Fecal Calprotectin as a Predictor of COVID-19 Severity

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Abstract

Coronavirus disease 2019 (COVID-19) is highly transmittable through contact with respiratory droplets. The virus is also shed in fecal matter. Some patients may present with effects in more than one system; however, there are no defined biomarkers that can accurately predict the course or progression of the disease. The present study aimed to estimate the severity of the disease, to correlate the severity of the disease with biochemical predictors, to identify valuable biomarkers indicative of gastrointestinal disease, and to determine the cutoff values. A cross-sectional study was conducted on COVID-19 patients admitted to the Kafrelsheikh University Hospital (isolation unit) between July 10, 2020, and October 30, 2020. The diagnosis of COVID-19 was confirmed via reverse transcription-polymerase chain reaction (RT-PCR), which was employed for the detection of the viral RNA. We conclude that lymphopenia, elevated C-reactive protein (CRP) level, and liver enzymes were among the most important laboratory findings in COVID-19 patients. Statistically significant differences in platelet count, neutrophil count, D-dimer level, and fecal calprotectin levels were observed among patients presenting with chest symptoms only and patients with both chest and gastrointestinal symptoms ($p = 0.004$; < 0.001; 0.010; 0.003; and < 0.001, respectively). C-reactive protein, D-dimer, and fecal calprotectin levels positively correlated with disease severity. The cutoff value for fecal calprotectin that can predict gastrointestinal involvement in COVID-19 was 165.0, with a sensitivity of 88.1% and a specificity of 76.5%.

Keywords

- coronavirus disease 2019
- severe acute respiratory syndrome coronavirus 2
- predictors in reflection of the severity in Covid 19 patients

Introduction

In Wuhan, Hubei Province, China, in December 2019, a COVID-19 outbreak caused by the 2019 novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred. Coronaviruses are a large family of viruses. It has been found that people are commonly infected with 4 human coronaviruses: 229E, NL63, OC43, and HKU1. Middle East respiratory syndrome

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(MERS), severe acute respiratory syndrome (SARS), and the most recently discovered coronavirus disease 2019 (COVID-19) cause infectious disease, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] COVID-19 is highly transmittable, mainly through contact with respiratory droplets. In addition, the virus can spread when small droplets released from the upper respiratory tract secretions of an infected individual land on surfaces and then individuals touch these surfaces and then, subsequently, touch their eyes, nose, or mouth.[2] The virus is also shed for an extended period in fecal matter.

The typical clinical manifestations of COVID-19 include fever, cough, and pneumonia, which can eventually lead to more severe respiratory failure and acute respiratory distress syndrome (ARDS). In addition, gastrointestinal manifestations include nausea and vomiting, abdominal pain, anorexia, and diarrhea in some cases, which can be explained by an abundant expression of Angiotensin-Converting Enzyme 2 (ACE2) in the epithelial cells of the gastrointestinal (GI) tract and the tissue distribution of ACE2 in the human body may also suggest potential infection routes and targets of SARS-CoV-2.[3] In $\sim$ 50% of patients, COVID-19 RNA was detected in feces. The virus may actively infect cells of the GI tract, replicating itself in the epithelium of the small and large intestines, which causes an excessive immunological reaction. The immunological reaction results in the production of numerous cytokines, including interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and interferon α (INF-α), by activated leukocytes and neutrophils. Acute liver injury in healthy individuals has been reported in a few studies. Mortality from COVID-19 was particularly high among patients with more advanced cirrhosis and those with alcohol-related liver disease.[4–6]

Calprotectin is a calcium- and zinc-binding protein of the S-100 family of proteins. It is widely considered as a useful tool for identifying damage to the intestinal mucosa. In fact, calprotectin is useful for the diagnosis of any organic intestinal disease that causes inflammation of the intestinal wall. The expression of calprotectin is mainly restricted to the intracellular compartment of neutrophils.[7]

D-dimer is a degradation product of cross-linked fibrin resulting from plasmin cleavage. The role of D-dimer in COVID-19 patients has not been fully investigated.[8]

To the best of our knowledge, no Egyptian studies that address the indicators of COVID-19 and the predictors of severity exist. The present study aimed to estimate the severity of the disease in patients admitted to the Kafrelsheikh University Hospital (isolation unit), to correlate the severity of the disease with biochemical predictors, to identify valuable biomarkers for gastrointestinal disease, and to determine the cutoff values.

