Original paper

Faecal calprotectin in COVID-19 patients with intestinal symptoms

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Abstract

Introduction: Extra-pulmonary manifestations of the Coronavirus disease of 2019 (COVID-19) have been increasingly reported, especially gastrointestinal and hepatic system dysfunction. The concern of faecal-oral transmission for COVID-19 was raised.

Aim: To study the trend of faecal calprotectin in COVID-19 patients with intestinal symptoms.

Material and methods: Forty confirmed cases of COVID-19 infection presenting with diarrhoea were subjected to a thorough history taking, clinical examination, and routine laboratory investigations. They were treated according to the Egyptian MOH guidelines. Faecal calprotectin (FC) concentration was measured at initial presentation and after 3 months. Those who had persistently elevated levels ≥ 200 µg/g were subjected to colonoscopic examination and histopathological examination. Forty confirmed cases of COVID-19 without diarrhoea were recruited as a control group in the initial FC evaluation.

Results: Faecal calprotectin was found to be significantly elevated in the studied COVID-19 patients who presented with diarrhoea, with a mean value 260 ±80 µg/g compared to the those without diarrhoea, with a mean value of 31.6 ±12.9 µg/g ($p < 0.001$). Moreover, 20% (8 patients) had an elevated level exceeding 200 µg/g 3 months after recovery; among them, 5 patients showed mild colonoscopic changes whereas 3 patients showed severe ileocolitis. Out of the 3 patients with marked ileocolitis, 2 showed histopathological changes raising the diagnosis of Crohn's disease.

Conclusions: Faecal calprotectin was found to be elevated in COVID-19 patients with intestinal symptoms, especially diarrhoea, with or without colonoscopic and histopathological changes.

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a novel coronavirus that was named after causing an outbreak in the city of Wuhan Province in China. It was named as COVID-19 by the World Health Organization after a highly contagious viral pneumonia outbreak in December 2019 and has evolved into a pandemic.

SAR-CoV2 is an enveloped, non-segmented, positive sense RNA virus. Its diameter is about 65–125 nm, containing single strands of RNA, and with crown-like spikes on the outer surface. Structurally, SARS-CoV-2 has 4 main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, as well as several accessory proteins [1].

COVID-19 is the seventh coronavirus known to infect humans. Others include 229E, NL63, OC43, and HKU1, which only cause symptoms of the common cold and upper respiratory tract infection. Conversely, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) can cause atypical pneumonia [1–3].

The main clinical presentation of COVID-19 is respiratory in nature with cough, sputum expectoration, fever, and dyspnoea, which together comprise serious lower respiratory tract infection accompanied by acute respiratory distress syndrome (ARDS). Other prevalent clinical symptoms in patients with COVID-19 include

loss of taste and smell. Moreover, generalized fatigue and bone aches were evidently relevant [4].

The extrapulmonary manifestations of COVID-19 were interestingly evident in an increasing manner. This highlighted the gastrointestinal and hepatic system involvement in the course of the novel disease with an incidence of gastrointestinal symptoms higher than 20% [5].

It is known that the main route of transmission is via respiratory droplet. Extraction of SARS-CoV-2 ribonucleic acid (RNA)from the stool specimen of the first COVID-19 patient in the United States raised speculation that it could be transmitted via faeco-oral route originating from infected enterocytes of the patient's ileum and colon [6].

All coronaviruses encode a surface glycoprotein and spike protein, which binds to host cell receptors and mediates virus entry. Betacoronavirus (β-CoVs) uses human angiotensin-converting enzyme 2 (ACE2) as an entry receptor. ACE2 is widely found in human small intestinal epithelial cells and is more strongly expressed in type II epithelial cells. Because ACE2 is highly expressed in intestinal epithelial cells, oesophagus, and lungs, coronavirus may infect the gastrointestinal tract and cause evident primary damage. Indeed, COVID patients with gastrointestinal predominant symptoms typically present with abdominal discomfort, nausea, and/or vomiting as well as severe diarrhoea with or without preceding respiratory symptoms [7, 8].

