A Preliminary Study on Blood Lipid Profile in Patients with COVID-19

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Research

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Abstract

Background: Recently, dyslipidemia was observed in the patients with coronavirus disease 2019 (COVID-19). This study aimed to investigate the blood lipid profile in the patients with COVID-19, and explore their predictive value for COVID-19 severity.

Methods: 142 consecutive patients with COVID-19 admitted to HwaMei Hospital, University of Chinese Academy of Sciences, from January 23 to April 20, 2020, and 77 age- and gender-matched healthy subjects were included in this retrospective study. The blood lipid profile in the patients with COVID-19 were investigated, and their predictive values for COVID-19 severity were analysed.

Results: There were 125 and 17 cases in the non-severe and severe group, respectively. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A1 (ApoA1) gradually decreased across healthy controls, non-severe group, and severe group. ApoA1 was recognized as an independent risk factor for COVID-19 severity and 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 prediction efficiency (AUC: 0.977, 95% CI: 0.932-0.995).

Conclusion: The blood lipid profile in the patients with COVID-19 is quite abnormal from healthy subjects, especially in the severe cases. Serum ApoA1 might serve as a good indicator 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. 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 indicators 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, 7]. Although MS analysis is not commonly performed, blood lipid is routinely examined using automatic biochemical instruments in clinical laboratories. Thus, blood lipid may be considered as a potential and available indicator of COVID-19 severity.
To investigate the blood lipid profile in the patients with COVID-19 and determine their predictive value for COVID-19 severity, a retrospective study was performed.

**Methods**

**Study design and patient selection**

This was a single-centre retrospective study approved by the institutional ethics board of HwaMei Hospital, University of Chinese Academy of Science (PJ-NBEY-KY-2020-061-01). A total of 142 consecutive patients with COVID-19, from January 23 to April 20, 2020, and 77 age- and gender-matched healthy subjects were included.

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 swab or nasopharynx swab. Severe patients exhibited one of the following features: a) respiratory distress 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 (1 mmHg = 0.133 kPa); or d) lesion rapidly progressed by more than 50% within one or two days on pulmonary imaging.

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

**Determination of blood lipid**

Blood lipid was 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 (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; apolipoprotein A1 (ApoA1), ApoB and lipoprotein (a) were assessed using the immunoturbidimetric method.

**Statistical analysis**

SPSS software, version 16.0 (IBM, Armonk, NY, USA) were 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 (%). Kruskal-Wallis test was used to compare the blood lipids among severe group, non-severe group and healthy subjects,
and post hoc pairwise comparisons using the Nemenyi test. The differences between 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 of the COVID-19 severity, and receiver operator characteristic (ROC) curves were generated and the areas under ROC curves (AUCs) were calculated to evaluate their prediction efficiency. A $P$-value $< 0.05$ indicates statistical significance.

Results

General clinical characteristics

In total, 142 consecutive patients with confirmed COVID-19 and 77 healthy subjects were enrolled in this study. The mean age was 49.10 ± 16.36 years and 49.81 ± 13.00 years, and male proportion was 38.73% and 35.6%, respectively. There were no significant differences in age and gender between patients with COVID-19 and healthy subjects ($P = 0.727$ and 0.592, respectively). 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 group, respectively. Significant differences in age, body mass index (BMI), hypertension 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).
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/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)             | 0.007   |
| 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   |

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.
| Variables                  | All patients (n = 142) | Non-severe group (n = 125) | Severe group (n = 17) | P-value |
|---------------------------|------------------------|----------------------------|----------------------|---------|
| 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.

**Baseline blood lipid**

The baseline blood lipid was obtained within 5 days of admission. It was showed that TC, HDL-C, LDL-C and ApoA1 gradually decreased across healthy controls, non-severe group, and severe group. TG was higher in the non-severe group when compared with healthy controls, however, no significant differences
were found between the severe and non-severe group, and the severe group and healthy controls. There were no significant differences in ApoB and lipoprotein (a) among the three groups (Fig. 1).

