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Evaluation of serum IL-6 and fecal calprotectin in covid-19 positive patients with GIT symptoms as markers of intestinal inflammation

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Abstract

Generally, people who acquire infection with the COVID-19 virus exhibit a fever and respiratory illness. However, certain individuals also exhibit gastrointestinal (GIT) symptoms, involving anorexia, diarrhea, abdominal pain, nausea, and vomiting. This study aimed to quantify and assess serum interleukin 6 (IL-6) and fecal calprotectin (FC) in COVID-19-positive individuals who exhibit diarrhea and other GIT symptoms as indicators of inflammation in the intestinal tract. The investigation included 80 cases with diarrhea and other GIT symptoms. They were divided into two groups: group A (cases) consisted of 40 COVID-19 patients with GIT symptoms and group B (controls) consisted of 40 COVID-19 patients without GIT symptoms. Serum IL-6 and FC were assessed in both groups. The most effective cut-off value for predicting intestinal inflammation was >63, with a sensitivity of 67.5% and a specificity of 65%. The most effective cut-off value for predicting intestinal inflammation was >194, with a sensitivity of 87.6% and a specificity of 77.3%. Although the FC was more significant than serum IL-6, the difference in the area under curve (AUC) was insignificant (0.075; z-test= 1.632, p>0.05). In COVID-19 cases with experienced intestinal symptoms, serum IL-6 and FC were increased.

Keywords: COVID-19; Serum IL-6; Fecal Calprotectin; Intestinal Inflammation.

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Introduction

By the end of January 2020, severe acute respiratory syndrome corona virus 2 (SARS-Cov-2) was designated as an international health crisis by the World Health Organization. The virus, which is a member of the β-corona virus family, propagates primarily via the respiratory tract from person to person. For S spike-protein priming, it employs the transmembrane serine protease 2 and the angiotensin-converting-enzyme 2 (ACE2) receptors, which are in the pulmonary epithelium and other regions, such as the renal and gastrointestinal (GIT) systems. [1]

Fevers, coughs, and interstitial pneumonia are the most frequent symptoms of SARS-CoV-2 infection. Respiratory failure and acute respiratory distress syndrome are detected in

more severe cases. In besides respiratory symptoms, cases are increasingly experiencing vertigo and anorexia, vomiting, abdominal pain, and diarrhea. In certain instances, cases are asymptomatic. [2]

The virus vigorously invades the GIT district cells, replicated in the small and large intestine epithelium, and eliciting a significant immunological response in the host, as indicated by numerous studies. This response leads to the numerous cytokines synthesis, such as interleukin 6 (IL-6), interferon alpha (INF), and tumor necrosis factor alpha (TNF), via activated leukocytes. [3]

Calprotectin, a calcium and zinc binding protein of the S-100 proteins family, is produced by neutrophils (NEU). This protein was extensively investigated in inflammatory bowel disease and is a valuable instrument for identifying the injury to the intestinal mucosa. It is true that calprotectin is a positive acute phase protein and contributes in a variety of cellular physiological functions, such as NEU phagocytosis, adhesion, migration, and differentiation. Therefore, the NEU migration into the GIT as a result of an infection or inflammation is the cause of the calprotectin presence in the stool. [4] Fecal calprotectin (FC) was developed into a dependable fecal biomarker that enables the identification of intestinal inflammation in inflammatory bowel disease (IBD) and infectious colitis. [5]

SARS-CoV-2 is recognized for its ability to infect the lower respiratory system and induce viral pneumonia; however, it may also impact the GIT tract. According to reports, individuals who get infected with corona virus disease 2019 (COVID-19) may exhibit digestive symptoms such as nausea, diarrhea, and vomiting as disease presenting features. Nevertheless, the COVID-19 patients prognosis with GIT symptoms is largely unknown. The presence of SARS-CoV-2 in fecal samples and its viral RNA in intestinal mucosa indicate that the GIT may be a likely route for transmission in approximately 50% of COVID-19 cases.[6]

According research on SARS-CoV-2, its receptor ACE2 is an essential part of gastric mucosa and GIT cells. Consequently, the gastric mucosa or GIT tract may be regarded as a vulnerable position for SARS-CoV-2 infection. The virus's persistent presence in the gastric mucosa may suggest that gastric glandular epithelial cells serve as an incubation center for the virus. This is further supported by the viral nucleocapsid protein's presence in the cytoplasm of the GIT after it has been cleared from respiratory sputum over a period of days. [7] This study intended to assess serum IL-6 and FC as intestinal inflammation indicators in COVID-19-positive cases exhibiting GIT symptoms.