During gastrointestinal involvement for SARS-CoV-2, hepatic involvement and liver injury was noted despite the lack of expression for high-level ACE2 on hepatocytes. This was analysed by different suggestions as the high level of ACE2 expression in cholangiocytes suggests an indirect cause of elevated liver enzymes as cholangiocyte dysfunction. Also, drug hepatotoxicity as a sort of drug induced liver injury like acetaminophen was proposed. Moreover, the evident systemic inflammatory response syndrome sharing in the cytokine storm development may contribute to liver injury. Lastly, the occurrence of SARS can lead to hypoxic injury, which leads to liver dysfunction [9].

Calprotectin (aka S100A8/A9, calgranulin A and B, alarmins, CLP) is a 36.5 kD small calcium and zinc-binding heterodimer derived from neutrophils and macrophages that often associates with its main receptor, Toll-like receptor 4 (TLR4) to mediate downstream signalling with active involvement in inflammation. As an acute phase reactant, its expression level is often increased following infection, trauma, and inflammatory diseases. Faecal calprotectin represents a reliable biomarker in the context of inflammatory bowel disease, which might gain additional value during the COVID-19 pandemic [10].

Aim

The aim of the study was to assess faecal calprotectin as a marker of intestinal involvement in patients with COVID-19 and gastrointestinal symptoms.

Material and methods

The current study was carried out on 40 subjects aged from 28 to 68 years with a mean of 46.25 ±12.99 years (26 males and 24 females) during the period from July 2020 to January 2021 in Alexandria Main University Hospitals, Alexandria, Egypt. Forty COVID-19 positive patients of matched age (45.25 ±11.56 years) and sex (27 males and 23 females) without diarrhoeal presentation were recruited as a control group. The sample size was calculated using the Epi info 7 software program with a confidence level of 95% and a power of 80%. Inclusion criteria were as follows: confirmed case of COVID-19 by a nasopharyngeal and/or oropharyngeal swab real-time polymerase chain reaction (RT-PCR positive for SARS-CoV-2-RNA), and presenting with diarrhoea. Any patient with previous history of inflammatory bowel disease, lactose intolerance, celiac disease, previous history of radiation proctitis, or previous history of colorectal cancer was excluded.

Six millilitres of whole blood were collected from every subject by aseptic venepuncture from the ante-cubital vein and divided into 3 Vacutainer® tubes: the first one for CBC containing tri-potassium ethylenediamine tetra acetic acid (K3EDTA), the second one a plain vacutainer tube to obtain serum samples for chemical analysis, and the third one a Vacutainer containing sodium citrate for D-dimer. Stool samples were collected in sterile containers for FC measurement and stool analysis.

All patients were subjected to a thorough history taking and clinical examination with stress on respiratory and intestinal stigmata of COVID-19. RT-PCR of nasopharyngeal and/or oropharyngeal swab for SARS-CoV-2-RNA was done using a VIASURE SARS-CoV-2 Real Time PCR Detection kit (CerTest BIOTEC, Spain) on a QuantiStudio Real-Time PCR system (Thermo Fisher Scientific, USA) after RNA extraction with a Prepito Viral DNA/RNA kit (PerkinElmer, USA). Complete blood count (CBC) was performed on an automated cell counter ADVIA 2120 haematology system (Siemens Healthcare Diagnostics, USA). Serum ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), alanine transaminase (ALT), and aspartate aminotransferase (AST) were automatically performed on a Dimension RxL Max Chemistry System auto analyser (Siemens Healthcare Diagnostics, USA). D-dimer was measured on a CA-1500 analyser (Siemens Healthineers, Germany). Faecal calprotectin

Table I. Presenting initial clinical findings of the studied COVID-19 patients

Presenting clinical findings	COVID-19 patients with diarrhoea (*N* = 40) *n* (%)	COVID-19 patients without diarrhoea (*N* = 40) *n* (%)
Diarrhoea	40 (100%)	0 (0%)
Nausea	32 (80%)	0 (0%)
Vomiting	10 (25%)	1 (2.5%)
Fever	27 (67.5%)	30 (75%)
Respiratory symptoms	26 (65%)	29 (72.5%)
CT chest changes	29 (72.5%)	28 (70%)

(FC) concentration was determined by enzyme-linked immunosorbent assay (ELISA) using a Calprest ELISA kit (Eurospital, Italy) according to the manufacturer's instructions. Complete stool analysis was done for all patients. All patients were subjected to a plain computerized tomography (CT) scan of the chest.