**Other laboratory parameters**

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-10 (IL-10), interleukin-6 (IL-6), interferon-γ (INF-γ), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH), as well as reduced levels of lymphocyte count, platelet count, lymphocyte%, and albumin (ALB) (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 (× 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 (× 10^9)          | 3.31 (2.48–4.39)       | 3.27 (2.48–4.30)           | 3.72 (2.38–6.22)      | 0.295   |
| Lymphocyte count (× 10^9)          | 1.23 (0.87–1.61)       | 1.30 (0.91–1.66)           | 0.74 (0.48–1.16)      | 0.001   |
| Platelet count (× 10^9)            | 205.50 (155.75–252.25) | 212.00 (165.00–256.00)     | 152.00 (120.50–205.00)| 0.004   |
| RBC count (× 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   |
| 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   |
| 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  |

Data are presented as medians and inter-quartile ranges.

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

| Variables                     | All patients (n = 142) | Non-severe group (n = 125) | Severe group (n = 17) | P-value |
|-------------------------------|------------------------|-----------------------------|-----------------------|---------|
| 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   |
| 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.

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 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). Therefore, a risk model was build using the combination of ApoA1 and IL-6.
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/m²)          | 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 (× 10⁹)         | 0.154               | 0.043–0.549           | 0.004     |                      |                      |           |
| Platelet count (× 10⁹)           | 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     |                      |                      |           |

COVID-19: coronavirus disease 2019, OR: odds ratio, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.
| Variables                              | Univariate analysis |                  |          |                  |          | Multivariate analysis |                  |          |
|----------------------------------------|---------------------|------------------|----------|------------------|----------|-----------------------|------------------|----------|
|                                       | OR                  | 95% CI           | P-value  | OR               | 95% CI   | P-value               |                  |          |
| 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.

To predict the severity of COVID-19, the area under ROC curves (AUC, 95% CI) for 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 (Fig. 2, Table 4). Especially, the sensitivity and specificity of Apo A1 was 94.12% (95% CI: 71.20%-99.00%) and 80.80% (95% CI: 72.80%-87.30%) respectively, which were both highest among the above single markers. Moreover, the risk model enlarged both the level of sensitivity and specificity, with 100.00% (95% CI: 80.30%-100.00%) and 89.89% (95% CI: 81.40%-94.10%), respectively.
Table 4
Predictive performance of blood lipid, interleukin-6 and the risk model for COVID-19 severity.

| Variables               | AUC     | Cut-off value | Sensitivity % | Specificity % | PPV %     | NPV %     |
|-------------------------|---------|---------------|---------------|---------------|-----------|-----------|
|                         | (95% CI)| (95% CI)      | (95% CI)      | (95% CI)      | (95% CI)  | (95% CI)  |
| Total cholesterol       | 0.726   | 3.70          | 70.59         | 72.80         | 26.10     | 94.80     |
| (mmol/L)                | 0.645–  |              | (44.10–89.60) | (64.10–80.40) | (14.30–   | (88.30–   |
|                         | 0.798)  |               |               |               | 41.10)    | 98.30)    |
| HDL-C (mmol/L)         | 0.674   | 1.00          | 82.35         | 62.40         | 23.00     | 96.30     |
|                        | 0.590–  |              | (56.60–96.00) | (53.30–70.90) | (13.20–  | (89.50–  |
|                        | 0.750)  |               |               |               | 35.50)    | 99.20)    |
| LDL-C (mmol/L)         | 0.669   | 2.33          | 70.59         | 64.80         | 21.40     | 94.20     |
|                        | 0.585–  |              | (44.10–89.60) | (55.80–73.10) | (11.60–  | (86.90–  |
|                        | 0.746)  |               |               |               | 34.40)    | 98.10)    |
| Apolipoprotein A1      | 0.896   | 1.09          | 94.12         | 80.80         | 40.00     | 99.00     |
| (g/L)                  | 0.834–  |              | (71.20–99.00) | (72.80–87.30) | (24.90–  | (94.60–  |
|                        | 0.941)  |               |               |               | 56.70)    | 99.80)    |
| Interleukin-6 (pg/ml)  | 0.855   | 9.65          | 88.24         | 77.60         | 34.90     | 98.00     |
|                        | 0.786–  |              | (63.50–98.20) | (69.30–84.60) | (21.00–  | (92.90–  |
|                        | 0.908)  |               |               |               | 50.90)    | 99.70)    |
| Risk model             | 0.977   | /             | 100.00        | 88.89         | 58.60     | 100.00    |
|                        | 0.932–  |              | (80.30–100.00)| (81.40–94.10) | (38.90–  | (96.20–  |
|                        | 0.995)  |               |               |               | 76.50)    | 100.00)   |

COVID-19: coronavirus disease 2019, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, PPV: Positive predictive value, NPV: Negative predictive value.