Patients and Methods

The study population: COVID-19 positive patients treated at Ain Shams University (ASU) Isolation Hospitals (El Midani Hospital, Geriatrics Hospital and Elobour Hospital).

Subjects were divided as follow:

The study included 80 patients divided into two groups: Group A (Cases) included 40 COVID-19 cases who experienced GIT symptoms, while Group B (Control) included 40 COVID cases who did not experience GIT symptoms. The criteria for exclusion included individuals diagnosed with IBD disease, cases under the age of 18, and patients with non-COVID-related intestinal inflammation (gastroenteritis).

Methods

All patients were subjected to history taking and clinical examination. For all study subjects, full laboratory investigations were performed at ASU hospitals. These included complete blood count (CBC) with Neutrophil/lymphocyte ratio, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). Also, we performed liver function tests including: aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, total bilirubin, international normalized ratio (INR). In addition, kidney function tests including: blood urea nitrogen (BUN), serum creatinine, Sodium, Potassium, uric acid. Ferritin, lactate dehydrogenase (LDH) and D-dimer were also assessed. COVID-19 was assessed by the polymerase chain reaction (PCR). Nasal and Oropharngeal swabs were performed. IL-6 was assessed by ELISA. Finally, FC was assessed by stool analysis.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Inc., Chicago, Illinois, USA, was used to analyze the recorded data. The mean± standard deviation (SD) and ranges were used for parametric (normal) quantitative data. The median with inter-quartile range (IQR) was used for non-normally distributed variables (non-parametric data). Qualitative variables are represented as percentages and numerical values. The data normality was confirmed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The following tests were done including the Mann-Whitney U test, the Chi-square test and Fisher's exact test. The Spearman's rank correlation coefficient (rs) was used. A scatter plot was used to displays the values of two variables along two axes. The overall predictivity of the parameter was determined through receiver operating characteristic (ROC) curve analysis. A 95% confidence interval was established, and a margin of error of 5% was established. A statistically significant result was indicated at *p*-value of less than 0.05 ($p<0.05$).

Results

Table 1 showed no difference in the demographic data among the two study groups. Also, the difference in the special habits between two study groups was statistically insignificant. There was no difference in the medical history among the study groups. There was a statistically significant increase in the mean platelets value between the control group, (252.68±66.61), compared to the cases group, (208.48±60.51), $p<0.05$. However, there was no significant difference in the total leucocyte count (TLC), and hemoglobin among the study groups.

Table 1. Comparison of demographic data, special habits, medical history and complete blood count (CBC) between the studied groups.

			Cases Group (n=40)	Control Group (n=40)	*p*-value
Demographic data	Age "years"	Mean ± SD	51.48±12.38	49.23±13.61	NS
		Range	22-83	19-83	
	Sex	Female	18 (45.0%)	16 (40.0%)	NS
		Male	22 (55.0%)	24 (60.0%)	
Special habits	Smoker		11 (27.5%)	12 (30.0%)	NS
	Alcohol		4 (10.0%)	0 (0.0%)	
	No		25 (62.5%)	28 (70.0%)	
Medical history	Free		12 (30.0%)	10 (25.0%)	NS
	CKD		1 (2.5%)	0 (0.0%)	NS
	DM		14 (35.0%)	15 (37.5%)	NS
	AF		2 (5.0%)	5 (12.5%)	NS
	HTN		20 (50.0%)	25 (62.5%)	NS
CBC	TLC	Median (IQR)	7.3 (4.8-12.3)	8.2 (6.3-10.1)	NS
		Range	2.3-32.5	3.3-33	
	Hb	Mean ± SD	12.34±2.40	12.07±1.95	NS
		Range	6.5-18.5	7-18	
	Platelets	Mean ± SD	208.48±60.51	252.68±66.61	0.029
		Range	17-515	112-486	

CBC: complete blood count, TLC: Total Leucocyte Count, Hb: hemoglobin, CKD: chronic kidney disease, DM: diabetes mellitus, AF: Atrial Fibrillation, HTN: hypertension, U=Mann-Whitney test for non-parametric data "Median (Interquartile range IQR)", X2: Chi-square test for Number (%) or Fisher's exact test, when appropriate, $p > 0.05$ is not significant (NS)

