and reduces macrophage activation. IL-6 is the main participant in the cytokine storm, and macrophages are the primary source of IL-6. Therefore, ApoA1 may exhibit therapeutic potential in treating patients with COVID-19. It might be worthwhile to test the efficacy and safety of ApoA1 in these patients.

Regarding study strengths, this study included all consecutive patients with COVID-19 admitted at HwaMei Hospital, University of Chinese Academy of Sciences, which received most local COVID-19 patients, for analysis of the predictive value of blood lipids for disease severity. Moreover, the predictive values of verified clinical characteristics and laboratory parameters were selected for comparison with blood lipids, which made the results more credible.

However, there were some limitations to this study. First, it was a single-centre retrospective study. Second, the sample size was relatively small, especially the number of severe cases. Third, the study was not validated with internal and external cohorts. Therefore, a prospective study with a large sample size is strongly encouraged.

Conclusion

In conclusion, this study shed light on a different blood lipid profiles in severe COVID-19 patients compared with non-severe patients. Specifically, low levels of total cholesterol, HDL-C, LDL-C and ApoA1 were noted in the severe group. ApoA1 is the best predictor of COVID-19 severity among all the single markers in this study, and the combination of ApoA1 and IL-6 enhanced the predictability. Furthermore, the dynamic increase in ApoA1 paralleled disease improvement. Therefore, ApoA1 might be a good indicator of COVID-19 severity that can be used to monitor the disease course. These findings might be helpful in disclosing the pathogenesis of and developing novel therapeutic strategies for COVID-19.

Abbreviations

COVID-19: coronavirus disease 2019; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA1: apolipoprotein A1; IL-6: interleukin-6; AUC: highest area under the receiver operator characteristic curve; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; EMR: electronic medical record.

Declarations

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Authors' Contribution

Yayun Yang and Zhe Zhu analyzed the data and wrote the manuscript. Linyan Fan collected clinical data and follow up. Shuyuan Ye and Kehong Lou collected the library data. Xin Hua, Zuoan Huang and Qiaoyun Shi performed laboratory analysis. Guosheng Gao designed the study and revised the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hwa Mei Hospital, University of Chinese Academy of Sciences (Certificate no. PJ-NBEY-KY-2020-061-01). Written informed consent was obtained from all participants.

Consent for publication

Written informed consent was obtained from all participants.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1. General clinical characteristics of patients with confirmed COVID-19.

Variables	All patients (n=142)	Non-severe group (n=125)	Severe group (n=17)	*P*-value
Age (years)	49.10±16.36	48.04±16.66	56.88±11.61	0.010
Men (%)	55 (38.73)	47 (37.60)	8 (47.06)	0.453
Body mass index (kg/m^2)	23.81±3.80	23.50±3.42	26.13±5.47	0.007
Comorbidities (%)				
Diabetes	12 (8.45)	11 (8.80)	1 (5.88)	>0.999
Hypertension	37 (26.06)	28 (22.40)	9 (52.94)	0.007
Cardiovascular disease	6 (4.23)	4 (3.20)	2 (11.76)	>0.999
Hepatic disease	10 (7.04)	6 (4.80)	4 (23.53)	0.131
Chronic lung disease	9 (6.34)	7 (5.60)	2 (11.76)	0.654
Cancer	5 (3.52)	4 (3.20)	1 (5.88)	>0.999
Initial symptoms (%)				
Fever	84 (59.15)	70 (56.00)	14 (82.35)	0.038
Nasal congestion	6 (4.23)	5 (4.00)	1 (5.88)	>0.999
Sore throat	18 (12.68)	16 (12.80)	2 (11.76)	>0.999
Headache/dizziness	10 (7.04)	9 (7.20)	1 (5.88)	>0.999
Chill	17 (11.9)	13 (10.4)	4 (23.53)	0.243
Dry mouth	1 (0.70)	0 (0.00)	1 (5.88)	0.120
Fatigue	27 (19.01)	24 (19.20)	3 (17.65)	>0.999
Nausea	3 (2.11)	2 (1.60)	1 (5.88)	0.320
Myalgia	10 (7.04)	9 (7.20)	1 (5.88)	>0.999
Chest distress	6 (4.23)	4 (3.20)	2 (11.76)	0.315
Cough	61 (42.96)	51(40.80)	10 (58.82)	0.159
Expectoration	32 (22.54)	27 (21.60)	5 (29.41)	0.670
Diarrhoea	5 (3.52)	5 (4.00)	0 (0.00)	>0.999
Anosmia	2 (1.41)	2 (1.60)	0 (0.00)	>0.999
No obvious symptoms	18 (12.68)	18 (14.40)	0 (0.00)	0.199
Treatment (%)				
Gamma globulin	88 (61.97)	78 (62.40)	10 (58.82)	0.776

