Low serum level of apolipoprotein A1 may predict the severity of COVID-19: A retrospective study

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Abstract

Background: Dyslipidemia has been observed in patients with coronavirus disease 2019 (COVID-19). This study aimed to investigate blood lipid profiles in patients with COVID-19 and to explore their predictive values for COVID-19 severity.

Methods: A total of 142 consecutive patients with COVID-19 were included in this single-center retrospective study. Blood lipid profile characteristics were investigated in patients with COVID-19 in comparison with 77 age- and gender-matched healthy subjects, their predictive values for COVID-19 severity were analyzed by using multivariable logistic regression analysis, and their prediction efficiencies were evaluated by using receiver operator characteristic (ROC) curves.

Results: There were 125 and 17 cases in the non-severe and severe groups, respectively. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A1 (ApoA1) gradually decreased across the groups in the following order: healthy controls, non-severe group, and severe group. ApoA1 was identified as an independent risk factor for COVID-19 severity (adjusted odds ratio [OR]: 0.865, 95% confidence interval [CI]: 0.800–0.935, p < 0.001), along with interleukin-6 (IL-6) (adjusted OR: 1.097, 95% CI: 1.034–1.165, p = 0.002). ApoA1 exhibited the highest area under the ROC curve (AUC) among all single markers (AUC: 0.896, 95% CI: 0.834–0.941); moreover, the risk model established using ApoA1 and IL-6 enhanced prediction efficiency (AUC: 0.977, 95% CI: 0.932–0.995).

Conclusion: Blood lipid profiles in patients with COVID-19 are quite abnormal compared with those in healthy subjects, especially in severe cases. Serum ApoA1 may represent a good indicator for predicting the severity of COVID-19.

Keywords
ApoA1, blood lipid, COVID-19, disease severity, SARS-CoV-2
INTRODUCTION

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. Although approximately 80% of patients infected with SARS-CoV-2 exhibit mild symptoms, the remaining severe cases may experience acute respiratory distress syndrome (ARDS), multiorgan failure (MOF), and death. 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 diseases, and patients who develop severe disease are likely to suffer from aberrant inflammatory reactions and cytokine storms. Consequently, several clinical characteristics, the inflammation index, and cytokine levels have been used as indicators for predicting the severity of COVID-19 by us and others. Emerging evidence suggests that lipid metabolism dysregulation might promote the progression of COVID-19, as revealed by mass spectrometry (MS)-based proteomics analysis. Although MS analysis is not commonly performed, blood lipids are routinely examined using automatic biochemical instruments in clinical laboratories. Additionally, dyslipidemia has also been observed in other respiratory infectious diseases. Therefore, blood lipids may be considered potential and available indicators of COVID-19 severity.

In a former study, serum hypolipidemia was identified in patients with COVID-19. However, that study did not analyze other blood lipid components, such as apolipoprotein A1 (ApoA1), ApoB, and lipoprotein (a), and their predictive values for COVID-19 severity are not fully understood. Therefore, to more comprehensively investigate blood lipid profiles in patients with COVID-19 and determine their predictive value for disease severity, a retrospective study was performed.

MATERIAL AND METHODS

Study design and participants selection

This was a single-center retrospective study approved by the institutional ethics board (PJ-NBEY-KY-2020–061–01). A total of 142 consecutive patients with COVID-19 were included from January 23 to April 20, 2020. In addition, 77 age- and gender-matched healthy subjects were selected for evaluating the characteristics of blood lipid profiles in patients with COVID-19.

The diagnosis of COVID-19 and its severity were determined according to the National Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia (6th 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 sputum, throat swabs, or nasopharyngeal swabs. Severe patients exhibited one of the following features: (a) respiratory distress with respiration rate (RR) greater than 30 breaths 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 (1 mmHg = 0.133 kPa); or (d) lesion rapidly progressed by more than 50% within one or two days as determined by pulmonary imaging.

General clinical characteristics, including gender, age, comorbidities, initial symptoms, treatment, and laboratory test data, were collected from the electronic medical records (EMRs).

Determination of blood lipids

Blood lipids were assessed using a fully automatic biochemical analyzer (ADVIA2400, Siemens) according to the manufacturer’s instructions (Purebio Biotechnology Co., Ltd). Briefly, total cholesterol (TC) was measured using the cholesterol oxidase-p-aminophenazone (CHOD-PAP) method; triglyceride (TG) was 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; and ApoA1, ApoB, and lipoprotein (a) were assessed using the immunoturbidimetric method.