Table 2 shows that significant elevated the median value of lymphocytes in the control group was 1.0 (0.3-2.0) significantly elevated compared to the cases group which was 0.7 (0.5-1.0), when (p<0.05). Also, in the cases group the neutrophil lymphocyte median value -ratio was statistically significantly elevated, neutrophil lymphocyte median value -ratio was 15.5 (7.0-35.0), compared to the control group which was 6.0 (3.0-15.0), (p<0.05). The inflammatory markers (CRP and ESR) showed no difference between both groups. In both groups, there was insignificant difference regarding the kidney function tests (BUN and serum creatinine). The average total bilirubin value in the cases group was significantly elevated (0.95±0.24), than that in the control group (0.78±0.23), (p<0.05). In contrast, the remaining parameters exhibited no difference between the two study groups (p<0.05). This table demonstrated that the mean value of LDH and D-Dimer in the patient group was significantly higher compared to the control group (p<0.05). Whereas, the ferritin exhibited on insignificant difference between the two study groups.

Table 2. Comparison of differential White blood cells (WBCs) count, inflammatory markers, kidney function, liver function and other laboratory parameters among the studied groups.

			Cases Group (n=40)	Control Group (n=40)	*p*-value
Differential WBCs count	Lymphocytes	Median (IQR)	0.7 (0.5-1.0)	1.0 (0.3-2.0)	0.014
		Range	0.3-2	0.2-3	
	Neutrophils	Median (IQR)	6.0 (3.8-10.4)	6.9 (4.0-8.0)	NS
		Range	1-30.7	2-31.9	
	Netrophil-lymphocyte ratio	Median (IQR)	15.5 (7.0-35.0)	6.0 (3.0-15.0)	0.008
		Range	2-65	1-81	
Inflammatory markers	CRP	Median (IQR)	17.7 (9.6-56.1)	21.0 (15.0-83.1)	NS
		Range	0.1-302	4.5-330	
	ESR	Median (IQR)	19.0 (12.0-28.8)	26.0 (18.3-61.3)	NS
		Range	2.5-120	2-300	
Kidney function	BUN	Median (IQR)	19.5 (15.0-37.8)	41.5 (21.3-62.8)	NS
		Range	8-270	10-198	
	Serum Creatinine	Median (IQR)	0.9 (0.7-1.1)	0.9 (0.6-1.4)	NS
		Range	0.3-9	0.4-3.1	
Liver function	AST	Median (IQR)	26.5 (22.3-42.8)	29.0 (17.0-75.8)	NS
		Range	9-215	4-212	
	ALT	Median (IQR)	30.0 (20.8-45.0)	22.0 (15.3-63.5)	NS
		Range	9-229	10-338	
	Total bilirubin	Mean ± SD	0.95±0.24	0.78±0.23	0.012
		Range	0.4-1.6	0.3-1.6	
	Serum Albumin	Mean ± SD	3.33±0.47	3.35±0.53	NS
		Range	1.8-4.2	2.1-4.5	

Table 2. Continued.

			Cases Group (n=40)	Control Group (n=40)	*p*-value
Other laboratory	Ferritin	Median (IQR)	292.5 (250.0-588.0)	446.6 (307.0-775.1)	NS
		Range	56-1434.3	26.7-2100	
	LDH	Mean ± SD	528.93±155.00	372.00±117.16	0.007
		Range	125-986	110-663	
	D-DIMER	Median (IQR)	1.4 (0.6-2.6)	0.5 (0.3-0.8)	0.000
		Range	0.212-6.9	0.2-2.9	

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, BUN: Blood Urea Nitrogen, AST: aspartate aminotransferase, ALT: alanine transaminase, LDH: Lactate dehydrogenase, Using: U=Mann-Whitney test for non-parametric data "Median (Interquartile range IQR)" $p > 0.05$ is not significant (NS).

Table 3, demonstrated a highly statistically significant increase in the median value of serum IL-6 in the cases group, which was 134.8 (39.5-319.2), compared to the control group, which was 44.3 (16.8-104.9), $p<0.001$. The *p*-value fell below 0.001. Also, for fecal calprotectin, the control group had a median value of 134.5 (99.8-168.5), while the cases group had a significantly elevated median value of 240.8 (175-285.4), which was highly statistically significant ($p<0.001$).

Table 3. Comparison of Serum IL-6 and fecal calprotectin between the studied groups.

