Low serum level of apolipoprotein A1 is an indicator of severity in patients with coronavirus disease 2019

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Research

Keywords: COVID-19, SARS-CoV-2, blood lipid, ApoA1

Posted Date: May 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31251/v1

Abstract

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

Methods: All patients with COVID-19 who 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 analyzed.

Results: 142 consecutive patients with COVID-19 were included. There were 125 cases in the non-severe group and 17 cases in the severe group. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), 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 the severity of COVID-19. ApoA1 had the highest area under the receiver operator characteristic curve (AUROC) among all the single markers (AUROC: 0.896, 95% CI: 0.834-0.941). Moreover, the risk model established upon ApoA1 and IL-6 enhanced the predictability (AUROC: 0.977, 95% CI: 0.932-0.995). On the other hand, ApoA1 in the severe group elevated during the treatment, there was no significant difference between the severe and non-severe groups in the recovery stage of disease.

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

Introduction

The recent emerged pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) is a highly transmissible coronavirus which caused coronavirus disease 2019 (COVID–19) since December 2019, and spread worldwide rapidly. 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 ongoing COVID–19 pandemic has brought a huge pressure to the medical system globally. Although about 80% patients infected with SARS-CoV2 are mild [1], the remain severe cases may suffer from acute respiratory distress, multi-organ failure and death [2]. Therefore, it is necessary to discriminate the severe cases from mild cases.

Previous studies have found that the development of severe COVID–19 is associated with age, underlying disease, and severe patients are vulnerable to suffer from aberrant inflammation reaction and cytokine storm [3, 4]. Consequently, some clinical characteristic, inflammation index and cytokines have been used as markers to reflect the severity of COVID–19 by us and others [5, 6]. Recently, emerging evidence suggested that lipid metabolism dysregulation may involve into the progression of COVID–19 revealed bymass spectrometry (MS)-based proteomics analysis [7–9]. Although MS analysis is not common

performed, blood lipid is routinely examined by automatic biochemical instrument in clinically laboratory. Thus, blood lipid maybe considered as a potential and available marker for the severity of COVID–19.

In order to determine the predictive value of blood lipid for the severity of COVID–19, a retrospective study was carried out in Ningbo HwaMei Hospital, University of Chinese Academy of Sciences.

Materials And Methods

Study site and design

This was a single-center retrospective study performed at HwaMei Hospital, University of Chinese Academy of Sciences, a 2100-bed tertiary general hospital integrated with medical treatment, health care, disease prevention, teaching and scientific research. It was a designated hospital for COVID-19 during the SARS-CoV-2 epidemic, and received most of the patients with COVID-19 at Ningbo, Zhejiang province, China. This study was approved by the institutional ethics committee (Certificate no. PJ-NBEY-KY-2020-061-01).

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 Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia (Trial Version 6). All patients were divided into mild, moderate, severe and critical based on the severity of COVID-19. Mild and moderate patients were classified into the non-severe group, while severe and critical patients were categorized as the severe group. Severe patients should have one of the following features: a) shortness of breath with respiration rate (RR) more than 30 times per minute; b) blood oxygen saturation ≤93% at the state of rest; c) arterial blood oxygen partial pressure / inhaled oxygen concentration ≤300mm Hg. Lesion progressed more than 50% within 24-48 hours on pulmonary imaging were also considered as severe patients. Critical patients meet any of the following: a) respiratory failure, needing mechanical ventilation for therapy; b) shock; c) additional other organ failure, needing treatment in the intensive care unit.

General clinical characteristics including gender, age, comorbidities, initial symptoms and treatment, laboratory examination and follow-up data were collected from the electronic medical record (EMR).

Laboratory examination

SARS-CoV-2 RNA was detected by the Real-Time Fluorescent reverse transcription polymerase chain reaction (RT-PCR) (Daangene, China). Routine blood test was analyzed with the XS-1000i automatic hematology analyzer (Sysmex, Japan). Blood coagulation test was determined by the ACLTOP750

coagulation analyzer (Instrumentation Laboratory, USA). Biochemical parameters, including blood lipid, liver function indices and renal function indices, etc. were tested using a fully automatic biochemical analyzer (ADVIA2400, Siemens, Germany). Cytokines were detected by the flow cytometry with human Th1/2 cytokine kit (CellGene, China).