Statistical analysis

SPSS software, version 16.0 (IBM) was used for statistical analysis. Normally and non-normally distributed continuous data were expressed as the mean ± SD (standard deviation) and median (interquartile range [IQR]), respectively. Categorical variables were reported as numbers (%). The Kruskal-Wallis test was used to compare blood lipids among the severe group, non-severe group, and healthy subjects, and post hoc pairwise comparisons were performed using the Nemenyi test. Differences between the two 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 adopted to explore independent risk factors for COVID-19 severity, receiver operator characteristic (ROC) curves were generated, and the areas under ROC curves (AUCs) were calculated to evaluate prediction efficiency. 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 38.73% of the patients were male. 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%).

Among the 142 patients, 17 (11.97%) and 125 (88.03%) patients were classified into the severe and non-severe groups during admission, respectively. Significant differences in age, body mass index (BMI), hypertension, hepatic disease, and fever were noted between the severe and non-severe groups. Regarding clinical treatment, a greater proportion of patients in the severe group received glucocorticoids, antibiotics, oxygen, invasive mechanical ventilation, and intensive care unit treatment (Table 1).

| 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/m²)    | 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)             | 0.017   |
| Cardiovascular disease     | 6 (4.23)               | 4 (3.20)                    | 2 (11.76)             | 0.152   |
| Hepatic disease            | 10 (7.04)              | 6 (4.80)                    | 4 (23.53)             | 0.019   |
| Chronic lung disease       | 9 (6.34)               | 7 (5.60)                    | 2 (11.76)             | 0.654   |
| Cancer                     | 5 (3.52)               | 4 (3.20)                    | 1 (5.88)              | 0.477   |
| 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)              | 0.542   |
| 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)             | 0.152   |
| Cough                      | 61 (42.96)             | 51 (40.80)                  | 10 (58.82)            | 0.159   |
| Expectoration              | 32 (22.54)             | 27 (21.60)                  | 5 (29.41)             | 0.679   |
| 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   |

Note: Data are presented as mean ± standard deviation or n (%). p-value indicates the comparison between the non-severe group and severe group.

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.
### 3.2 Laboratory findings

We first compared the general laboratory parameters between healthy controls and COVID-19 patients. Neutrophil%, C-reactive protein (CRP), aspartate aminotransferase (AST), and lactic dehydrogenase (LDH) were elevated, while white blood cell (WBC) count, lymphocyte%, lymphocyte count, platelet count, red blood cell (RBC) count, hemoglobin, albumin, total bilirubin (TBil), blood urea nitrogen (BUN), and blood uric acid (BUA) were decreased in patients with COVID-19 compared with healthy controls (Table 2).

We next compared general laboratory parameters, coagulation tests, and cytokine levels between severe and non-severe COVID-19 patients. Compared with those in the non-severe group, patients in the severe group exhibited increased neutrophil%, fibrinogen, activated partial thromboplastin time (aPTT), CRP, interleukin-10 (IL-10), interleukin-6 (IL-6), interferon-γ (INF-γ), AST, and LDH levels, as well as reduced lymphocyte count, platelet count, lymphocyte%, and albumin levels (Table 3).