		Cases Group (n=40)	Control Group (n=40)	*p*-value
Serum IL-6	Median (IQR)	134.8 (39.5-319.2)	44.3 (16.8-104.9)	0.001
	Range	9.712-615	6.356-515	
Fecal Calprotectin	Median (IQR)	240.8 (175-285.4)	134.5 (99.8-168.5)	0.001
	Range	150.5-340.3	49.7-257.1	

IL-6: interleukin-6, Using: U=Mann-Whitney test for non-parametric data "Median (Interquartile range IQR)".
$p \leq 0.05$ is significant.

According to the PCR test for COVID and COVID-19 reporting and data system (CO-RADS) classification, Table 4 demonstrated no difference between the control group and the cases group ($p>0.05$).

Table 4. Comparison of PCR OF COVID, CO-RADS classification among the two study groups.

		Cases Group (n=40)	Control Group (n=40)	*p*-value
PCR of COVID	Positive	40 (100.0%)	40 (100.0%)	NS
CO-RADS classification	CO-RADS 3	26 (65.0%)	18 (45.0%)	NS
	CO-RADS 4	9 (22.5%)	11 (27.5%)	
	CO-RADS 5	5 (12.5%)	11 (27.5%)	

Data are presented as frequency (%). CO-RADS: reporting and data system, Using: x2X2: Chi-square test for Number (%) or Fisher's exact test, when appropriate, $p > 0.05$ is not significant (NS)

Utilizing the Spearman's rank correlation coefficient (rs), serum IL-6 exhibited a statistically significant positive correlation with FC, FC, Age "years", TLC, and NEU (p<0.05) (Table 5). Conversely, serum IL-6 exhibited a statistically significant negative correlation with Hemoglobin, as (p<0.05). Moreover, a statistically significant positive correlation was demonstrated in FC and Age "years," TLC, and NEU, (p<0.05). Conversely, the remaining parameters did not reveal any correlation.

Table 5. Correlation between Serum interleukin-6 (IL-6) and Fecal Calprotectin with several studied parameters in the Cases Group.

Cases Group	Serum IL-6		Fecal Calprotectin	
	r-value	*p*-value	r-value	*p*-value
Serum IL-6	--	--	0.383	0.011
Fecal Calprotectin	0.383	0.011	--	--
Age "years"	0.302	0.048	0.333	0.036
TLC	0.399	0.011	0.325	0.041
Hemoglobin	-0.314	0.048	-0.107	NS
Platelets	0.167	NS	0.069	NS
Lymphocytes	-0.005	NS	-0.208	NS
Neutrophils	0.425	0.006	0.348	0.028
Netrophil-lymphocyte ratio	-0.108	NS	0.292	NS
CRP	0.184	NS	0.243	NS
ESR	0.107	NS	-0.093	NS
Serum Creatinine	-0.043	NS	0.055	NS
AST	-0.113	NS	0.121	NS
ALT	-0.122	NS	-0.151	NS
Total bilirubin	-0.113	NS	0.157	NS
Serum Albumin	0.043	NS	-0.043	NS
Ferritin	0.156	NS	0.101	NS
LDH	0.237	NS	0.268	NS
D-DIMER	0.168	NS	0.017	NS

IL-6: interleukin-6, TLC: Total Leucocyte Count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, BUN: Blood Urea Nitrogen, AST: aspartate aminotransferase, ALT: Alanine Transaminase, LDH: Lactate dehydrogenase, Using: Spearman's rank correlation coefficient (rs), p > 0.05 is not significant (NS)

Serum IL-6 was positively correlated with FC, age "years," and the netrophil-lymphocyte ratio. Conversely, serum IL-6 and serum albumin exhibited a statistically significant negative correlation (p<0.05). The remaining parameters did not exhibit any correlation. Additionally, there was a statistically significant positive correlation between FC and lymphocytes, CRP, and serum albumin with (p<0.05). Meanwhile, the remaining parameters did not exhibit any significant correlation, (Table 6).

Table 6. Correlation of Serum interleukin-6 (IL-6) and fecal calprotectin with different parameters in control group, using Spearman's rank correlation coefficient (rs).

