Plasma lipid profile: a predictive marker of disease severity among COVID-19 patients—an opportunity for low-income countries

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Abstract

Objective This study aimed to assess the correlation between body mass index (BMI) and plasma lipid profile levels in mild and severe COVID-19 patients.

Method This was a prospective, observational, cohort study, conducted in a medical referral center specializing in management of COVID-19 cases. Patients were divided into two groups according to infection severity (mild and severe). Blood samples were obtained from all patients who tested positive to a PCR test for measuring biochemical and inflammatory markers such as lactate dehydrogenase, ferritin, C-reactive protein, and d-dimer, as well as lipid profile, including total cholesterol, triacylglycerols, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), which were analyzed and compared between the two groups. Pearson’s correlation was used to assess the correlation between BMI and plasma lipid profile among mild and severe cases.

Results The levels of plasma triacylglycerols, d-dimer, lactate dehydrogenase, ferritin, and C-reactive protein with severe infection were significantly different between patients with mild and severe COVID-19 symptoms (p = 0.036, 0.03, 0.001, 0.014, and 0.006, respectively). A positive correlation between BMI and triglyceride levels was observed only in the severe infection group. However, HDL-C was negatively correlated with BMI.

Conclusion A routine lipid profile test might help as a marker of inflammation and risk stratification in patients with COVID-19. Especially in middle- or low-income countries, the test can rapidly help clinicians to delineate prognostic measures and hence management and treatment plans for this disease as the levels of the lipid profile were correlated with the patients’ BMI and infection severity.

Key Points
Plasma lipid levels may change in response to hyperinflammation that develops in severe COVID-19 infection.

COVID-19 patients with severe infection experience temporary hypertriglyceridemia.

A routine lipid profile may be used for evaluating severity of COVID-19 patients.

Introduction
Coronavirus disease 2019 (COVID-19), a life-threatening infectious disease, was seen for the first time in Wuhan 2019. The causative agent is the severe acute respiratory syndrome...
coronavirus 2 (SARS-CoV-2) [1–5]. It spread in a global pattern to become a serious pandemic [6–8]. As of March 2022, more than 485,243,022 people were infected with SARS-CoV-2, and about 6,137,553 have died as a result of this infection worldwide [9]. Even though a lot of information has been accumulated about the disease process and its pathophysiological aspects, the effects of this virus on some metabolic processes and physiological functions still need to be thoroughly investigated.

Patients with COVID-19 could have variations in the levels of their plasma lipid profiles. For example, triglyceride levels may be elevated or inappropriately average for a relatively poor nutritious status, while levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol may be decreased [10–20]. Several recent studies reported significantly decreased levels of LDL-C, HDL-C, and phospholipids in plasma in patients with acute COVID-19 when compared to normal individuals [11, 21, 22].

Moreover, contemporary data reported that patients who have dyslipidemia (i.e., increased plasma levels of cholesterol) are more vulnerable to infection with this virus. It is hypothesized that those patients are mostly receiving medications to treat hypercholesterolemia. This type of medication might inhibit the synthesis of cholesterol or decrease its absorption from the small intestine. Though it can increase angiotensin-converting enzyme 2 (ACE2) expression, such ACE2 receptors are located in lipid rafts enriched in cholesterol, which serve as an entry site for SARS-CoV-2 [23, 24]. On the other hand, 13,981 cases were evaluated in a recent cohort study conducted on patients receiving statins regularly as a treatment for hypercholesterolemia [25]. They concluded that these patients were at a lower risk for mortality and aggravated inflammatory response when they were infected with COVID-19 [25]. Furthermore, acute respiratory distress syndrome (ARDS) was seen to involve increased activity of secretory phospholipase A2 (sPLA2) in the lungs [26, 27]. The components of the surfactant are phospholipids, which include phosphatidylglycerol, and are hydrolyzed or degraded by sPLA2 [28]. Indeed, these data were reported in a recent study that verified lower levels of prostaglandins (PGs) in the broncho-alveolar lavage (BAL) fluid in ARDS patients when compared to normal volunteers. They justified their data by the hydrolysis of PGs through the increased activity of sPLA2 [26]. Previous studies have also revealed a correlation between COVID-19 infection and lipid profile levels (total cholesterol, LDL-C, and HDL-C) [10–20]. However, the correlation between body mass index (BMI) of patients with COVID-19 infection and their plasma lipid profile levels needs further evaluation. Our study aimed to evaluate the relation between the plasma lipid profile levels and BMI in patients infected with COVID-19.