| Variables                  | Healthy controls (n = 77) | COVID-19 patients (n = 142) | p-value |
|----------------------------|---------------------------|-----------------------------|---------|
| Age (years)                | 49.81 ± 13.00             | 49.10 ± 16.36               | 0.744   |
| Men (%)                    | 27 (35.06)                | 55 (38.73)                  | 0.592   |
| WBC count (x10^9)          | 5.75 (4.90–6.85)          | 5.10 (4.20–6.80)            | 0.010   |
| Neutrophil% (%)            | 57.00 (52.40–61.58)       | 66.25 (58.33–74.50)         | <0.001  |
| Lymphocyte% (%)            | 34.20 (29.03–38.98)       | 24.45 (18.50–32.65)         | <0.001  |
| Neutrophil count (x10^9)   | 3.19 (2.57–4.11)          | 3.31 (2.48–4.39)            | 0.722   |
| Lymphocyte count (x10^9)   | 1.90 (1.64–2.20)          | 1.23 (0.87–1.61)            | <0.001  |
| Platelet count (x10^12)    | 213.50 (187.25–259.00)    | 205.50 (155.75–252.25)      | 0.022   |
| RBC count (x10^12)         | 4.77 (4.36–5.15)          | 4.48 (4.18–4.93)            | 0.005   |
| Hemoglobin (g/L)           | 139.50 (131.00–153.00)    | 135.50 (125.00–143.25)      | 0.006   |
| CRP (mg/L)                 | 0.60 (0.35–1.33)          | 8.20 (1.64–28.82)           | <0.001  |
| Albumin (g/L)              | 46.60 (44.85–48.90)       | 41.45 (38.13–44.85)         | <0.001  |
| TBil (μmol/L)              | 9.90 (8.45–14.35)         | 9.20 (6.70–13.65)           | 0.036   |
| DBil (μmol/L)              | 3.40 (3.10–4.40)          | 3.30 (2.40–4.30)            | 0.056   |
| AST (IU/L)                 | 20.00 (17.00–24.00)       | 23.00 (17.00–29.00)         | 0.026   |
| ALT (IU/L)                 | 19.00 (14.00–26.50)       | 21.00 (14.00–31.00)         | 0.210   |
| LDH (IU/L)                 | 169.00 (154.50–199.00)    | 216.00 (175.00–248.25)      | <0.001  |
| BUN (mmol/L)               | 4.91 (3.99–5.40)          | 4.23 (3.33–5.04)            | <0.001  |
| BUA (μmol/L)               | 292.30 (251.85–359.25)    | 267.75 (215.82–346.52)      | 0.028   |
| Scr (μmol/L)               | 56.60 (50.05–74.55)       | 57.35 (48.45–70.60)         | 0.712   |

Note: Data are presented as mean ± standard deviation, n (%), or medians (interquartile ranges). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUA, blood uric acid; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DBil, direct bilirubin; LDH, Lactic dehydrogenase; RBC, red blood cell; Scr, serum creatinine; TBil, total bilirubin; WBC, white blood cell.

### 3.3 Baseline blood lipids

Baseline blood lipids were obtained within 5 days of admission. TC, HDL-C, LDL-C, and ApoA1 gradually decreased from the healthy controls to the non-severe group and the severe group. TG was higher in the non-severe group than in the healthy controls; however, no significant differences were found between the severe and non-severe groups or between the severe group and the healthy controls. There were no significant differences in ApoB or lipoprotein (a) among the three groups (Figure 1).

### 3.4 Risk factors for COVID-19 severity

Potential risk factors, including several general clinical characteristics, immunoinflammatory markers, and blood lipids, were first identified by univariate logistic analysis. Age, BMI, hypertension, neutrophil%, lymphocyte%, lymphocyte count, platelet count, fibrinogen, CRP, IL-6, IL-10, HDL-C, ApoA1, ALB, AST, and LDH were associated with the severity of COVID-19 (p < 0.05). However, aPTT, interferon-γ (IFN-γ), TC, and LDL-C were unrelated to COVID-19 severity (p > 0.05) (Figure 2). Next, variables with p < 0.1 in the univariate logistic analysis were entered into the multivariate logistic analysis. However, after adjusting for other potential risk factors, only IL-6 (adjusted odds ratio [OR]: 1.097, 95% confidence interval [CI]: 1.034–1.165, p = 0.002) and ApoA1 (adjusted OR: 0.865, 95% CI: 0.800–0.935, p < 0.001) were identified as independent risk factors by multivariate logistic analysis (Figure 3).
Therefore, a risk model was built using the combination of ApoA1 and IL-6. The mathematical formula of the risk model was log 
\( P \) = 12.303 + 0.093 * IL-6 – 0.145 * ApoA1.

In the prediction of COVID-19 severity, the AUCs (95% CI) of TC, HDL-C, LDL-C, ApoA1, IL-6, and the risk model were 0.726 (0.645–0.798), 0.674 (0.590–0.750), 0.669 (0.585–0.746), 0.896 (0.834–0.941), 0.855 (0.786–0.908), and 0.977 (0.932–0.995), respectively (Figure 4, Table 4). In particular, the sensitivity and specificity of Apo A1 were 94.12% (95% CI: 71.20%–99.00%) and 80.80% (95% CI: 72.80%–87.30%), respectively, which were both the highest among the above single markers. Moreover, the risk model increased the levels of sensitivity and specificity to 100.00% (95% CI: 80.30%–100.00%) and 89.89% (95% CI: 81.40%–94.10%), respectively.