Control Group	Serum IL-6		Fecal Calprotectin	
	r-value	*p*-value	r-value	*p*-value
Serum IL-6	---	---	0.323	0.031
Fecal Calprotectin	0.323	0.031	---	---
Age "years"	0.348	0.028	0.197	NS
TLC	0.216	NS	0.209	NS
Hemoglobin	-0.193	NS	0.185	NS
Platelets	-0.208	NS	0.096	NS
Lymphocytes	-0.304	NS	-0.357	0.024
Neutrophils	0.233	NS	0.257	NS
Netrophil-lymphocyte ratio	0.507	0.001	0.206	NS
CRP	0.063	NS	0.444	0.004
ESR	0.149	NS	0.207	NS
BUN	0.286	NS	0.225	NS
Serum Creatinine	0.170	NS	0.191	NS
AST	0.038	NS	0.068	NS
ALT	0.079	NS	-0.055	NS
Total bilirubin	-0.041	NS	0.009	NS
Serum Albumin	-0.444	0.004	-0.359	NS
Ferritin	-0.017	NS	-0.204	NS
LDH	0.038	NS	0.082	NS
D-DIMER	-0.077	NS	0.301	NS

IL-6: interleukin-6, TLC: Total Leucocyte Count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, BUN: Blood Urea Nitrogen, AST: Aspartate aminotransferase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, Using: Spearman's rank correlation coefficient (rs), $p > 0.05$ is not significant (NS).

The ROC curve analysis demonstrated that the area under the curve for serum IL-6 was 0.718 (0.61 to 0.81), $p<0.001$. The most effective cut-off value for predicting intestinal inflammation was >63, with a sensitivity of 67.5% and a specificity of 65%. Additionally, the FC exhibited an area under the curve of 0.793 (0.68 to 0.89) $p<0.001$. The most effective cut-off value for predicting intestinal inflammation was >194, with a sensitivity of 87.6% and a specificity of 77.3%. The FC was the most significant factor compared to serum IL-6, but the difference in the area under curve (AUC) was insignificant (0.075; z-test= 1.632, $p>0.05$), Table 7.

Table 7. Correlation between interleukin-6 (IL-6) and fecal calprotectin as markers of intestinal inflammation.

Items	Cut-off	Sen.	Spe.	PPV	NPV	AUC (C.I.95%)	*p*-value
Serum IL-6	>63	67.5%	65%	65.9%	66.7%	0.718 (0.61 to 0.81)	0.003
Fecal Calprotectin	>194	87.6%	77.3%	74.7%	77.8%	0.793 (0.68 to 0.89)	<0.001

Data are presented as frequency. IL-6: interleukin 6, Sen.: sensitivity, Spe.: Specifcity, PPV: positive predictive value, NPV: Negative predictive value, AUC: area under curve. $p \leq 0.05$ is significant.

Discussion

The COVID-19 was correlated with an elevation in the reporting of extra-pulmonary manifestations, particularly dysfunction of the GIT and hepatic system. The fecal-oral transmission issue for COVID-19 was brought to light.[8] This case-control investigation was performed at the isolation hospitals of ASU during February to October 2022. The study participants were divided into two groups: group A (cases) consisted of 40 COVID-19 patients with GIT symptoms and group B (control) consisted of 40 COVID-19 patients without GIT symptoms, all of whom met the same inclusion and exclusion criteria.

All the study cases underwent a comprehensive clinical examination and history taking, and comprehensive laboratory investigations, which included CBC with a neutrophil/lymphocyte ratio, liver function tests (AST, Bilirubin, ALT, S. albumin, INR) ESR, CRP, kidney function tests (BUN, S. creatinine, Sodium, Potassium, Uric Acid, Ferritin, LDH, D. dimer), assessment of COVID-19 by PCR, stool analysis, and a high-resolution chest computed tomography. Serum IL-6 and FC were also assessed in both groups.

The present COVID-19 investigation revealed an elevated proportion of males than females (55% vs. 45%), as also indicated by Li et al., 2020[9] and Wang et al. 2020. [10] In the present study, the mean age of COVID-19 cases was 51.48±12.38 years. The study by Effenberger et al., 2020, [11] stated that the mean age range of cases without diarrhea, ceased diarrhea cases (> 48 hours), and acute diarrhea cases (<48 hours) were 58.4 ±17.1, 66.3 ±13.1, and 78.3 ±13.8 years, respectively. The study by Ai et al., 2020,[12] showed that 35 to 75 years was the age range of COVID-19 cases having GIT signs as their primary symptoms and constant for more than three days.

In the current study, there was no difference in smoking between cases and controls. This is aligned with findings of the study by Butt et al., 2023,[13] indicated that smoking habits did not significantly influence the COVID-19 incidence. As the percentage of smokers was 12% and the non-smokers 88%. This demonstrated that the incidence of COVID-19 did not increase as a result of being a smoker.