Materials and Methods

Study Population

This was a prospective, non-randomized observational cohort study conducted from October 2020 to March 2021 at the Nasser General Hospital, which was considered a referral medical center located in Shoubra Al Kheimah, Al Qalyubia Governorate Egypt. Eligible patients were aged 25–84 years with PCR (polymerase chain reaction)-confirmed COVID-19. Patients were diagnosed as having COVID-19 disease when they had general COVID-19 symptoms in addition to respiratory symptoms (fever, sense of fatigue, dry cough, or hard breathing). These patients were tested using the COVID-19 IgG/IgM Rapid Test Kit (Abbexa, Cambridge, UK) to confirm the diagnosis. Patients were assessed by the treating specialists and were classified as group 1 (mild COVID-19) or group 2 (severe COVID-19) according to grade and stage.

Patients with any disorders that could interfere with lipid metabolism or cytokine cascades (autoimmune diseases), a known past medical history of dyslipidemia, chronic or acute kidney injury, and inadequate vascular access were excluded. Additionally, patients who had received medications such as corticosteroids, anti-inflammatory medications, and antibiotics prior to blood sampling were excluded to avoid any interference that might be caused by these medications. Clinical valuations involving history taking, present and past medication, as well as disease history were conducted to check that the patients had not had recent surgery or concomitant treatments listed under the exclusion criteria.

The study protocol was exempted from ethics approval from both Nasser General Hospital local ethics committee and Al Ain University as it was an observational non-interventional study. All study participants gave consent to be enrolled in the study.

Variables

Venous blood samples (4 mL) were obtained from all persons who tested positive to a COVID-19 PCR test and were divided into two aliquots: one aliquot was anticoagulated and divided into two test tubes. The first one was for hematological examinations of total leucocytes count (WBCs) using a Hema Screen 18-Automated Haematology Analyser (Hospitex Diagnostics, Sesto Fiorentino, Italy), and detection of hs-C-reactive protein (CRP) with a Hitachi Model 7600 Series Automatic Analyzer (Hitachi High Technologies Corporation, Hitachi, Japan).
The kits used in the experiments were \( \text{d-dimer PLUS} \) (Siemens Healthcare Diagnostics Products GmbH) and reagent kit for hs-CRP test (latex agglutination assay). Their reference values were 0.1417 (90% CL 0.00–0.55) \( \mu \text{g/mL} \) for \( \text{d-dimer} \), and < 6 mg/L for hs-CRP, respectively.

From other aliquots of blood, samples could clot, and sera were then separated by centrifugation (3,500 rpm, 20 min, 25°C) and stored at −20°C for later biochemical determinations (serum creatinine and lactate dehydrogenase (LDH)). Plasma levels of total cholesterol, LDL-C, HDL-C, triacylglycerols, and phospholipids were estimated using Synchron cx5 autoanalyzer (Beckman, USA) and calculated with the Friedewald formula.

**Statistical Analysis**

Based on a previous trial [29], we conducted a power analysis (G power version 3.1 statistical software, Franz Faul, Universität Kiel, Kiel, Germany). The findings indicated a minimum sample size of \( n = 110 \) patients (55 patients for each group) based on an \( \alpha \) of 5% and a power of 80%, considering a possible loss of about 10% of patients. All quantitative variables were tested for normality using the Shapiro–Wilks test, assessing normal distribution graphical presentations, skewness, and kurtosis coefficients. For normally distributed quantitative variables, descriptive data are presented as mean and standard deviation, for non-normally distributed quantitative variables, median and interquartile ranges are used to present central tendency and variability, while for qualitative data frequency and percentages are used. Continuous normally distributed data were tested with the independent \( t \) test, and non-normally distributed quantitative data with the Mann–Whitney \( U \) test. Qualitative data were tested using the chi-square and Fisher’s exact tests. All statistical tests were two-tailed and considered statistically significant at a \( p \) value < 0.05. Correlations between BMI and lipid profile parameters were investigated by Pearson’s correlation test. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) version 21.0.0.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Of 132 patients included in study, 20 patients were excluded as they did not fulfill inclusion criteria, while 112 patients were assigned to informed consent. Baseline characteristics between patients with mild and severe COVID-19 infection (i.e., groups 1 and 2) were not statistically different (Table 1).