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 mean ± SD (standard deviation) and medians and interquartile range (IQR), respectively. Categorical variables were descripted as number (%). We assessed the differences between the non-severe and severe group using Student's *t*-test or Mann-Whitney U test for the normally or non-normally distributed continuous data, and using chi square or Fisher's exact test for the categorical variables. We used multivariate logistic regression analysis to explore independent risk factors for the severity of COVID-19, and performed receiver operator characteristic (ROC) curves 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

142 consecutive patients with confirmed COVID-19 were included in this study. The mean age was 49.10±16.36 years, 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%). There were still 18 cases (12.68%) showed no obvious symptoms when admission. All included patients received antivirals treatment, besides, 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 categorized as the severe group. There were 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/m2 vs 23.50±3.42 kg/m2, 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) between the severe and non-severe groups. As for clinical treatment, there were higher proportion in the severe group who received glucocorticoids, antibiotics, oxygen, invasive mechanical ventilation and intensive care unit treatment when compared with the non-severe group (Table 1).

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
Diarrhea	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 mean ± standard deviation or n (%).

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

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

Baseline laboratory parameters

The baseline laboratory parameters were obtained within 5 days of admission. Compared with those in the non-severe group, patients in the severe group had a higher level 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), and a lower level of lymphocyte%, lymphocyte count, platelet count, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1) and albumin (ALB). There were no significant differences in white blood cell (WBC) count, neutrophil count, red blood cell (RBC) count, hemoglobin, D-dimer, prothrombin time (PT), erythrocyte sedimentation rate (ESR), interleukin-2 (IL-2), interleukin-4 (IL-4), tumor necrosis factor-α (TNF-α), triglyceride (TG), apolipoprotein B (ApoB), lipoprotein (a), total bilirubin (TBil), Direct bilirubin (DBIL), alanine aminotransferase (ALT), blood urea nitrogen (BUN), blood uric acid (BUA) and serum creatinine (Scr) between the two groups (Table 2).

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
Hemoglobin (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
Tumor 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 indicated the comparison between the non-severe group and severe group.

* 107 cases in the non-severe group and 11 cases in the severe group tested D-dimer.

98 cases in the non-severe group and 13 cases the non-severe group tested erythrocyte sedimentation rate.

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.

Risk factors of the severity of COVID-19

The 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).

Table 3
Logistic regression of risk factors for the severity of COVID-19

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: odd ratio, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

A risk model was established upon ApoA1 and IL-6. For predicting the severity of COVID-19, the area under ROC curves (AUROCs) for ApoA1, IL-6 and 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).

Table 4

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

Variables	AUROC (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

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), while 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 change of ApoA1

The baseline ApoA1 in the severe group was significantly lower than that in the non-severe group (*P*<0.001). While, the ApoA1 level in the severe group elevated during the treatment (*P*<0.001), but it was

not found in the non-severe group (*P*=0.223). In the recovery stage of COVID-19, no significant difference was found between the two groups (*P*=0.560) (Figure 3).

Discussion

In this study, we found that the blood lipid in the severe patients with COVID–19 was differ from that in the non-severe patients, which showed baseline total cholesterol, HDL-C, LDL-C ApoA1 in the severe group were much lower than those in the non-severe group, while TG, ApoB and Lipoprotein (a) had no significant differences between the two groups. Additionally, ApoA1 was recognized as an independent risk factor for the severity of disease revealed by multivariate logistic analysis. Furthermore, ApoA1 had the highest AUROC among all the single markers for the severity of COVID–19, and the combination of ApoA1 and IL–6 got a higher AUROC. On the other hand, the dynamic raise of ApoA1 in the severe patients was parallel to the improvement of the disease.

Previous studies have found that lipid metabolism impairment may involve in the pathogenesis of sepsis secondly to pneumonia and influenza [10–12]. Similarly, recent studies observed the dyslipidemia in the patients infected with SARS-CoV–2 by MS analysis, especially in the severe cases[7–9], which reminded us that blood lipid might serve as a maker for the severity of COVID–19. While among the altered lipids, ApoA1 was very obviously decreased.

ApoA1, a major protein component of HDL complex, is known to involved in the “reverse cholesterol transport” by transporting cholesterol excess from peripheral cells back to the liver for excretion. Apart from it, ApoA1 also takes a part in the anti-inflammatory [13]. In acute inflammatory disease, serum amyloid A (SAA), an acute phase protein, displace ApoA1 from the HDL complex, then the free ApoA1 is easily eliminated by the kidney, resulting in a low level in the peripheral blood [14]. On the other hand, liver is susceptible to be attacked by SARS-CoV–2, especially in the severe cases [15], therefore, a decrease synthesis by the injured liver may also played a role.