Glucocorticoids	23 (16.20)	9 (7.20)	14 (82.35)	<0.001
Antibiotics	52 (36.62)	40 (32.00)	12 (70.59)	0.002
Antivirals	142 (100)	125 (100.00)	17 (100.00)	>0.999
Oxygen inhalation	53 (37.32)	36 (28.80)	17 (100.00)	<0.001
Invasive mechanical ventilation	2 (1.41)	0 (0.00)	2 (11.76)	0.014
Intensive care unit admission	3 (2.11)	0 (0.00)	3 (17.65)	0.001
ECMO	1 (0.70)	0 (0.00)	1 (5.88)	0.120

Data are presented as the mean ± standard deviation or n (%).

P-value indicates the comparison between the non-severe group and severe group.

COVID-19: coronavirus disease 2019, ECMO: extracorporeal membrane oxygenation.

Table 2. Baseline laboratory parameters of patients with confirmed COVID-19.

Variables	All patients (n=142)	Non-severe group (n=125)	Severe group (n=17)	*P*-value
WBC count ($\times 10^9$)	5.10 (4.20-6.80)	5.10 (4.25-6.70)	5.30 (4.15-7.35)	0.806
Neutrophil% (%)	66.25 (58.33-74.50)	65.70 (57.70-73.15)	73.00 (65.15-88.55)	0.005
Lymphocyte% (%)	24.45 (18.50-32.65)	25.80 (19.05-33.15)	19.20 (8.55-22.40)	0.004
Neutrophil count ($\times 10^9$)	3.31 (2.48-4.39)	3.27 (2.48-4.30)	3.72 (2.38-6.22)	0.295
Lymphocyte count ($\times 10^9$)	1.23 (0.87-1.61)	1.30 (0.91-1.66)	0.74 (0.48-1.16)	0.001
Platelet count ($\times 10^9$)	205.50 (155.75-252.25)	212.00 (165.00-256.00)	152.00 (120.50-205.00)	0.004
RBC count ($\times 10^{12}$)	4.48 (4.18-4.93)	4.50 (4.22-4.90)	4.32 (3.93-5.17)	0.660
Haemoglobin (g/L)	135.50 (125.00-143.25)	136.00 (125.50-143.00)	131.00 (121.00-151.00)	0.875
D-dimer (ng/ml) *	100.00 (75.00-163.22)	100.00 (75.00-159.00)	158.00 (73.00-245.00)	0.247
Fibrinogen (mg/dl)	430.50 (370.75-561.00)	429.00 (362.00-538.50)	574.30 (406.30-662.00)	0.012
Prothrombin time (s)	12.50 (11.50-12.70)	12.00 (11.50-12.60)	12.70 (11.55-13.50)	0.121
Activated partial thromboplastin time (s)	32.45 (30.45-35.80)	32.30 (30.30-35.40)	34.80 (32.05-41.00)	0.048
Erythrocyte sedimentation rate (mm/h) #	68.00 (41.00-96.00)	68.00 (38.00-93.25)	82.00 (57.50-104.50)	0.152
C-reactive protein (mg/L)	8.20 (1.64-28.82)	4.95 (1.26-25.41)	43.95 (15.36-71.79)	<0.001
Interleukin-2 (pg/ml)	0.90 (0.56-1.47)	0.90 (0.56-1.48)	0.91 (0.49-1.51)	0.725
Interleukin-4 (pg/ml)	1.85 (1.17-2.50)	1.85 (1.17-2.50)	1.99 (1.06-2.63)	0.688
Interleukin-6 (pg/ml)	3.79 (1.87-11.66)	3.66 (1.84-8.57)	24.11 (11.45-51.38)	<0.001
Interleukin-10 (pg/ml)	3.00 (2.02-4.60)	2.98 (1.91-4.39)	6.39 (2.89-9.55)	0.001
Interferon-γ (pg/ml)	1.19 (0.87-1.62)	1.16 (0.84-1.51)	1.96 (1.27-2.54)	<0.001
Tumour necrosis factor-α (pg/ml)	1.34 (0.98-1.69)	1.34 (0.97-1.69)	1.48 (1.17-1.73)	0.377