In the current study, there was no significant difference regarding alcohol consumption. This is in contrary to several studies like Bailey et al., 2021,[14] Testino, 2020[15] and Saengow et al., 2021.[16] These findings indicated that alcohol use disorder (AUD), as recorded in their medical records, indicated that COVID-19 patients are more hospitalized and have an elevated all-cause mortality rate than those without an AUD. Additionally; they indicated that heavy alcohol consumption may influence COVID-19 cases to undesirable clinical outcomes. One of the advantages of this analysis was the large, multicenter database utilization that encompassed fort four centers. This analysis encompassed over one million COVID-19 individuals across the United States. It encompasses urban and rural centers. Temporarily, it encompasses patients from both the initial surge and the later phases of the pandemic.

The present study indicated significant differences in cardiovascular diseases. This finding is consistent with Liang et al., 2020,[17] who demonstrated independent correlations among severe COVID-19 and diabetes and hypertension in a fairly large sample of 1,590 patients. Also, there was biological plausibility. There is confirmation that COVID-19 harms these organs, and hypertension and diabetes are the primary risk variables for cardiovascular disease (CVD) and kidney disorders.

Clinical studies had not demonstrated a correlation among COVID-19 and CVD, as indicated by Nishiga et al. 2020.[18] COVID-19 individuals who have CVD are more likely to experience many complications and a greater mortality rate.

Our findings indicated that the netrophil-lymphocyte ratio was elevated, platelets were reduced, and total bilirubin was elevated. LDH and D-dimer were elevated, respectively. However, no distinctions were observed among the study groups regarding, sex, special behaviors, associated medical co-morbidities,

hemoglobin, TLC, and NEU count, CRP and ESR levels, kidney and liver function tests, and serum ferritin level.

We observed that the number and percentage of WBC, LYM, and NEU were substantially different for COVID-19 cases between positive and negative RT-PCR. In contrast to the normal range, in COVID-19 cases, we observed that patients with positive RT-PCR had low WBC and LYM counts, while their NEU counts were higher. This finding is consistent with that reported by Qu et al., 2022.[19]

This investigation demonstrated that there was a statistically significant correlation between neutrophils to lymphocytes ratio (NLR) in the two study groups. This finding is consistent with that reported by Liu et al., 2020,[20] who included 245 COVID-19 cases and reported a total in-hospital mortality rate of 13.47%.

In this study, LDH, AST, ALT, and albumin were significantly high. This outcome, of LDH and albumin, is in agreement with those of Chen et al., 2020, [21] however, ALT and AST did not demonstrate any substantial alterations. Another study performed by Zhang et al., 2020,[3] confirmed that liver comorbidities were in 2–11% of cases with COVID-19, and abnormal ALT and AST levels were present in 14–53% of cases during the progression of the disease. Moreover, the study by Shi et al., 2020[22] revealed that the AST abnormal incidence in these individuals was substantially lower than that of cases diagnosed after the symptom's onset. Consequently, hepatic damage is more frequent in COVID-19 severe cases than in moderate cases. An additional investigation by Yang et al., 2020[23] disclosed no difference in the prevalence of aberrant liver function between non-survivors (28%) and survivors (30%). According to the study by Zhang et al., 2020,3 liver injury in moderate cases of COVID-19 is frequently temporary and can revert to its prior state without the need for any specific therapy. According to a recent meta-analysis study, ALT was the most frequently increased liver enzyme among COVID-19 patients. [24]

In addition, it has been reported that D-dimer elevation is one of the most frequently observed laboratory investigations in COVID-19 cases who required hospitalization. The present investigation indicated statistical significant correlations among D-dimer and severity of COVID-19 patients. This is in agreement with a study by Guan et al., 2020,[25] that investigated 1099 individuals suffering from laboratory-confirmed COVID-19 from more than 550 hospitals in China. The study noted that individuals who did not survive had a considerably elevated D-dimer (median, 2.12 µg/ml) than that of survivors (median, 0.61 µg/ml). The study by Ning et al., 2020[26] noticed unusual coagulation outcomes, specifically highly raised D-dimer in mortality with COVID-19. The study by Fei et al., 2020,[27] found that (D-dimer >1 µg/ml) on admission was related with in-hospital mortality (CI, 2.64- 128.55, HR, 18.42; 95%), The study by Huang et al., 2020[28] indicated that individuals with required critical care support exhibited greater D-dimer values on admission than those who were not required it (median, 0.5 µg/mL).