Some previous studies have revealed that serum ApoA1 is associated with the outcome of patients with sepsis, acute respiratory distress syndrome induced by pneumonia, and critical ill [16–19]. A recent research observed that low level ApoA1 was associated with the severity of COVID–19, with an AUROC of 0.728 in predicting its severity [20]. Our study confirmed its role in distinguishing the severe cases, however, the predictability of ApoA1 in our study was even higher than the former, with an AUROC as high as 0.896 (95% CI:0.834–0.941), and recognized as a risk factor for the severity of COVID–19. The discrimination may be related to the different patients included. Our study group enrolled all clinical types which consist of mild, moderate, severe and critical, while the former excluded the critical type. Moreover, although the sample size in our study was larger, the patients in the severe group (17, 11.97%) was smaller than the former (25, 25.77%). Additionally, the former study performed in Wuhan, the most affected area by the COVID–19 outbreak in China, therefore, the laboratory examination may be delayed. Thus, the different time of baseline detection may also take a part.

As well known, IL–6 plays a key role in the development of COVID–19, and its predictive value have been revealed by us previously and others [5, 21]. In this study, IL–6 and ApoA1 were observed to be independent risk factors. Additionally, there was no significant correlation between IL–6 and ApoA1. Based on their complementarity, the risk model established by these two markers exhibited the highest predictability with AUROC of 0.977 (95% CI: 0.932–0.995).

ApoA1, and its mimetic peptide D-amino acids (D–4F) have showed their 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 [13, 22–25]. In addition, it was noteworthy that ApoA1 could inhibit the release of IL–6 and reduce the activation of macrophage. IL–6 was the main participant in cytokine storm, and macrophage was the primary source of IL–6. Therefore, ApoA1 may have therapeutic potential in treating patients with COVID–19.

There were some limitations in this study. First, it was a single center retrospective study. Second, the sample size was relatively small, especially of the severe cases. Third, it was not validated by internal and external cohorts. Therefore, a prospective study with a large sample size is warranted.

Conclusion

In conclusion, our study shed light on a different blood lipid profile in the severe patients with COVID–19 from non-severe patients, which manifest as low level of total cholesterol, HDL-C, LDL-C and ApoA1 in the severe group. ApoA1 is the best predictor for the severity of COVID–19 among all the single markers in this study, and the combination of ApoA1 and IL–6 enhanced the predictability. Furthermore, ApoA1 could serve as a tool to monitor the course of 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; AUROC: highest area under the receiver operator characteristic curve; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; EMR: electronic medical record.

Declarations

Acknowledgements

We thank all the medical staff of HwaMei Hospital, University of Chinese Academy of Sciences for their hard work and enormous contributions during the outbreak of COVID-19.

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.

Funding

This study was supported by the COVID-19 Platform Program of Hwa Mei Hospital, University of Chinese Academy of Sciences (2020HMZD21, 2020HMZD27).

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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Figures

