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Post-COVID-19 enterocolitis – a cause of rebellious diarrhea, acute abdomen and liver failure

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Abstract

Currently, worldwide, the coronavirus disease 2019 (COVID-19) pandemic, which first appeared in Wuhan, China, in December 2019, is capsizing the medical system and turning the attention of the entire healthcare system through the many aspects it presents, both from a pathophysiological and from a semiological view, insufficiently studied aspects. With a high rate of morbidity and mortality, the COVID-19 pandemic was initially observed as a pathology leading to a severe acute respiratory syndrome, but over time gastrointestinal and hepatic manifestations have been reported. The study includes an analysis of 21 patients in the stage of the clinical disease of COVID-19 or in the stage of recovery, hospitalized in the Departments of General Surgery II or Gastroenterology, Emergency Clinical County Hospital of Craiova, Romania, with predominantly digestive symptoms, with the clinical expression of infectious enterocolitis, although stool culture was negative for pathogenic bacteria. The evolution of patients was influenced by the appearance of peritonitis through colonic necrosis or remission of clinical symptoms under empirical therapy.

Keywords: COVID-19, gut microbiota, liver, immune response.

Introduction

Coronavirus disease 2019 (COVID-19) is a severe inflammatory disease affecting, but not limited to, the respiratory tract. Upon its initial spreading in 2020, it was declared a pandemic by the *World Health Organization* (WHO). This infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral pathogen has spread globally at a rapid rate and is still actively spreading in 2023. Clinical manifestations are predominantly of the respiratory tract; however, it has been observed that 2–10% of SARS-CoV-2 positive patients have gastrointestinal (GI) symptoms, such as diarrhea, nausea, abdominal pain, and vomiting [1]. The understanding of this pathology is ongoing, but there is evidence that SARS-CoV-2 is transmissible in the intestinal tract, due to its affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed on the surface of small intestine cells. Thus, this can be a potential route of virus entry, triggering GI symptoms [2].

SARS-CoV-2 direct action determines an immune response, recruiting macrophages and monocytes to respond to infection. Normally, an immune competent organism would respond adequately by releasing cytokines and activating the B- and T-cells, which are responding in the mediated immune response; however, in some cases, organisms do not respond accordingly, leading to severe damage, pulmonary or even systemic destruction. This virus can induce apoptosis of infected cells and, consequently, tissues, as an integral part of the viral replicative cycle [3].

The intestinal flora plays multiple roles in the proper functioning of the human body. It is known that the microbiota has both local and systemic effects, through the production of anti-inflammatory metabolites, such as short-chain fatty acids (SCFAs) [4]. Changes in the intestinal flora can affect the immune function of the host. The link between respiratory infections and changes in the microbiota has been demonstrated [5, 6]. One study found that intestinal absorption of tryptophan is low due to low ACE2 activity, leading to reduced antimicrobial peptide secretion and thus an increased survival rate of the pathogen, with changes in intestinal flora [7].

Digestive symptoms are often associated with intestinal inflammation, along with a loss of mucosal integrity and microbial flora, which can subsequently activate immune system cells to release proinflammatory cytokines into the systemic circulation, leading to systemic inflammation. Knowing these aspects, we want to present a potential link between affecting the integrity of the intestinal tract and the pathology given by COVID-19, falsely giving the symptoms of an acute surgical abdomen and liver failure.

Aim

There are currently no studies attesting to the existence of post-COVID-19 enterocolitis as a cause of acute diarrhea and acute abdomen, but in the case study on the Department of General Surgery II, Emergency Clinical County Hospital of Craiova, Romania, we found a strong correlation between positive COVID-19 patients in their medical history, predominantly respiratory form, and alteration of the GI tract at a distance of up to one month after contact with the disease.

Patients, Materials and Methods

After obtaining ethical clearance from the Hospital's Board (Approval No. 21395/13.05.2022), we retrospectively analyzed the medical records of patients who were hospitalized between May 2020 and February 2021 in the Departments of General Surgery II and Gastroenterology within the Emergency Clinical County Hospital of Craiova.

Inclusion criteria consisted of clinical symptoms of enterocolitis or acute abdomen, being in the stage of clinical disease of COVID-19 or during the recovery phase (up to 30 days after SARS-CoV-2 negativity). Patients experienced moderate or severe respiratory forms of COVID-19. During hospitalization for COVID-19, two patients received antibiotic treatment with Meropenem and Ceftriaxone, and another with Linezolid and Metronidazole.