All COVID-19 patients were treated according to the Egyptian Ministry of Health (MOH) standard of care treatment strategy in the Egyptian MOH 2020 guidelines [11]. COVID-19 patients with diarrhoea received loperamide as an anti-motility, racecadotril as an anti-secretory, and nitazoxanide as an intestinal antiseptic.

After a period of 3 months, FC was repeated for all the study patients. Those who had persistently elevated measurements (≥ 200 µg/g) were subjected to colonoscopic examination, and tissue biopsy taking was done as indicated, and the samples were sent for histopathological examination.

Ethics approval and consent to participate

The proposal of the current study was approved by the Ethical Committee of the Faculty of Medicine-Alexandria University, Alexandria, Egypt. Written informed consent was signed by all participants or their caregivers before the study. The committee's reference number is not available. The current study is original and has not been published elsewhere in any form or language (partially or in full). The results of the current study are presented honestly and without fabrication, falsification, or inappropriate data manipulation. No data, text, or theories by others are presented as if they were the author's own ('plagiarism').

Statistical analysis

Data were analysed using IBM SPSS software package version 20.0. The distributions of quantitative variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed using mean ± standard deviation and were compared using independent *t* test or one-way ANOVA. Abnormally distributed data were described using minimum, maximum, and median and were compared using the Mann-Whitney test or Kruskal-Wallis H test. Statistical significance was considered at $p < 0.05$.

Results

The most common clinical finding among the studied patients of COVID-19 was diarrhoea in 40 (100%) patients, while nausea, fever and vomiting were found in 80%, 67.5%, and 25%, respectively.

Among the selected group of patients, 26 showed a variable degree of respiratory symptoms (65%) including cough, dyspnoea, and chest tightness, whereas 29 patients showed evident CT chest changes (72.5%) (Table I).

Regarding laboratory investigations, no significant difference was detected between COVID-19 patients who presented with diarrhoea and those without diarrhoea, except for faecal calprotectin. The mean of D-dimer among the COVID-19 patients who presented with diarrhoea was 400 ±80 ng/ml compared to 430 ±73 ng/ml in patients without diarrhoea ($p = 0.0837$). CRP was 18 ±10 mg/l in patients with diarrhoea and 8 ±9 mg/l in patients without diarrhoea ($p = 0.8148$). Serum ferritin level had a mean value of 400 ±280 ng/ml in patients with diarrhoea and 460 ±270 ng/ml in those without diarrhoea ($p = 0.3323$). LDH, ALT, and AST showed mean values of 240 ±90.5 IU/l, 42 ±9.3 IU/l, and 58 ±8.5 IU/l, respectively, in patients who presented with diarrhoea versus 260 ±80 IU/l, 44 ±8.7 IU/l, and 59 ±10 IU/l, respectively, in patients without diarrhoea, with *p*-values of 0.2982, 0.3237, and 0.6312, respectively. Regarding white blood cell count, it showed a mean of 5.2 ±2.4 × 10^3/ml in patients with diarrhoea and 4.7 ±3.6 × 10^3/ml in patients without diarrhoea, with predominant absolute lymphopaenia in most of studied patients in both groups, with a mean value of 1 ±0.7 × 10^3/ml and 1.2 ±0.9 × 10^3/ml for absolute lymphocyte count ($p = 0.4670$ for leucocyte count and $p = 0.2707$ for absolute lymphocyte count). Complete stool analysis did not show any findings of remarkable significance in the studied patients. The chief laboratory finding for the current study was the elevation of faecal calprotectin in the studied patients, especially those with a predominant severe diarrhoea having a mean 260 ±80 µg/g) (Table II). Faecal calprotectin was measured in 40 COVID-19 patients without diarrhoeal presentation and showed a mean value of 31.6 ±12.9 µg/g compared to 80 ±260 µg/g in those with diarrhoeal presentation ($p < 0.001$).