Methods

Study Population

A cross-sectional study was conducted on COVID-19 patients admitted to the Kafrelsheikh University Hospital (isolation unit), a tertiary hospital, between July 10, 2020, and October 30, 2020. The diagnosis of COVID-19 was confirmed via reverse transcription-polymerase chain reaction (RT-PCR), which was used to detect the viral RNA (cobas 6800 system; Roche, Basel, Switzerland), according to the definitions by the World Health Organization (WHO) and the Egyptian Ministry of Health and Population (MOH).[8] The inclusion criteria included hospitalization due to COVID-19 (confirmed via RT-PCR test). We excluded every patient with a history of autoimmune disease, inflammatory bowel disease, or confirmed deep vein thrombosis or pulmonary embolism.

Laboratory and Imaging Methods

Complete blood count, coagulation profile, renal and liver function, D-dimer level, ferritin level, C-reactive protein (CRP) level, and fecal calprotectin level were determined routinely upon admission. The D-dimer level was measured via an immunoturbidimetric assay with a reference range of < 250 mg/L (CS-5100; Sysmex Corporation, Kobe, Japan). The seventh edition of the Chinese Novel Coronavirus Pneumonia Diagnosis and Treatment Plan incorporates computed tomography (CT) imaging into the criteria that clinically define COVID-19.[9]

Classification of Participants

The target group was subdivided into two groups according to the presentation of the disease. Group A consisted of patients who were positive for COVID-19 according to the PCR test and presented with chest symptoms only. Group B consisted of patients that were positive for COVID-19 according to the PCR test and presented with both chest and GI symptoms.

Severity Assessment

The clinical severity of the COVID-19 symptoms was classified into mild/moderate (►**Fig. 1a**) or severe/critically ill (►**Fig. 1b**), according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline developed by the National Health Commission of the People's Republic of China.[9] Radiologically, the area of the affected lungs consistent with viral pneumonia was determined from each the first chest CT of each patient after admission.

Sampling

The selected sample for our study included COVID-19 patients admitted to the isolation unit in the Kafrelsheikh University Hospital between July 10, 2020, and October 30, 2020.

Statistical Analyses

Data sorting and analysis were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). The qualitative variables were described using numbers and percentages. The chi-squared test was employed for the analysis (the Fisher exact test was used as an alternative to the chi-squared test if there were many small expected values). Numerical variables were expressed as medians (interquartile range [IQR]). The Mann–Whitney U-test (for non-normally distributed data) was employed for the