### DISCUSSION

In this study, baseline TC, HDL-C, LDL-C, and ApoA1 gradually decreased across the groups in the following order: healthy controls, non-severe group, and severe group, indicating that they had potential roles in predicting the severity of COVID-19. Other blood lipids, including TG, ApoB, and lipoprotein (a), had little value in distinguishing COVID-19 severity. Additionally, we found that ApoA1 was most obviously decreased among the altered lipids in this study, representing an independent risk factor for COVID-19 severity. The combination of ApoA1 and IL-6 yielded even higher prediction efficiency.

In a recent study, Wei et al.\(^\text{11}\) observed that serum levels of TC, HDL-C, and LDL-C in patients with COVID-19 were significantly

| Variables                      | Non-severe group (n = 125) | Severe group (n = 17) | p-value |
|-------------------------------|-----------------------------|-----------------------|---------|
| WBC count (×10^9)             | 5.10 (4.25–6.70)            | 5.30 (4.15–7.35)      | 0.806   |
| Neutrophil% (%)               | 65.70 (57.70–73.15)         | 73.00 (65.15–88.55)   | 0.005   |
| Lymphocyte% (%)               | 25.80 (19.05–33.15)         | 19.20 (8.55–22.40)    | 0.004   |
| Neutrophil count (×10^9)      | 3.27 (2.48–4.30)            | 3.72 (2.38–6.22)      | 0.295   |
| Lymphocyte count (×10^9)      | 1.30 (0.91–1.66)            | 0.74 (0.48–1.16)      | 0.001   |
| Platelet count (×10^11)       | 212.00 (165.00–256.00)      | 152.00 (120.50–205.00)| 0.004   |
| RBC count (×10^12)            | 4.50 (4.22–4.90)            | 4.32 (3.93–5.17)      | 0.660   |
| Hemoglobin (g/L)              | 136.00 (125.50–143.00)      | 131.00 (121.00–151.00)| 0.875   |
| Fibrinogen (mg/dl)            | 429.00 (362.00–538.50)      | 574.30 (406.30–662.00)| 0.012   |
| PT (s)                        | 12.00 (11.50–12.60)         | 12.70 (11.55–13.50)   | 0.121   |
| aPTT (s)                      | 32.30 (30.30–35.40)         | 34.80 (32.05–41.00)   | 0.048   |
| CRP (mg/L)                    | 4.95 (1.26–25.41)           | 43.95 (15.36–71.79)   | <0.001  |
| IL-2 (pg/ml)                  | 0.90 (0.56–1.48)            | 0.91 (0.49–1.51)      | 0.725   |
| IL-4 (pg/ml)                  | 1.85 (1.17–2.50)            | 1.99 (1.06–2.63)      | 0.688   |
| IL-6 (pg/ml)                  | 3.66 (1.84–8.57)            | 24.11 (11.45–51.38)   | <0.001  |
| IL-10 (pg/ml)                 | 2.98 (1.91–4.39)            | 6.39 (2.89–9.55)      | 0.001   |
| IFN-γ (pg/ml)                 | 1.16 (0.84–1.51)            | 1.96 (1.27–2.54)      | <0.001  |
| TNF-α (pg/ml)                 | 1.34 (0.97–1.69)            | 1.48 (1.17–1.73)      | 0.377   |
| Albumin (g/L)                 | 41.90 (38.85–45.20)         | 37.30 (32.10–41.25)   | <0.001  |
| TBil (μmol/L)                 | 9.10 (6.70–13.60)           | 11.60 (7.30–14.35)    | 0.321   |
| DBil (μmol/L)                 | 3.20 (2.35–4.15)            | 3.80 (3.15–6.15)      | 0.069   |
| AST (IU/L)                    | 22.00 (17.00–28.00)         | 28.00 (19.50–40.50)   | 0.036   |
| ALT (IU/L)                    | 20.00 (14.00–31.00)         | 26.00 (18.00–41.50)   | 0.089   |
| LDH (IU/L)                    | 212.00 (173.50–239.50)      | 245.00 (209.50–350.00)| 0.006   |
| BUN (mmol/L)                  | 4.22 (3.29–5.02)            | 4.58 (3.62–5.35)      | 0.259   |
| BUA (μmol/L)                  | 276.50 (220.35–344.95)      | 253.80 (193.40–379.40)| 0.572   |
| Scr (μmol/L)                  | 57.30 (48.40–70.55)         | 64.40 (47.60–82.35)   | 0.483   |