Table II. Laboratory findings of the studied COVID-19 patients with and without diarrhoea

Laboratory parameters	Laboratory values in COVID-19 patients with diarrhoea (*n* = 40) *n* (%)	Laboratory values in COVID-19 patients without diarrhoea (*n* = 40) *n* (%)	*t*	*P*-value
CRP [mg/dl]	8.5 ±10	8 ±9	0.235	0.8148
D-dimer [ng/ml]	400 ±80	430 ±73	1.752	0.0837
Leukocytes [× 10^3/ml]	5.2 ±2.4	4.7±3.6	0.731	0.4670
Lymphocytes [× 10^3/ml]	1 ±0.7	1.2 ±0.9	1.109	0.2707
Ferritin [ng/ml]	400 ±280	460 ±270	0.976	0.3323
LDH [IU/l]	240 ±90.5	260 ±80	1.047	0.2982
AST [IU/l]	58 ±8.5	59 ±10	0.482	0.6312
ALT [IU/l]	42 ±9.3	44 ±8.7	0.993	0.3237
Faecal calprotectin [µg/g]	80 ±260	12.9 ±31.6	18.169*	< 0.001*

*t – Student's t-test, p – p-value for comparing between the studied groups. *Statistically significant at p ≤ 0.05.*

In the follow-up profile 3 months after recovery, 8 patients previously diagnosed with severe gastrointestinal COVID-19 (20%) had an elevated level of faecal calprotectin exceeding 200 µg/g.

The main gastrointestinal sequelae observed in the COVID-19 patients after 3 months of recovery, using 2 consecutive negative RT-PCR tests from nasopharyngeal swabs, were persistent diarrhoea (75%), mucorrhoea (50%), abdominal discomfort/distention (75%), and bleeding per rectum (12.5%) (Table III).

Among the 8 patients with a persistently elevated faecal calprotectin exceeding 200 µg/g, 5 showed mild colonoscopic changes in the form of mild erythematous rectal erythema that showed a non-specific form of rectosigmoiditis (12.5%), whereas 3 patients showed severe ileocolitis revealed endoscopically as atrophic villi, aphthoid ileal ulceration, and marked rectosigmoiditis (7.5%).

Out of the 3 previously diagnosed patients with marked ileocolitis induced by COVID-19, 2 patients showed a histopathological diagnosis of additive cryptitis, crypt abscess, and crypt distortion involving lymphoplasmocytic and neutrophilic infiltration raising the diagnosis of Crohn's disease (5%).

Table III. Three-month follow-up findings of the studied COVID-19 patients with diarrhoea

Follow up findings	COVID-19 patients with diarrhoea (*n* = 40) *n* (%)
3-month faecal calprotectin ≥ 200 µg/g	8 (20%)
Colonoscopy changes:	8 (20%)
Minimal*	5 (12.5%)
Severe**	3 (7.5%)
Pathological diagnosis of IBD	2 (5%)

**Minimal colonoscopic changes: non-specific mild rectosigmoiditis. **Severe ileocolonoscopic changes: atrophic ileal villi with aphthoid ulcerations, marked erythema of rectosigmoid. IBD – inflammatory bowel disease (both patients were pathologically diagnosed as having Crohn's disease).*

Discussion

The first evidence of excretion of SARS-CoV-2 RNA in a stool specimen was in the first reported COVID-19 patient in the United States [6]. Recently, it has become well-known that some COVID-19 patients have gastrointestinal manifestations as the presenting or the main symptom in the course of the disease [12–14]. Although diarrhoea and other gastrointestinal symptoms are frequent in COVID-19 patients, the significance remains undetermined [15, 16]. In the same context, diarrhoea was a frequent symptom in severe acute respiratory syndrome (SARS) patients (40%). Intestinal affection was associated with worse disease outcomes. In Middle East respiratory syndrome (MERS), despite the same observation of frequent occurrence of diarrhoea (14% to 50% of cases), a less severe fate of the disease was associated with gastrointestinal symptoms [17–20].

The question is raised from such a study: Does COVID-19 infection trigger intestinal dysbiosis or alter the immunological responses that may lead to inflammatory bowel disease?

Zhang *et al.* isolated SARS-CoV-2 RNA in oral swabs, anal swabs, and blood, and concluded that infected subjects can shed the virus in respiratory, faecal–oral, or body fluid routes [21]. Xiao *et al.* found 39 (53.4%) patients to be positive for COVID-19 in stool for 1 to 12 days, with 17 patients of them persisting to have positive stool specimens even after a negative PCR in their respiratory specimens [22]. Wong *et al.* found

8 children persisting to be positive on rectal swabs even after nasopharyngeal negativity for the virus [23].