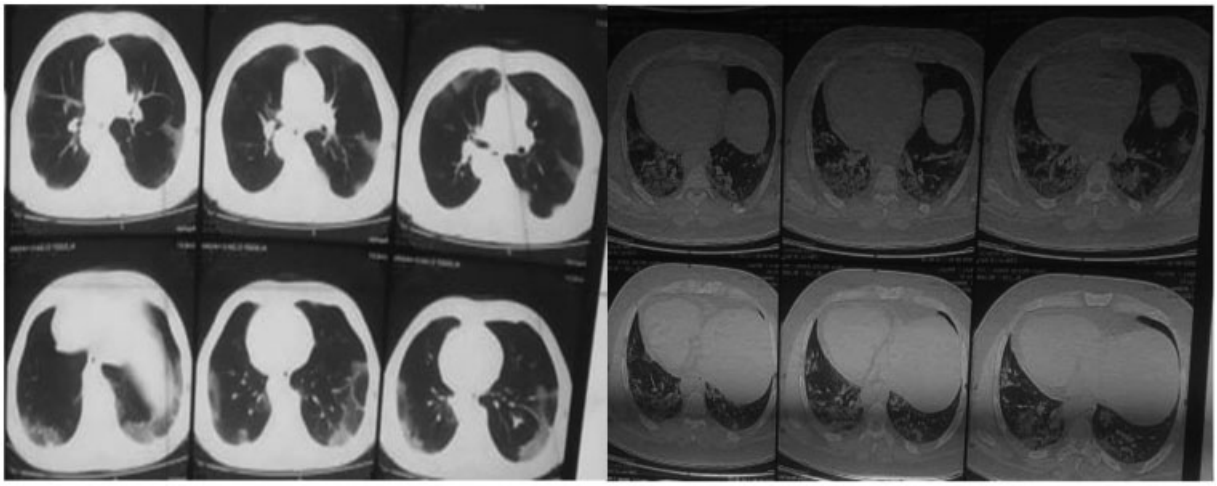

Fig. 1 (A) female patient, 40 years old, with mild covid 19 infection (B) male patient, 60 years old, with severe symptoms.

comparisons between the groups. The Spearman correlation coefficient was used for the correlation analysis between ordinal and non-normally distributed variables. Receiver operating characteristic (ROC) curves were used to determine the optimum cutoff points of parameters in severe patients. A p-value < 0.05 was adopted as the level of significance.

Ethics and Consents

Written informed consent was obtained from all adult participants or from the parents or legal guardians of patients < 18 years old. The study protocol was approved by the ethics committee of the Faculty of Medicine, Kafrelsheikh University. The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements.

Results

A total of 211 patients diagnosed with COVID-19 were selected to fulfill the inclusion criteria and were enrolled in the study. ►**Table 1** presents the demographics and laboratory information of the enrolled patients. The mean age of the patients was 40 years old, with no statistically significant difference between the groups ($p = 0.390$). The study participants consisted of 103 (48.8%) males and 108 (51.2%) females, with no significant difference between the groups. Platelet count, neutrophil count, D-dimer level, and serum and fecal calprotectin levels were significantly different between the groups ($p = 0.004$; < 0.001; 0.010; 0.003; and < 0.001, respectively). Disease severity was higher in Group B patients (with both GI and chest symptoms) compared with Group A patients (with chest manifestations only) ($p < 0.001$). No other significant differences in laboratory parameters between the groups were observed.

►**Table 2** presents the correlation between laboratory tests and disease severity in Group A. The CRP levels were significantly different between the disease severity groups ($p = 0.038$). No other significant differences were observed. ►**Table 3** presents the correlation between laboratory tests and disease severity in Group B. D-dimer and fecal calprotectin levels were significantly different between the disease severity groups ($p = 0.031$ and $p > 0.001$, respectively).

As presented in ►**Tables 4** and **5**, Spearman correlation analysis was conducted to determine the relationship between disease severity, CRP, D-dimer and fecal calprotectin levels in COVID-19 patients in group B (with both GI and chest symptoms). Disease severity was moderately correlated with fecal calprotectin, and such a correlation was statistically significant ($r = 0.672$; $n = 59$; $p < 0.001$). To better detect severe illness in COVID-19 patients in Group B (with both GI and chest symptoms), the ROC curve of fecal calprotectin was generated, as presented in ►**Fig. 2** (AUC $= 0.921$; 95% confidence interval [CI]: 0.855–0.987; $p < 0.001$). The best cutoff point to identify patients with GI symptoms using fecal calprotectin was 165.0, which results in a sensitivity of 88.1% and a specificity of 76.5%.

Discussion

The COVID-19 pandemic represents a catastrophic event worldwide. In patients, more than one system may be affected by COVID-19. In the present study, the relationship between disease severity and clinical and biochemical indicators was comprehensively analyzed.

The median age of the enrolled patients with COVID-19 was 40 years old, with no statistically significant differences in age or gender between the groups. The average age was slightly lower than the average age of COVID-19 patients reported by Huang et al. (median, 58 years; IQR, 39–67; range, 14–84 years old).[10] In our study, the most frequent laboratory abnormalities in both groups were lymphopenia, elevated CRP level, liver enzymes, platelet and neutrophil counts, D-dimer, and serum and fecal calprotectin levels. These results agreed with the published studies by Liu et al. and Wan et al.[11,12]

Hoffmann, Zhang, and colleagues indicated that SARS-CoV-2 binds to cells in the GI tract (for example, small and large intestinal epithelial cells), likely via specific receptors,