Note: Data are presented as medians (interquartile ranges).
Abbreviations: COVID-19, coronavirus disease 2019; WBC, white blood cell; RBC, red blood cell; PT, prothrombin time; aPTT, activated partial thromboplastin time; CRP, C-reactive protein; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; TBil, total bilirubin; DBil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, Lactic dehydrogenase; BUN, blood urea nitrogen; BUA, blood uric acid; Scr, serum creatinine.
FIGURE 1 Comparisons of blood lipids among the healthy controls, non-severe group, and severe group. Data are presented as medians (interquartile ranges). (A) The total cholesterol levels in the healthy controls, non-severe group, and severe group were 4.97 (4.55–5.79), 4.08 (3.69–4.63), and 3.58 (3.06–3.85) mmol/L, respectively. (B) The triglyceride levels in the healthy controls, non-severe group, and severe group were 1.04 (0.85–1.43), 1.44 (0.98–2.00), and 1.22 (0.83–2.29) mmol/L, respectively. (C) The HDL-C levels in the healthy controls, non-severe group, and severe group were 1.62 (1.35–1.92), 1.09 (0.91–1.29), and 0.93 (0.82–1.00) mmol/L, respectively. (D) The LDL-C levels in the healthy controls, non-severe group, and severe group were 2.77 (2.40–3.42), 2.54 (2.18–2.85), and 2.21 (1.93–2.49) mmol/L, respectively. (E) The ApoA1 levels in the healthy controls, non-severe group, and severe group were 1.45 (1.31–1.65), 1.22 (1.12–1.34), and 0.98 (0.89–1.08) g/L, respectively. (F) The ApoB levels in the healthy controls, non-severe group, and severe group were 0.86 (0.72–1.01), 0.81 (0.71–0.94), and 0.76 (0.66–0.86) g/L, respectively. (G) The lipoprotein (a) levels in the healthy controls, non-severe group, and severe group were 114.80 (62.20–202.90), 87.15 (47.75–161.15), 94.45 (36.55–135.40) mg/L, respectively. The Kruskal-Wallis test was used to compare differences among the three groups, and post hoc pairwise comparisons were performed using the Nemenyi test. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

FIGURE 2 Univariate logistic regression of risk factors for COVID-19 severity. Old age, high BMI, hypertension, increased neutrophil%, fibrinogen, C-reactive protein, interleukin-6, interleukin-10, aspartate aminotransferase, and lactic dehydrogenase and decreased lymphocyte%, lymphocyte count, platelet count, HDL-C, apolipoprotein A1, and albumin were associated with the severity of COVID-19 in univariate logistic regression analysis (all \( p < 0.05 \)). COVID-19: coronavirus disease 2019; OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol
FIGURE 3 Multivariate logistic regression of independent risk factors for COVID-19 severity. After adjusting for other potential risk factors, increased IL-6 (OR: 1.097, 95% CI: 1.034–1.165, \( p = 0.002 \)) and decreased ApoA1 (OR: 0.865, 95% CI: 0.800–0.935, \( p < 0.001 \)) were recognized as independent risk factors for COVID-19 severity. COVID-19: coronavirus disease 2019, OR: odds ratio, CI: confidence interval

FIGURE 4 Receiver operator characteristic curves of total cholesterol, HDL-C, LDL-C, ApoA1, IL-6, and risk model for the severity of COVID-19. COVID-19: coronavirus disease 2019, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ApoA1: apolipoprotein A1, IL-6: interleukin-6

| Variables                  | OR  | 95% CI            | \( p \)-value |
|----------------------------|-----|-------------------|---------------|
| Interleukin-6 (pg/ml)      | 1.097 | 1.034–1.165     | 0.002         |
| Apolipoprotein A1 (mg/dl)  | 0.865 | 0.800–0.935     | <0.001        |