This study demonstrated a statistically significant correlation with higher neutrophil count, D-Dimer, LDH, BUN, and creatinine, which are frequently observed during hospitalization in non-survivor patients with SARS-CoV-2. These results align with findings of the study by Wang et al., 2020.[10] In the same manner, COVID-19 was associated with a raise in CRP and IL-6 inflammatory markers.[28]

The results of this study indicated that serum IL-6 and FC were statistically significantly greater in COVID individuals with GIT symptoms than in the control group. We noted a statistically significant positive correlation between serum IL-6 and FC and TLC and NEU. Serum IL-6 and hemoglobin, however, did not exhibit a statistically significant correlation. However, there was no significant correlation observed for the remaining parameters.

According to the present investigation, the optimal cut-off value for serum IL-6 in predicting intestinal inflammation was >63, with 67.5% sensitivity and 65% specificity. Furthermore, the optimal cut-off value for FC in the prediction of intestinal inflammation was >194, with a sensitivity of 87.6% and a specificity of 77.3%. FC was the most significant

factor compared to serum IL-6, but with insignificant difference.

Our findings are in agreement with those reported by Ellakany et al., 2022, [8] who claimed that FC raised in COVID-19 cases with intestinal symptoms, particularly diarrhea, regardless of the presence of colonoscopic and histopathological alterations. In the COVID-19 patients who presented with diarrhea, FC was substantially elevated, with a mean value of 260 ±80 µg/g, in contrast with those who did not suffer from diarrhea, with mean value of 31.6 ±12.9 µg/g (p< 0.001). Besides, 20% of the cases (8 patients) exhibited an increased level that exceeded 200 µg/g three months after recovery. Of these cases, five exhibited mild colonoscopic alterations, while three exhibited severe ileocolitis. Two out of the three cases with marked ileocolitis exhibited histopathological alterations, which led to diagnosis of Crohn's disease.

In correspondence with our findings, the studies by Mazza et al., 2020[29] and Effenberger et al., 2020 [11] indicated that FC measurement may be indispensable for the diagnosis and monitoring of diarrhea associated with COVID-19. This because of the inflammatory response that SARS-CoV-2 induced in the intestine, as evidenced by the elevated measured levels and the high blood IL-6 levels.

In this study, FC levels were elevated in all patients with a range of 240.8 (175-285.4) µg/g. Furthermore, the study by Effenberger et al., 2020[11] observed that the FC was substantially higher in the group of diarrhoea cases and to a greater extent in the group of patients with continuous diarrhoea than in the group of patients without diarrhoea (p< 0.001). However, they were unable to detect SARS-CoV-2-RNA in the excrement of patients with ongoing diarrhea. This was only identified in 8 cases with stopped diarrhea and in 4 cases have no diarrhea. However, there was no correlation between fecal SARS-CoV-2-RNA and additional biomarkers (FC, IL-6, CRP, or ferritin). The technique was not available in the local area, which prevented us from conducting an investigation into the detection of fecal viral RNA.

In a similar manner, the study by Ojetti et al., 2020[30] presented intriguing data that demonstrated a significant association between COVID-19 pneumonia and a elevated levels of FC in COVID-19 individuals. The pneumonia development is the disease's severity marker.

According to the study by Lin et al., 2020,[31] histopathological changes were observed in 60 individuals who exhibited endoscopic examinations that detected SARS CoV-2 RNA. Those modifications included interstitial edema in the lamina propria and a proliferation of infiltrating plasma cells and lymphocytes. This finding aligns with the present investigation, that five cases demonstrated moderate colonoscopic alterations in the form of mild erythematous rectal erythema, a non-specific form of rectosigmoiditis. Two cases were diagnosed with crypt abscess, additive cryptitis, and crypt distortion containing lymphoplasmocytic and neutrophilic infiltration, while three patients experienced pronounced ileocolitis induced by COVID-19. In contrast, the study by Xiao et al., 2020,[7] included a cohort of 73 patients, found that the stomach, duodenum, colon, and rectum did not exhibit any abnormalities, with the exception of mucosa injury in the oesophagus during endoscopy.

Additionally, the study by Liu et al., 2020[32] prompted the curiosity of small intestinal association in an 85-year-old man who experienced a segmental dilatation that alternated with stenosis during a COVID-19 autopsy, despite the fact that the color was normal. It is uncertain whether this discovery is the result of COVID-19 or a preexisting gastrointestinal comorbidity, such as ischemia.