Table 1 Demographics and baseline characteristics of COVID-19 patients

	Group A ($n = 152$)	Group B ($n = 59$)	Total ($n = 211$)	Test	*p-value*
Male gender	70 (64.1%)	33 (55.9%)	103 (48.8%)	U	0.198
Female	82 (53.9%)	26 (44.1%)	108 (51.2%)		
Age	40.0 (40.0-50.0)	40.0 (38.0-50.0)	40.0 (40.0-50.0)	U	0.390
Hemoglobin (g/l)	13.5 (10.5-15.2)	13.4 (11.9-14.4)	13.6 (11.3-14.9)	U	0.960
WBC count ($\times 10^9$/L)	10.5 (7.8–15.4)	13.4 (8.5–16.5)	10.8 (8.1–15.8)	U	0.221
Platelet count ($\times 10^9$/L)	197.3 (136.3-247.5)	140.7 (118.5-213.0)	187.9 (128.8-228.8)	U	0.004*
Basophil count ($\times 10^9$/L)	0.3 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.3–0.5)	U	0.728
Eosinophil count ($\times 10^9$/L)	0.2 (0.1–0.6)	0.2 (0.1–0.4)	0.2 (0.1–0.6)	U	0.198
Neutrophil count ($\times 10^9$/L)	78.2 (54.6-86.2)	86.2 (74.9-90.2)	79.7 (62.0-88.0)	U	0.000*
Lymphocyte count ($\times 10^9$/L)	11.6 (7.2–18.2)	8.2 (6.1–16.2)	11.1 (6.7–18.1)	U	0.079
Monocyte count ($\times 10^9$/L)	8.1 (4.5–14.0)	6.5 (4.1–11.2)	7.9 (4.5–13.0)	U	0.058
C-reactive protein (mg/l)	50.0 (16.0-96.4)	80.0 (24.0-112.0)	52.8 (16.0-109.0)	U	0.067
D-dimer (ng/ml)	100.0 (20.0-221.0)	221 (20.0-1120.0)	100.0 (20.0-400.0)	U	0.010*
AST (U/L)	59.8 (25.2-120.0)	62.6 (28.9-130.8)	62.6 (28.0-120.0)	U	0.539
ALT (U/L)	51.7 (32.0-120.3)	81.0 (32.0-140.4)	57.6 (32.0-132.0)	U	0.083
Bilirubin (µmol/L)	0.7 (0.6–0.8)	0.9 (0.5–1.0)	0.7 (0.6–0.9)	U	0.003*
Albumin (g/dl)	3.6 (3.1–3.9)	3.7 (3.3–3.9)	3.7 (3.2–3.9)	U	0.326
Ferritin (ng/ml)	120.0 (50.0-300.0)	180.0 (60.0-300.0)	120.0 (50.0-300.0)	U	0.269
Fecal calprotectin (mic/g)	40.0 (20.0-70.0)	200.0 (150.0-250.0)	60.0 (30.0-150.0)	U	0.000*
Disease severity					
Mild/Moderate	150.0 (98.7%)	17.0 (28.8%)	167.0 (79.1%)	125.7	0.000*
Severe	2.0 (1.3%)	42.0 (71.2%)	44.0 (20.9%)		

*$p < 0.05$

such as ACE2 and the transmembrane serine protease 2.[13,14] In our study, we found that fecal calprotectin levels increased in patients with GI symptoms and was positively correlated with disease severity. The fecal calprotectin cutoff value for predicting gastrointestinal symptoms was 165.0, with a sensitivity of 88.1% and a specificity of 76.5%.[13,14]

Most patients in our study had mild to moderately severe symptoms. Only 20.9% of the patients presented with severe or critical disease. The biomarkers that positively correlated with disease severity were CRP in Group A (chest symptoms only) and D-dimer and fecal calprotectin in Group B (chest and GI symptoms). Querol-Ribelles et al. found a correlation between elevated levels of D-dimer and severe COVID-19 disease and a higher mortality rate of community-acquired pneumonia. Chen et al. also reported that the level of plasma CRP positively correlated with the severity of COVID-19 pneumonia.[15,16]