TABLE 4 Predictive performance of blood lipids, interleukin-6, and the risk model for COVID-19 severity

| Variables                  | AUC (95% CI) | Cutoff value | Sensitivity % (95% CI) | Specificity % (95% CI) | PPV % (95% CI) | NPV % (95% CI) |
|----------------------------|--------------|--------------|------------------------|------------------------|----------------|----------------|
| Total cholesterol (mmol/L) | 0.726 (0.645–0.798) | 3.70          | 70.59 (44.10–89.60)  | 72.80 (64.10–80.40)  | 26.10 (14.30–41.10) | 94.80 (88.30–98.30) |
| HDL-C (mmol/L)             | 0.674 (0.590–0.750) | 1.00          | 82.35 (56.60–96.00)  | 62.40 (53.30–70.90)  | 23.00 (13.20–35.50) | 96.30 (89.50–99.20) |
| LDL-C (mmol/L)             | 0.669 (0.585–0.746) | 2.33          | 70.59 (44.10–89.60)  | 64.80 (55.80–73.10)  | 21.40 (11.60–34.40) | 94.20 (86.90–98.10) |
| ApoA1 (g/L)                | 0.896 (0.834–0.941) | 1.09          | 94.12 (71.20–99.00)  | 80.80 (72.80–87.30)  | 40.00 (24.90–56.70) | 99.00 (94.60–99.80) |
| IL-6 (pg/ml)               | 0.855 (0.786–0.908) | 9.65          | 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) |

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; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
lower than those in healthy subjects, especially in severe and critical cases, which was similar to our study. Another study also found that LDL-C performed well in discriminating COVID-19 severity, it was gradually decreased across moderate, severe, and critical cases; however, HDL-C exhibited no significant differences among the three groups.12 These small discrepancies may be related to the heterogeneity of disease severity, different sample sizes, and testing methods. However, our study and others11,12 all showed that blood lipids have potential auxiliary value in distinguishing severe COVID-19 patients.

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 has an anti-inflammatory characteristic,13 suggesting its role in inflammatory diseases. 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.14–17 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.18 On the other hand, the liver is susceptible to attack by SARS-CoV-2, especially in severe cases19; therefore, reduced synthesis by the injured liver may also play a role.

IL-6 plays a key role in the development of COVID-19, and its predictive value for disease severity has been revealed previously by us and others.4,20–22 It was also found that increased IL-6 was associated with poor outcomes.22,23 In this study, IL-6 and ApoA1 were identified as independent risk factors for COVID-19 severity. The risk model established using 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 for treating cancer, influenza, sepsis, and ARDS, primarily due to their anti-inflammatory, anti-oxidant, and anti-apoptotic properties.13,24–27 In addition, it is noteworthy that ApoA1 inhibits IL-6 release and reduces macrophage activation,25 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 and its mimetics in treating these patients.

The main strength of this study is that the patients included in this study were treated without delay when infected with SARS-CoV-2, which may represent an early stage of the disease. Second, this study enrolled healthy controls to analyze trends in blood lipids among healthy subjects, non-severe cases, and severe cases. Third, the predictive values of verified clinical characteristics and laboratory parameters were selected for comparison with blood lipids, making the results more credible. Finally, blood lipids were routinely tested by using an automatic biochemical analyzer, with clinical application value.

A limitation of this study is that it was a single-center retrospective study with a relatively small sample size that was not validated in internal or external cohorts. Therefore, a prospective study with a larger sample size is strongly encouraged.

In conclusion, this study sheds light on abnormal blood lipid profiles in patients with COVID-19 compared with healthy subjects, especially in severe cases. Specifically, TC, HDL-C, LDL-C, and ApoA1 gradually decreased from the healthy controls to non-severe and severe groups. Additionally, ApoA1 is a good indicator of COVID-19 severity, and the combination of ApoA1 and IL-6 enhances model predictability. These findings might be helpful in disclosing the pathogenesis of COVID-19 and developing novel therapeutic strategies for COVID-19.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
Zhe Zhu interpreted the data and wrote the paper. Yayun Yang, Linyan Fan, Shuyuan Ye, and Kehong Lou collected and analyzed the data. Xin Hua, Zuoan Huang, and Qiaoyun Shi performed laboratory analysis. Guosheng Gao designed the study and revised the paper.

ETHICAL APPROVAL
This study was approved by the institutional ethics board of HwaMei Hospital, Chinese Academy of Science (PJ-NBEY-KY-2020-061-01).

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

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