No prior literature was identified regarding the correlation between serum IL-6 and the presence of diarrhea and other gastrointestinal symptoms in COVID-19-positive cases. IL-6 and the C-reactive protein/albumin ratio were assessed for their ability to anticipate the prognosis and estimate the severity of COVID-19 by El-Shabrawy et al., 2021.[34] The severity of COVID-19 could be effectively differentiated by the level of IL-6, according to their report. An independent risk factor for the 30-day mortality rate in patients with COVID-19 was the

CRP/albumin ratio. In the assessment of the severity and COVID-19 prognosis, the CRP/albumin ratio and IL-6 appear to be valuable biomarkers.

The study conducted by El-Shabrawy et al. 2021[34] was designed to assess the effectiveness of laboratory diagnostic markers in predicting the prognosis and estimating the COVID-19 severity. To the best of our information, such research was the first to assess the CRP/albumin ratio contribution to the COVID-19 mortality prediction. This study demonstrated that severe patients exhibited significantly elevated levels of CRP, CRP/albumin ratio, and IL-6. Conversely, albumin levels were diminished in the severe cases. The ROC curve analysis demonstrated that IL-6 was the most effective indicator of disease severity, while most accurate predictor was the CRP/albumin ratio was the adverse outcomes

The study performed by El-Shabrawy et al. 2021[34] demonstrated that CRP was correlated with the disease severity and the clinical result. However, the CRP/albumin ratio and IL-6 outperformed CRP in terms of predicting the severity of the disease and an adverse outcome. According to Zhao 2020,[35] the National Health Commission of China (trial 7th iteration) has authorized the findings that the level of peripheral blood IL-6 elevated throughout the COVID-19.

In the study by De Brito et al., 2016,[36] IL-6 was classified as an acute-phase inflammatory cytokine, and its serum level was indicative of the lung inflammation severity. The IL-6 levels in COVID-19 cases were evaluated in the study performed by El-Shabrawy et al., 2021.[34] In comparison to non-severe patients, cases with severe COVID-19 showed high IL-6 levels. The diagnostic performance of IL-6, it appeared to be a valuable indicator for the early detection of severe disease. IL-6 exhibited a significant analytical power, even after being adjusted to various models that incorporate clinical and laboratory significant parameters. Therefore, IL-6 can be regarded as COVID-19 severity independent predictor.

A meta-analysis was conducted by Aziz et al., 2020[37] to evaluate the involvement of IL-6 in the COVID-19 severity assessment. The study confirmed that the serum IL-6 levels of patients with severe COVID-19 were substantially higher than those of non-severe patients. Lastly, these results corroborated with findings of the study by Liu et al., 2020[38] which asserted that viral infection induces lung injury through the impact of cytokines.

The present study had strength points, as it has a case-control study design. Before the analysis, individuals diagnosed with IBD disease and those with non-COVID intestinal inflammation (gastroenteritis) were initially excluded as possible confounders. This was the first study conducted at ASU Hospitals to assess serum IL-6 and FC in COVID-19 positive patients who presented with diarrhea and other gastrointestinal symptoms as intestinal inflammation indicators. We made every effort to confirm that all data were documented and that only comprehensive information was included in the facts analysis.

The laboratory and hospital databases were utilized to prospectively document the levels of serum IL-6 and FC, respectively. The identical devices were employed in the same laboratory to conduct all of the experiments, with identical parameters. Our network of hospitals encompassed both rural and urban populations, which were representative of the general population rather than the referral center for high-risk women. The same staff conducted all clinical assessments and evaluations of study results.

The study has certain limitations that should be acknowledged. This was a single hospital-based study, resulted in a limited number of cases and a relatively smaller sample size. In conclusion, serum IL-6 and FC could be utilized as intestinal inflammation markers in COVID-19 positive cases presented with diarrhea and other GIT symptoms while the FC being the most significant than serum IL-6, but with insignificant difference. FC was found to be increased in COVID-19 cases with intestinal symptoms, particularly diarrhea, regardless of colonoscopic and histopathological alterations.

Author Contributions

MNBA and AAA performed the laboratory work. NAE, AEK, and AEA performed the statistical analysis.

RNMG examined the patients. MNBA, NAEREN, AEA, and RNMG collected the samples. All authors participated in writing and reviewing the manuscript.-

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University (approval code: FMASU MD 105/2021**)**.

Informed consent

Each study participant provided a written consent for participating in the study.

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