The faecal calprotectin (FC) measurement may play a crucial role in the diagnosis and in the monitoring of COVID-19-related diarrhoea because SARS-CoV-2 causing an inflammatory response in the intestine was clearly shown by elevated measured levels, and this was correlated with elevated serum IL-6 levels [24, 25].

In our cohort of COVID-19 patients, there was a higher percentage of males (64% vs. 36%). This concurs with the results of many published articles and reviews [26–33]. The mean age of our patients was 49.6 ±9 years. Effenberger *et al.* reported the mean age of patients without diarrhoea, patients with ceased diarrhoea (> 48 h), and patients with acute diarrhoea (< 48 h) as 58.4 ±17.1, 66.3 ±13.1, and 78.3 ±13.8 years, respectively [24]. Ai *et al.* studied 7 COVID-19 patients with gastrointestinal symptoms as their initial or main symptoms and persistent for more than 3 days, and they found the age ranging from 35 to 75 years [13].

Many of our patients had fever at presentation (67.5%). In a systematic review published in March 2020, Li *et al.* reported fever as the most frequent presenting symptom in 88.5% of Chinese patients (83.0% to 100%) [26]. Later, Kim *et al.* published in April 2020 that fever was present in only 11.6% of South Korean mild COVID-19 patients [29]. Yang *et al.* found fever in 171 patients out of 200 hospitalized patents outside Wuhan (85.5%) [28]. Goyal *et al.* found fever in 25.5% of patients in New York City [32]. Al-Omari *et al.* found fever in 36.2% of non-intensive care unit COVID-19 Saudi Arabian patients [30].

All our study patients had elevated presenting FC (260 ±80 µg/g). Effenberger *et al.* also found significantly elevated FC in their group of patients with ceased diarrhoea, and to a larger extent in patients with ongoing diarrhoea, compared with patients without diarrhoea ($p < 0.001$). However, they did not find SARS-CoV-2-RNA in stools from patients with ongoing diarrhoea, and this was only detected in 8 patients with ceased diarrhoea and in 4 patients without diarrhoea, but there was no relation between faecal SARS-CoV-2-RNA and other biomarkers (FC, IL-6, CRP, or ferritin) [24]. Unfortunately, we could not investigate for detection of faecal viral RNA because of the local non-availability of the technique.

In the same direction, Ojetti *et al.* presented very interesting data regarding the significant correlation between COVID-19 pneumonia and high level of faecal calprotectin (expression of gastrointestinal involvement) in patients with COVID-19 infection. The presence of pneumonia is an expression of the disease's severity [34]. Similar results were reported by several studies [35, 36].

Lin *et al.* stated that 6 patients who underwent endoscopic examination that identified SARS CoV-2 RNA showed histopathological changes of numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria, in accordance with the current study in which 5 patients showed mild colonoscopic changes in the form of mild erythematous rectal erythema, which showed a non-specific form of rectosigmoiditis, whereas 3 patients had marked ileocolitis induced by COVID-19, and 2 patients showed a histopathological diagnosis of additive cryptitis, crypt abscess, and crypt distortion involving lymphoplasmocytic and neutrophilic infiltration [37].

On the contrary, Xiao *et al.* found that among a cohort of 73 patients, no abnormalities were observed in the stomach, duodenum, colon, and rectum, with the exception of mucosa damage in the oesophagus at endoscopy [22].

Moreover, Liu *et al.* raised the interest of small intestinal involvement in an 85-year-old man with a segmental dilatation alternating with stenosis with COVID-19 autopsy despite its colour being normal. Whether this finding is secondary to COVID-19 or a pre-existent GI comorbidity such as ischaemia remains unknown [27].

Our data suggest that faecal calprotectin is elevated in COVID-19 patients with intestinal symptoms, especially diarrhoea with or without colonoscopic and histopathological changes. Whether the expression of SARS-COV-2 receptors in the GI tract is related to calprotectin levels or COVID-19 only exacerbates pre-existing chronic inflammatory changes remains to be further illustrated in future larger-scale studies.

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Conflict of interest

The authors declare no conflict of interest.

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