Total cholesterol (mmol/L)	4.02 (3.57-4.55)	4.08 (3.69-4.63)	3.58 (3.06-3.85)	0.003
Triglyceride (mmol/L)	1.42 (0.95-2.00)	1.44 (0.98-2.00)	1.22 (0.83-2.29)	0.540
HDL-C (mmol/L)	1.08 (0.90-1.27)	1.09 (0.91-1.29)	0.93 (0.82-1.00)	0.020
LDL-C (mmol/L)	2.50 (2.15-2.81)	2.54 (2.18-2.85)	2.21 (1.93-2.49)	0.024
Apolipoprotein A1 (g/L)	1.20 (1.09-1.31)	1.22 (1.12-1.34)	0.98 (0.89-1.08)	<0.001
Apolipoprotein B (g/L)	0.81 (0.70-0.93)	0.81 (0.71-0.94)	0.76 (0.66-0.86)	0.223
Lipoprotein (a) (mg/L)	89.45 (47.20-147.27)	87.15 (47.75-161.15)	94.45 (36.55-135.40)	0.794
Albumin (g/L)	41.45 (38.13-44.85)	41.90 (38.85-45.20)	37.30 (32.10-41.25)	<0.001
Total bilirubin (μmol/L)	9.20 (6.70-13.65)	9.10 (6.70-13.60)	11.60 (7.30-14.35)	0.321
Direct bilirubin (μmol/L)	3.30 (2.40-4.30)	3.20 (2.35-4.15)	3.80 (3.15-6.15)	0.069
Aspartate aminotransferase (IU/L)	23.00 (17.00-29.00)	22.00 (17.00-28.00)	28.00 (19.50-40.50)	0.036
Alanine aminotransferase (IU/L)	21.00 (14.00-31.00)	20.00 (14.00-31.00)	26.00 (18.00-41.50)	0.089
Lactic dehydrogenase (IU/L)	216.00 (175.00-248.25)	212.00 (173.50-239.50)	245.00 (209.50-350.00)	0.006
Blood urea nitrogen (mmol/L)	4.23 (3.33-5.04)	4.22 (3.29-5.02)	4.58 (3.62-5.35)	0.259
Blood uric acid (μmol/L)	267.75 (215.82-346.52)	276.50 (220.35-344.95)	253.80 (193.40-379.40)	0.572
Serum creatinine (μmol/L)	57.35 (48.45-70.60)	57.30 (48.40-70.55)	64.40 (47.60-82.35)	0.483

Data are presented as medians and inter-quartile ranges.

P-value indicates the comparison between the non-severe group and severe group.

* D-dimer levels were assessed in 107 cases in the non-severe group and 11 cases in the severe group.

Erythrocyte sedimentation rate was assessed in 98 cases in the non-severe group and 13 cases the non-severe group.

COVID-19: coronavirus disease 2019, WBC: white blood cell, RBC: red blood cell, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

Table 3. Logistic regression of risk factors of COVID-19 severity.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	10.038	1.002-1.075	0.041			
Body mass index (kg/m^2)	1.186	1.041-1.351	0.010			
Hypertension	3.897	1.376-11.033	0.010			
Neutrophil% (%)	1.071	1.022-1.123	0.004			
Lymphocyte% (%)	0.924	0.872-0.978	0.007			
Lymphocyte count (×10^9)	0.154	0.043-0.549	0.004			
Platelet count (×10^9)	0.988	0.979-0.998	0.015			
Fibrinogen (mg/dl)	1.005	1.001-1.008	0.005			
Activated partial thromboplastin time (s)	1.083	0.997-1.176	0.060			
C-reactive protein (mg/L)	1.03	1.013-1.046	<0.001			
Interleukin-6 (pg/ml)	1.096	1.050-1.144	<0.001	1.097	1.034-1.165	0.002
Interleukin-10 (pg/ml)	1.121	1.020-1.231	0.017			
Interferon-γ (pg/ml)	0.996	0.955-1.038	0.840			
Total cholesterol (mmol/L)	0.558	0.288-1.081	0.084			
HDL-C (mmol/L)	0.088	0.008-0.931	0.043			
LDL-C (mmol/L)	0.591	0.258-1.352	0.213			
Apolipoprotein A1 (mg/dl)	0.885	0.839-0.934	<0.001	0.865	0.800-0.935	<0.001
Albumin (g/L)	0.791	0.700-0.893	<0.001			

Aspartate aminotransferase (IU/L)	1.036	1.006-1.066	0.016
Lactic dehydrogenase (IU/L)	1.009	1.003-1.016	0.003

COVID-19: coronavirus disease 2019, OR: odds ratio, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

Table 4. Predictive performance of apolipoprotein A1, interleukin-6 and the risk model for COVID-19 severity.