The present study has several limitations. First, it was conducted in a single center and on Egyptian patients only; therefore, we recommended further studies to confirm these findings. Second, we did not examine the serial values of the potential predictors while assessing COVID-19 patients. However, we believe that several points in the methodology overcome the limitations of previous studies. First, all patients in the study were examined and scored by the same experienced physician. Second, we classified the patients according to the National Health Commission of the People's Republic of China. Third, this was not a retrospective study; the investigation was conducted in a cross-sectional fashion and sometimes prospectively. Consequently, we collected all the potentially important clinical and laboratory parameters.

Conclusions

Lymphopenia, elevated CRP level, and liver enzymes are among the most important laboratory findings in COVID-19 patients. Platelet and neutrophil counts, D-dimer level, and fecal calprotectin level were significantly different between patients presenting only with chest symptoms and patients presenting with both chest and GI symptoms ($p = 0.004$; < 0.001; 0.010; 0.003; and < 0.001, respectively). C-reactive protein, D-dimer, and fecal calprotectin levels positively correlated with disease severity. The fecal calprotectin cutoff value for the prediction of gastrointestinal symptoms in COVID-19 patients is 165.0, with a sensitivity of 88.1% and a specificity of 76.5%.

Table 2 Correlation between disease severity and clinical and biochemical characteristics in COVID-19 patients presenting with chest symptoms only

	Mild/Moderate ($n = 150$)	Severe/Critical ($n = 2$)	Test	*p-value*
Male gender	70 (46.7%)	0 (0.0%)	FE	0.500
Female	80 (53.3%)	2 (100.0%)		
Age	40 (40–50)	40.0 (40.0–40.0)	U	0.639
Hemoglobin (g/l)	13.6 (10.5–15.3)	(8.1–9.7)	U	0.143
WBC count ($\times 10^9$/L)	10.7 (7.7–15.5)	(10.3–10.4)	U	0.884
Platelet count ($\times 10^9$/L)	197.3 (137.2-250.2)	(120.3–154.2)	U	0.352
Basophil count($\times$ 109/L)	0.3 (0.3–0.5)	(0.2–0.3)	U	0.585
Eosinophil count ($\times 10^9$/L)	0.2 (0.1–0.6)	(0.2–0.3)	U	0.915
Neutrophil count ($\times 10^9$/L)	78.0 (54.4–86.2)	(82.3–82.8)	U	0.410
Lymphocyte count ($\times 10^9$/L)	11.6 (7.2–18.4)	(11.1–11.7)	U	0.994
Monocyte count ($\times 10^9$/L)	8.5 (4.5–14.0)	(4.5–5.1)	U	0.336
C-reactive protein (mg/l)	49.0 (15.7–96.0)	(112.0–154.3)	U	0.038*
D-dimer (ng/ml)	100.0 (20.0–221.0)	(9.0–19.5)	U	0.168
AST (U/L)	57.0 (25.0–120.0)	(110.0–112.0)	U	0.378
ALT (U/L)	51.2 (32.0–120.0)	(60.3–90.1)	U	0.433
Bilirubin (mg/dl)	0.7 (0.6–0.8)	(0.5–0.6)	U	0.421
Albumin (g/dl)	3.7 (3.1–3.9)	(3.2–3.3)	U	0.436
Ferritin (ng/ml)	120.0 (50.0–300.0)	(30.0–115.0)	U	0.604
Fecal calprotectin (mic/g)	40.0 (20.0–62.5)	(70.0–80.0)	U	0.061

*$p < 0.05$

Table 3 Correlation between disease severity and clinical and biochemical characteristics in COVID-19 patients presenting with gastrointestinal and chest symptoms