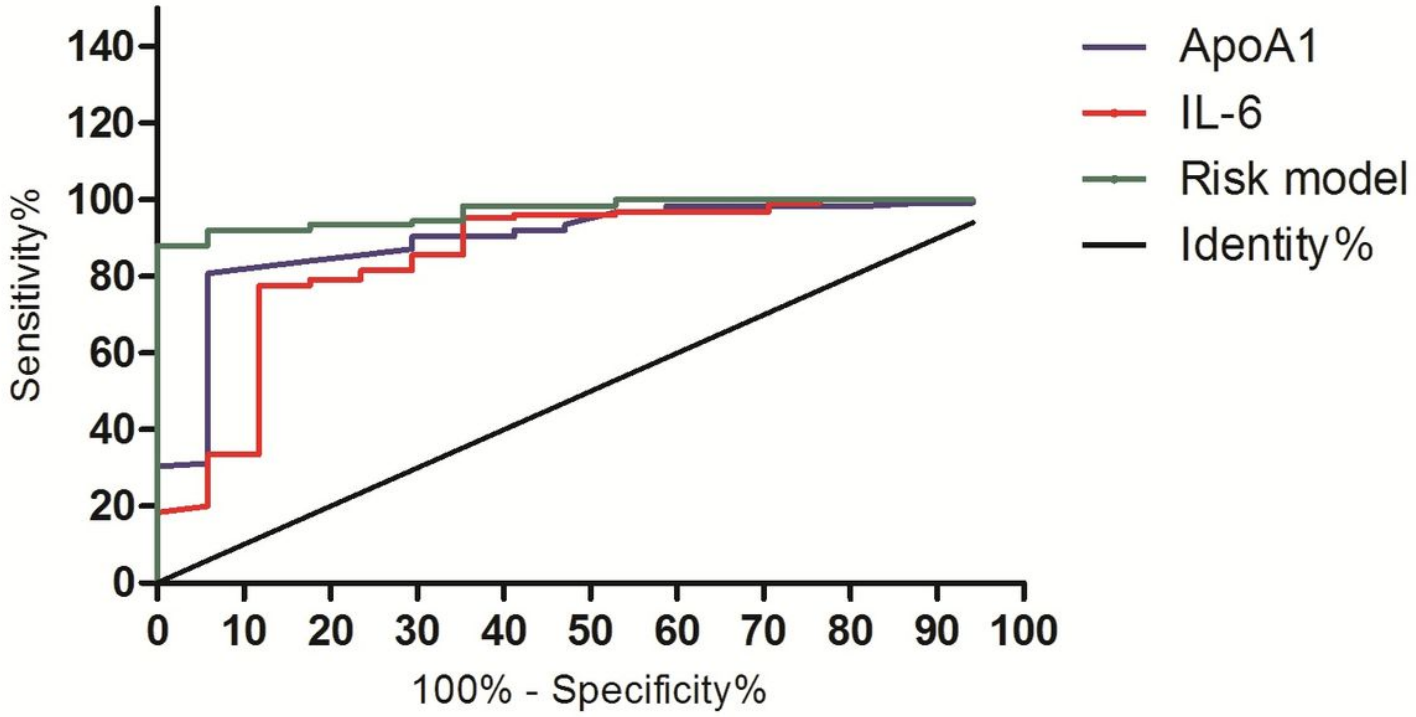

Figure 1

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

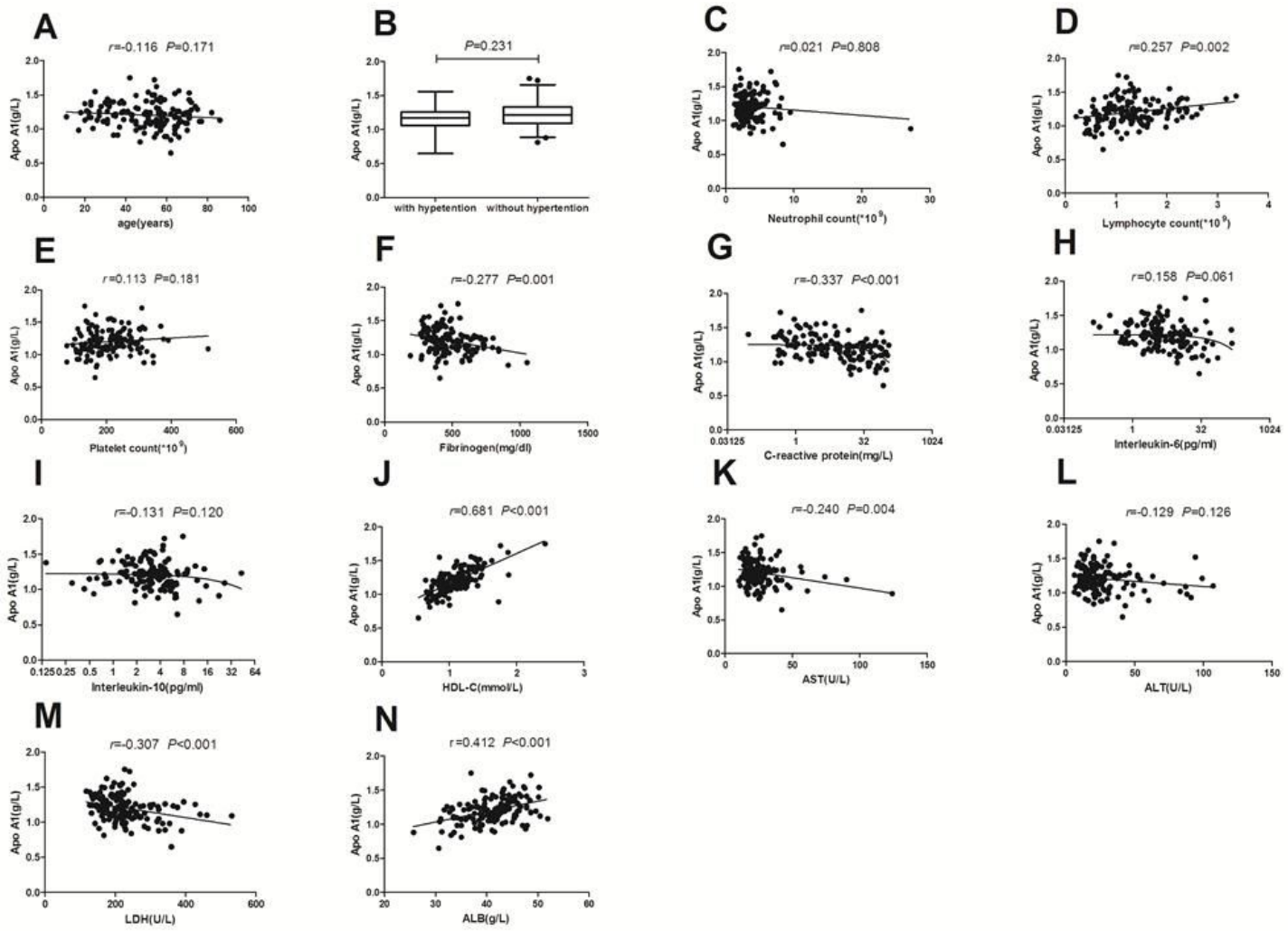

Figure 2