Variables	AUC (95% CI)	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Apolipoprotein A1	0.896 (0.834-0.941)	1.09 g/L	94.12 (71.20-99.00)	80.80 (72.80-87.30)	40.00 (24.90-56.70)	99.00 (94.60-99.80)
Interleukin-6	0.855 (0.786-0.908)	9.65 pg/ml	88.24 (63.50-98.20)	77.60 (69.30-84.60)	34.90 (21.00-50.90)	98.00 (92.90-99.70)
Risk model	0.977 (0.932-0.995)	/	100.00 (80.30-100.00)	88.89 (81.40-94.10)	58.60 (38.90-76.50)	100.00 (96.20-100.00)

COVID-19: coronavirus disease 2019, PPV: Positive predictive value, NPV: Negative predictive value.

Figures

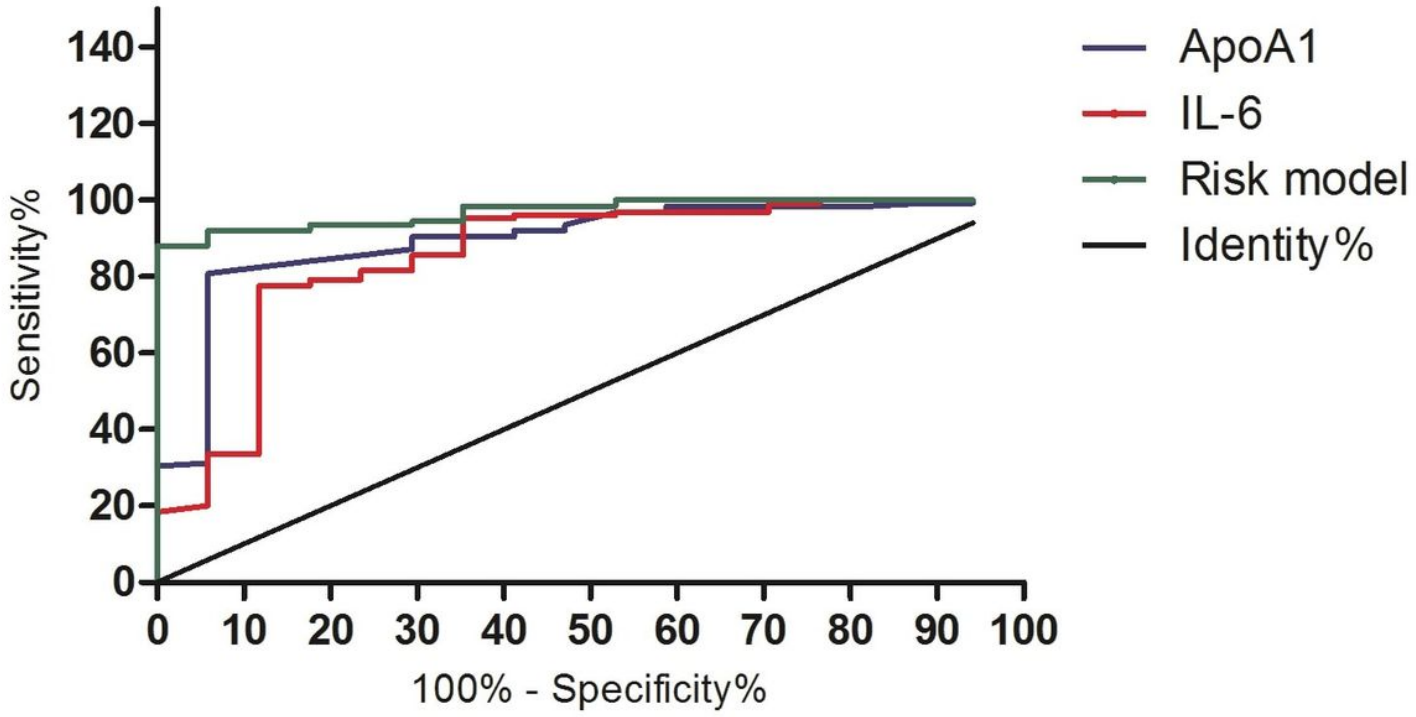

Figure 1

Receiver operator characteristic curves of ApoA1, IL-6 and risk model for the severity of COVID-19. COVID-19: coronavirus disease 2019, ApoA1: apolipoprotein A1, IL-6: interleukin-6.