	Mild/Moderate ($n = 17$)	Severe/Critical ($n = 42$)	Test	*p-value*
Male gender	11 (64.7%)	22 (52.4%)	0.746	0.388
Female	6 (35.3%)	20 (47.6%)		
Age	40.0 (35.0–45.0)	40.0 (39.0–55.0)	U	0.248
Hemoglobin (g/l)	13.4 (11.7–14.3)	13.7 (11.7–14.4)	U	0.893
WBC count ($\times 10^9$/L)	14.0 (8.5–17.1)	13.4 (7.4–15.9)	U	0.417
Platelet count($\times 10^9$/L)	154.0 (124.6–223.5)	140.2 (118.1-205.3)	U	0.332
Basophil count($\times 10^9$/L)	0.4 (0.2–0.5)	0.4 (0.3–0.5)	U	0.728
Eosinophil count ($\times 10^9$/L)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	U	0.864
Neutrophil count ($\times 10^9$/L)	86.7 (76.4–91.0)	83.7 (74.8–90.3)	U	0.947
Lymphocyte count ($\times 10^9$/L)	7.2 (5.5–17.6)	10.0 (6.0–16.7)	U	0.487
Monocyte count ($\times 10^9$/L)	5.2 (3.9–7.4)	7.2 (4.1–12.9)	U	0.119
C-reactive protein (mg/l)	112.0 (25.9–120.0)	76.8 (15.0–112.0)	U	0.113
D-dimer (ng/ml)	20.0 (15.0–855.0)	221.0 (45.0-1121.0)	U	0.031*
AST (units/L)	44.3 (24.7–100.4)	77.1 (28.9–142.9)	U	0.200
ALT (units/L)	60.0 (31.0–142.5)	109.6 (36.6–143.2)	U	0.389
Bilirubin (mg/dl)	0.7 (0.4–0.9)	0.9 (0.6–1.0)	U	0.194
Albumin (g/dl)	3.7 (3.3–3.8)	3.6 (3.3–3.9)	U	0.762
Ferritin ng/mL	120.0 (70.0–300.0)	190.0 (50.0–325.0)	U	0.847
Fecal calprotectin (mic/g)	150.0 (135.0–165.0)	200.0 (180.0-250.0)	U	0.000*

Values are expressed as median (IQR) or number (%).
*$p < 0.05$

Table 4 Correlation coefficient and p-value between disease severity and C-reactive protein in COVID-19 patients presenting with chest symptoms only

	rs	*p-value*
C-reactive protein (mg/l)	0.169	0.037*

*$p < 0.05$

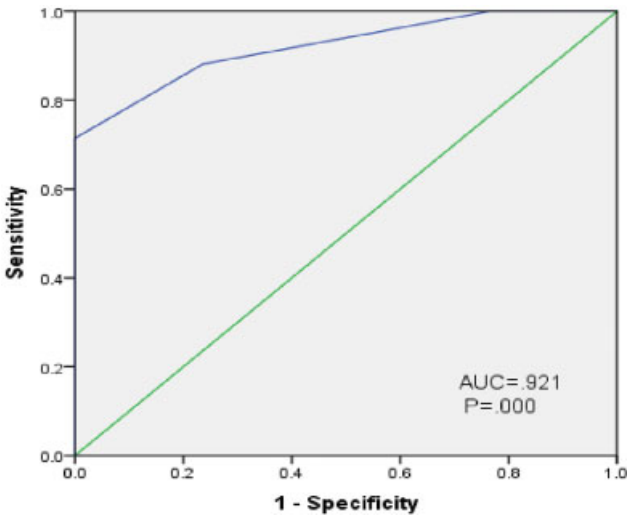

Fig. 2 ROC curve of fecal calprotectin between mild/moderate and severe/critical in COVID-19 patients group B (presenting with GI and chest symptoms).

Table 5 Correlation coefficient and p-value between disease severity and D-dimer and fecal calprotectin in COVID-19 patients group B (presenting with gastrointestinal and chest symptoms)

	rs	*p-value*
D-dimer (ng/ml)	0.284	0.029*
Fecal calprotectin (mic/g)	0.672	0.000*

*$p < 0.05$

Authors Contributions

Maksoud H. A. A. analyzed the data and Hussien M. interpreted the patient data. Mohamed A and Sherief D. E. collected the data. Nossier N. A. and Mabrok A. contributed with the writing of the manuscript.
All authors read and approved the final manuscript

Conflict of Interests

The authors have no conflict of interests to declare.

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