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

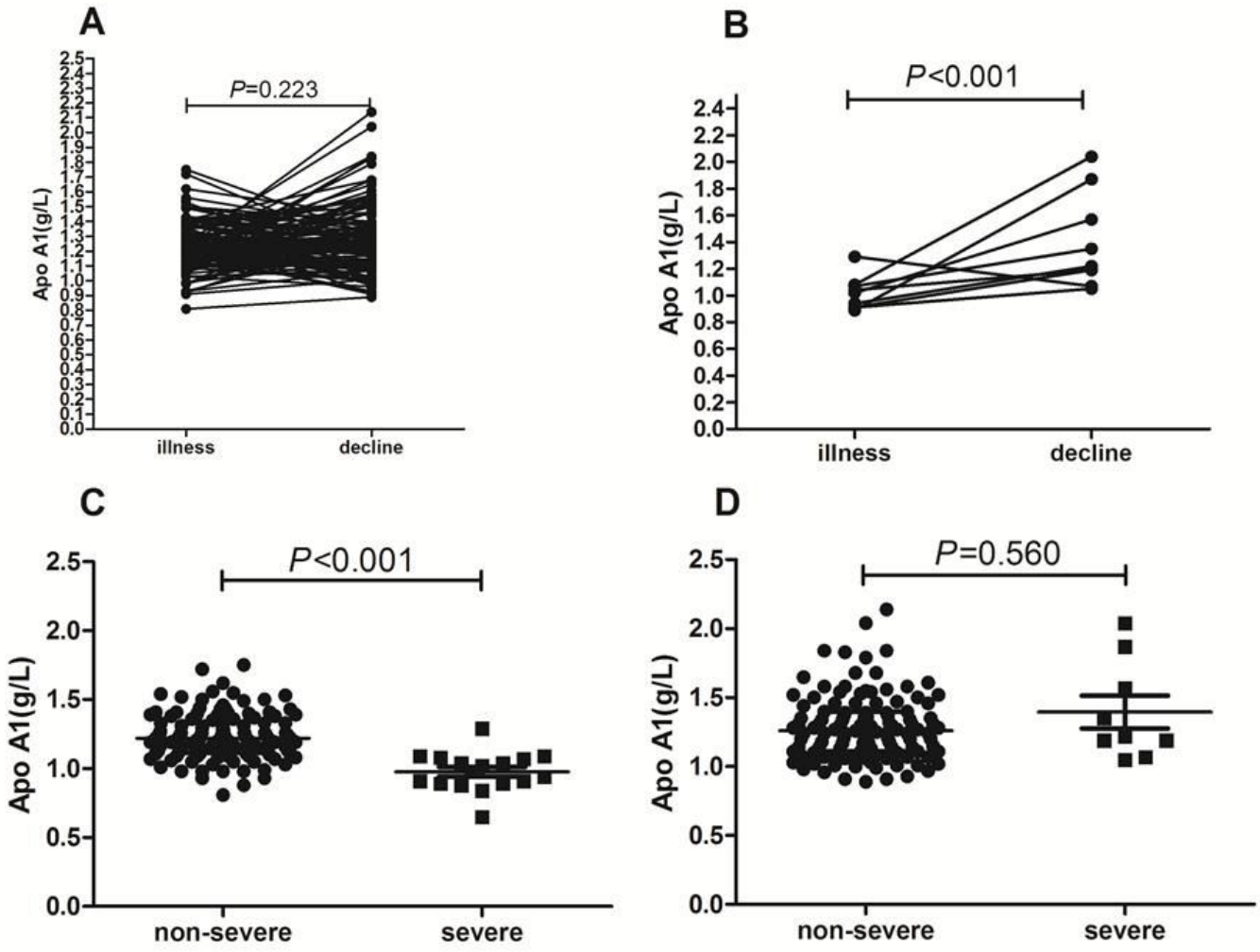

Figure 3

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