Discussion

In this study, blood lipid profile in the patients with COVID-19 patients was abnormal from healthy subjects. Specifically, baseline TC, HDL-C, LDL-C, and ApoA1 gradually decreased across healthy controls, non-severe group, and severe group, whereas ApoB and lipoprotein (a) exhibited no significant differences among the three groups. Although TG was higher in the non-severe group when compared with healthy controls, no significant differences were found between the severe and non-severe group, and the severe group and healthy controls. Additionally, ApoA1 was recognized as an independent risk factor of disease severity using multivariate logistic analysis, and had the highest AUC, sensitivity and specificity among all the single markers for COVID-19 severity. Moreover, the combination of ApoA1 and IL-6 yielded a higher prediction efficiency.
Previous studies have reported that lipid metabolism impairment may be involved in the pathogenesis of sepsis secondary to pneumonia and influenza [8–10]. Similarly, recent studies observed dyslipidemia in patients infected with SARS-CoV-2, using MS analysis [6, 7] and routine laboratory lipid tests [11], indicating that blood lipid might involve in the pathogenesis of COVID-19. In the study of Wei et al. [11], a serum hypolipidemia was found in the COVID-19 patients, which showed that the serum level of TC, HDL-C and LDL-C in the patients with COVID-19 were significantly lower than healthy subjects, especially in the severe and critical cases. The above phenomenon was revealed again in the present. However, the former study did not analyse other blood lipid component, such as ApoA1, ApoB and lipoprotein (a), which were also routine tested, and their predictive values for COVID-19 severity were not fully understood. Among the altered lipids in this study, ApoA1 was significantly decreased, and serve as an independent risk factor for the COVID-19 severity.

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. Besides, ApoA1 has an anti-inflammatory characteristic [12], suggest its role in the inflammatory diseases. Previous studies have revealed that serum ApoA1 was associated with the outcome of patients with sepsis and acute respiratory distress syndrome induced by pneumonia, as well as critically ill patients [13–16]. 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 [17]. On the other hand, liver is susceptible to attack by SARS-CoV-2, especially in severe cases [18]; 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 has been revealed previously by us and others [4, 19]. In this study, IL-6 and ApoA1 were identified as independent risk factors. 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 [21]. 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.

The main strength of this study was that the patients included in this study were treated without delay when infected by SARS-CoV-2, which may represent the early stage of the disease. Second, it enrolled healthy controls to analysis the trends of blood lipid among healthy subjects, non-severe cases and severe cases. Third, the predictive values of verified clinical characteristics and laboratory parameters were selected to compared with blood lipid, which made the results more credible. Last, blood lipids were routinely tested by automatic biochemical analyser, with clinical application value.
The weakness of this study was that it was a single-centre retrospective study with relatively small sample size, and 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 an abnormal blood lipid profile in patients with COVID-19 from healthy subjects, especially in the severe cases. Specifically, TC, HDL-C, LDL-C, and ApoA1 gradually decrease across healthy controls, non-severe group, and severe group. Additionally, ApoA1 is a good indicator of COVID-19 severity, and the combination of ApoA1 and IL-6 enhances the predictability. These findings might be helpful in disclosing the pathogenesis of and developing novel therapeutic strategies for COVID-19.

**Abbreviations**

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

**Declarations**

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**Authors’ Contribution**

Zhe Zhu and Yayun Yang interpreted the data and wrote the paper. 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.

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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 institutional ethics board of HwaMei Hospital, University of Chinese Academy of Science (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

None.

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Figure 1

The comparison of blood lipid among healthy controls, non-severe group and severe group. HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B.
Figure 2

Receiver operator characteristic curves of blood lipid, 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.
Receiver operator characteristic curves of blood lipid, 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.