As shown in Table 2, most of the biochemical parameters (i.e., plasma triacylglycerols, \( \text{d-dimer} \), lactate dehydrogenase, ferritin, CRP, and serum creatinine) evaluated in the study were statistically significantly different between the mild and severe COVID-19 infection groups.

### Table 1  Baseline characteristics of the patients in the two groups

| Parameter                        | Mild group \((n = 54)\) | Severe group \((n = 58)\) | \( p \) value |
|----------------------------------|-------------------------|---------------------------|---------------|
| Age, y, mean ± SD                | 55.22 ± 13.07           | 58.97 ± 14.40             | 0.154         |
| Gender, n%                       |                         |                           |               |
| Male                             | 42 (51.9%)              | 39 (48.1%)                | 0.291         |
| Female                           | 12 (38.7%)              | 19 (61.3%)                |               |
| BMI, kg/m\(^2\), mean ± SD       | 27.09 ± 3.15            | 27.41 ± 4.08              | 0.646         |
| Comorbidities, n%                |                         |                           |               |
| Hypertension                     | 22 (40.7%)              | 33 (56.9%)                | 0.094         |
| Diabetes                         | 23 (42.6%)              | 30 (51.7%)                | 0.351         |
| Ischemic heart disease           | 8 (14.8%)               | 12 (20.7%)                | 0.467         |
| Chronic kidney disease           | 3 (5.6%)                | 5 (8.6%)                  | 0.718         |
| Chronic liver disease            | 1 (1.6%)                | 4 (6.9%)                  | 0.365         |
| Heart failure                    | 2 (3.1%)                | 1 (1.7%)                  | 0.608         |
| Chronic obstructive pulmonary disease | 1 (1.9%)         | 1 (1.7%)                  | 1.0           |
| Asthma                           | 4 (7.4%)                | 3 (5.2%)                  | 0.71          |
| Medications, n%                  |                         |                           |               |
| Dexamethasone                    | 28 (51.9%)              | 19 (32.8%)                | 0.055         |
| Hydrocortisone                   | 6 (11.1%)               | 8 (13.8%)                 | 0.778         |
| Hydroxychloroquine               | 34 (63%)                | 45 (77.6%)                | 0.101         |

\( \text{BMI} \) body mass index

\( \Delta \) Adis
Table 3 represents a correlation between BMI and plasma lipid profile levels of patients with mild and severe COVID-19 infection using Pearson’s correlation. A relatively high correlation was observed between the BMI of severely infected patients and triacylglycerols levels ($p = 0.015$); however, a significantly negative correlation was observed with HDL-C ($p = 0.001$).

**Discussion**

Our study results revealed important changes in hematology parameters in COVID-19-positive patients. The hematology indices show that levels of white blood cells are higher when disease severity increases. Severe COVID 19 disease is usually associated with a significantly exaggerated inflammatory response known as a cytokine storm that is characterized by increased interleukins, leukocytes, neutrophils, other biomarkers such as CRP, and ferritin [30]. However, Zhang et al. reported decreasing leukocyte, lymphocyte, and eosinophil counts for patients infected with severe COVID-19 [31]. This can be explained by the fact that an uncontrolled COVID19 infection and immune response can lead to systemic breakdown and immune impairment [31].

In patients who tested positive for COVID-19, our results have shown a significant increase in LDH, CRP, serum creatinine, and ferritin in patients with severe COVID-19 compared with those with mild COVID-19. Gandini et al. confirmed that hyperferritinemia as a known inflammation factor has been found to be a predictor of ARDS in patients with COVID-19 infection [32]. In addition, hyperinflammation in patients with critical COVID-19 is likely to be beneficial for risk stratification by associated biomarkers (D-dimer, CRP, and ferritin) [33].

Several studies reported that SARS-CoV-2 infection could lead to blood dysfunction, leading to a hypercoagulable state [34–36]. Formation of micro-thrombosis that leads to occlusion of the small vessels in the pulmonary circulation of critically ill patients with COVID-19 has been demonstrated by recent evidence in lung pathology dissection [37]. CRP is also an acute-phase reactant (liver-produced inflammatory protein) that can increase under many conditions, such as infection and inflammation [34].