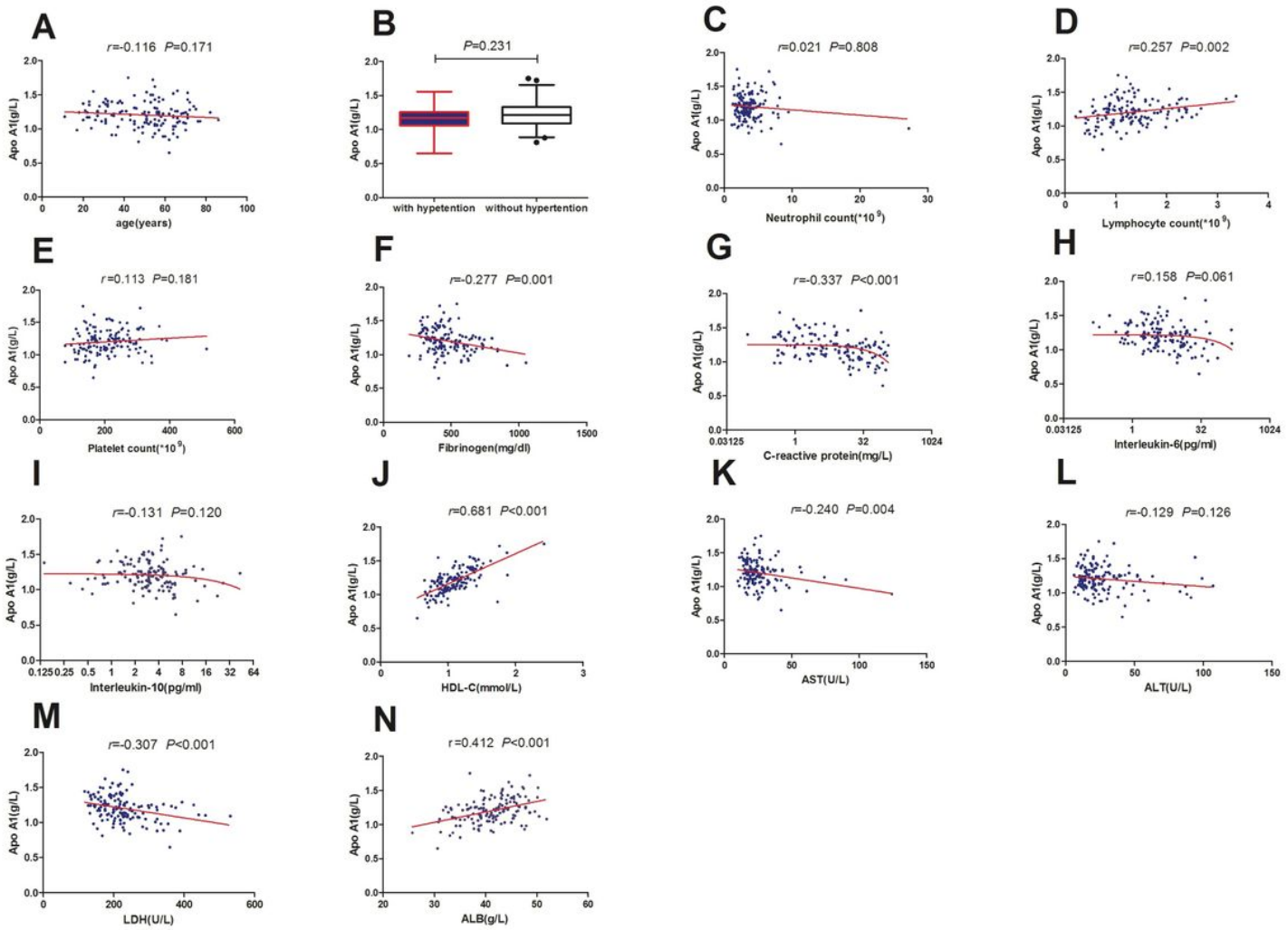

Figure 2

Correlations between ApoA1 and other parameters in patients with COVID-19. COVID-19: coronavirus disease 2019, ApoA1: apolipoprotein A1, HDL-C: high-density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, ALB: albumin.