Our results indicate that unlike the plasma total cholesterol, LDL-C and HDL-C levels, the plasma triglyceride

| Parameters            | Normal range | Mild group ($n = 54$) | Severe group ($n = 58$) | $p$ value |
|-----------------------|--------------|-----------------------|-------------------------|-----------|
| n-Dimer (UgFEU/mL), median (IQR) | Less than 0.50 | 0.65 (0.2–0.72) | 0.50 (0.25–1.0) | 0.03*     |
| Lactate dehydrogenase (LDH) (U/L), median (IQR) | 140–280 | 265.5 (220.5–407.2) | 509.0 (344–610) | 0.001*    |
| Ferritin (ng/mL), median (IQR) | 20–300 | 311.0 (171.5–582) | 432.5 (286.7–980.2) | 0.014*    |
| C-reactive protein (IU/mL), median (IQR) | Less than 10.0 | 58.5 (10.3–99.2) | 97.3 (33.2–164.2) | 0.006     |
| Serum creatinine (mg/dL), median (IQR) | 0.6–1.2 | 1.2 (1.0–1.5) | 1.0 (1.0–1.5) | 0.10      |
| WBCs ($\times 10^9$/µL), median (IQR) | 4.0–11.0 | 6.25 (4.5–8.8) | 8.3 (5.2–12.1) | 0.005*    |
| Total cholesterol (mg/dL), mean ± SD | 200–240 | 193.6 ± 47.3 | 197.3 ± 62.1 | 0.759    |
| Triacylglycerols (mg/dL), mean ± SD | Up to 150 | 176.5 ± 87.5 | 192.0 ± 53.5 | 0.036*    |
| LDL-C (mg/dL), mean ± SD | Up to 100 | 105.7 ± 39.7 | 90.7 ± 33.6 | 0.193     |
| HDL-C (mg/dL), mean ± SD | Up to 30 | 38.6 ± 12.8 | 41.0 ± 12.7 | 0.559     |

HDL-C high-density lipoprotein cholesterol, IQR interquartile range, LDL-C low-density lipoprotein cholesterol, SD standard deviation, WBC white blood cell count

*p value < 0.05 was accepted as statistically significant

Table 2  Biochemical markers and lipid profile levels of patients with mild and severe COVID-19

| Parameters             | Normal range | Mild group ($n = 54$) | Severe group ($n = 58$) | $p$ value |
|------------------------|--------------|-----------------------|-------------------------|-----------|
| d-Dimer (UgFEU/mL), median (IQR) | Less than 0.50 | 0.65 (0.2–0.72) | 0.50 (0.25–1.0) | 0.03*     |
| Lactate dehydrogenase (LDH) (U/L), median (IQR) | 140–280 | 265.5 (220.5–407.2) | 509.0 (344–610) | 0.001*    |
| Ferritin (ng/mL), median (IQR) | 20–300 | 311.0 (171.5–582) | 432.5 (286.7–980.2) | 0.014*    |
| C-reactive protein (IU/mL), median (IQR) | Less than 10.0 | 58.5 (10.3–99.2) | 97.3 (33.2–164.2) | 0.006     |
| Serum creatinine (mg/dL), median (IQR) | 0.6–1.2 | 1.2 (1.0–1.5) | 1.0 (1.0–1.5) | 0.10      |
| WBCs ($\times 10^9$/µL), median (IQR) | 4.0–11.0 | 6.25 (4.5–8.8) | 8.3 (5.2–12.1) | 0.005*    |
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HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

*p value < 0.05 was accepted as statistically significant
levels were increased in patients with serious COVID-19 infection in comparison with those with mild infection. A number of recently published studies showed similar changes in plasma lipid levels in patients with some other infections (Gram-negative bacterial, viral, tuberculosis). In particular, total cholesterol, LDL-C, and HDL-C levels decrease and plasma triglyceride levels in a relatively poor nutritious status are elevated or inappropriately normal [10, 34–39].

Our findings showed that there is a relationship between plasma lipid profile and BMI. A positive correlation between BMI and triglyceride levels and disease severity has been observed. On the other hand, HDL-C was negatively correlated with BMI. BMI usually increases due to an increase in adiposity. This is described by increased triglycerides and decreased HDL-C [41]. These data suggest that changes in metabolic parameters might be expected to be related to aerobic fitness and to body fat distribution.

Our results support the evidence that a routine lipid profile test could help as a marker of inflammation and risk stratification in COVID-19 patients. It can help clinicians to delineate prognostic measures and hence management and treatment plans for this disease as lipid profile levels are correlated with patient BMI and infection severity.

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Conclusions

A routine lipid profile test could help as a marker of inflammation and risk stratification in COVID-19 patients in addition to other traditional markers. It can help clinicians delineate prognostic measures and hence proper management and treatment plans for this disease as lipid profile levels are correlated with patient BMI and infection severity.

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