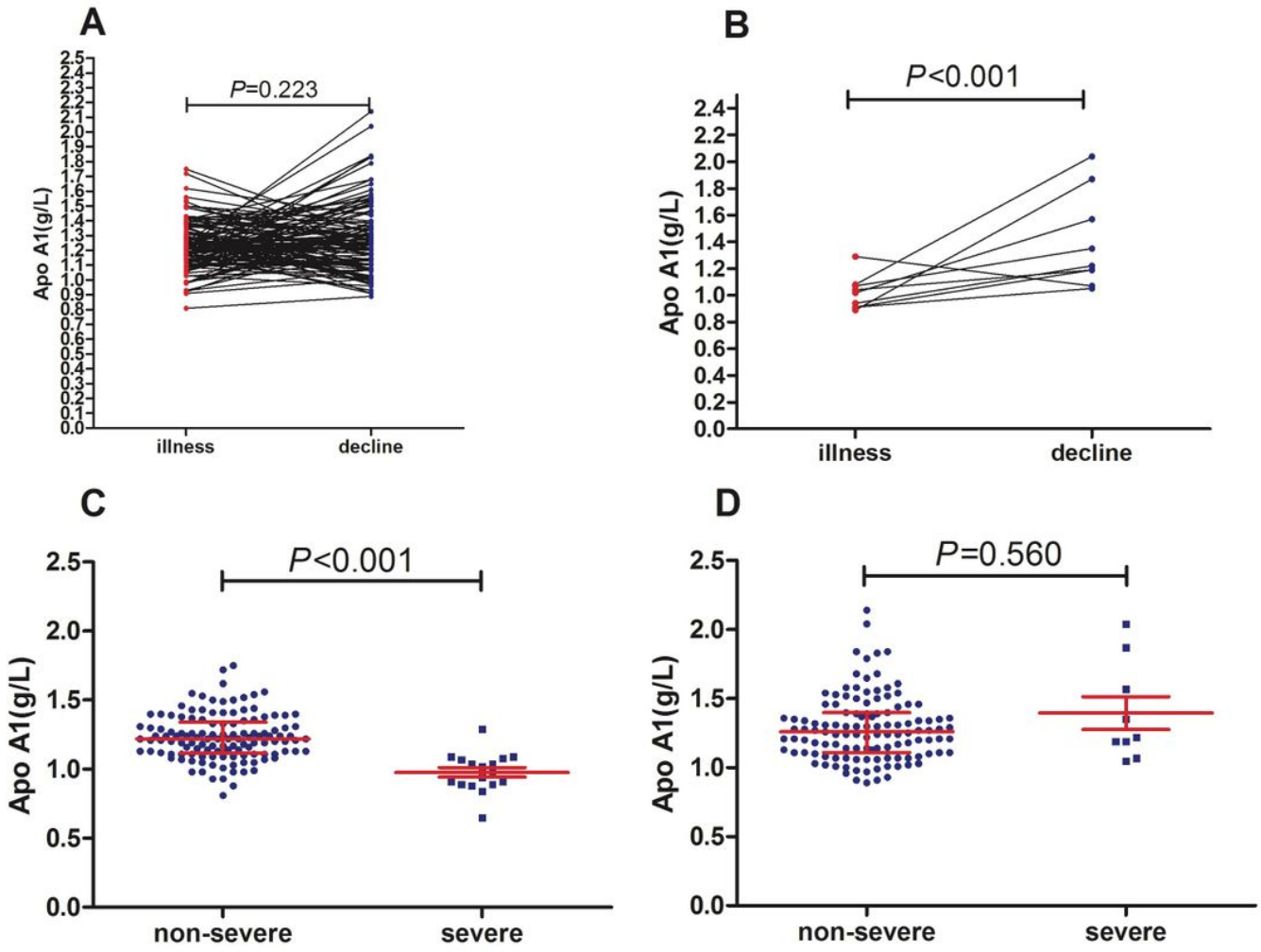

Figure 3

Dynamic change of ApoA1 in patients with COVID-19. (A). Dynamic change of ApoA1 in the non-severe group; (B). Dynamic change of ApoA1 in the severe group; (C). The comparison of ApoA1 between the non-severe and severe group at baseline. (D) The comparison of ApoA1 between the non-severe and severe group in the recovery stage of disease. COVID-19: coronavirus disease 2019, ApoA1: apolipoprotein A1.