The rest of the patients followed the treatment scheme proposed at national level during hospitalization. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Emergency Clinical County Hospital of Craiova (Approval No. 21395/13.05.2022).

Results

Following the inclusion criteria, we selected 21 patients who were admitted to the Departments of General Surgery II or Gastroenterology for acute diarrhea, abdominal pain and altered general condition. Of the 21 patients who presented for digestive symptoms, three tested positive for COVID-19 and 18 were declared negative [two successive negative SARS-CoV-2 polymerase chain reaction (PCR) tests] in a range of up to one month before the time of presentation for digestive symptoms. The clinical examination found movement of the abdominal wall with breathing (except for a patient with peritonitis), diffuse pain throughout the area, with generalized muscular defense (acute abdomen appearance) or with muscular defense sketches (Table 1).

Table 1 – ***Clinical manifestations of the studied patients***

Case No.	Symptoms				Clinical exam		SARS-CoV-2 PCR test		Antibiotic treatment during COVID-19 disease
	Abdominal pain	*Diarrhea*	*Nausea*	*Vomiting*	*Guarding/general muscular defense sketches*	*Abdominal tenderness*	*Positive*	*Negative (positive in their medical history)*	
1.	x	x			x			x	
2.	x	x			x		x		x
3.	x	x				x		x	x
4.	x	x	x	x		x		x	
5.	x	x	x	x	x		x		x
6.	x	x			x			x	
7.	x	x			x			x	
8.	x	x				x		x	x
9.	x	x	x	x		x		x	
10.	x	x	x	x	x		x		x
11.	x	x	x		x			x	
12.	x	x				x		x	
13.	x	x	x	x	x			x	x
14.	x	x				x		x	x
15.	x	x				x		x	x
16.	x	x	x			x		x	
17.	x	x	x		x			x	
18.	x	x			x			x	x
19.	x	x			x			x	x
20.	x	x				x		x	x
21.	x	x	x	x		x		x	x

COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

The initial biological evaluation showed increased values of lymphocytes, leukocytes, and erythrocyte sedimentation rate (ESR) increased by an average of 2–3 times. Except for a patient who presented with clinical signs of acute surgical abdomen, in whom lymphocytopenia was present and ESR was found to be approximately 10 times higher than normal. All patients had negative stool cultures for *Escherichia coli*, *Salmonella* spp., *Shigella* spp. The parasitic examination of the stool was also negative for various parasites. The test for *Clostridium difficile* toxins was positive in seven patients, with the remaining patients having a negative result (Table 2).

Imaging evaluation was performed by simple abdominal radiography and computed tomography (CT) examination. All 21 patients had hydro-aerial levels at the simple radiological examination, and two patients had pneumoperitoneum (corroborated with clinical data was the indication for emergency surgery). CT examination of the patients showed diffuse thickened walls at the level of the colic frame, with edematous appearance, with consecutive, asymmetrical narrowing of the distal lumen, with hypertrophic, flattened mucosal folds, suggestive appearance for entero-rectocolitis (Figures 1–4).

Table 2 – ***Stool examination***

Case No.	SARS-CoV-2 PCR test at the time of admission Positive	*Test for *Clostridium difficile* Positive	**Stool culture Negative	***Stool parasitic exam Negative	Colonoscopic appearance suggestive of pseudo-membranous colitis	Elevated ALT and AST
1.			x	x		x
2.	x		x	x		
3.			x	x	x	x
4.		x	x	x		x
5.	x		x	x		x
6.			x	x		x
7.		x	x	x		
8.			x	x	x	
9.			x	x		
10.	x		x	x		
11.		x	x	x		x
12.			x	x		
13.			x	x	x	x
14.		x	x	x		x
15.		x	x	x		
16.		x	x	x		x
17.			x	x		
18.			x	x	x	x
19.			x	x	x	x
20.		x	x	x		
21.			x	x	x	x

ALT: Alanine transaminase; AST: Aspartate transaminase; PCR: Polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. *Test for *C. difficile*: toxin A and/or toxin B. **Stool culture – Enteropathogenic *Escherichia coli*; *Salmonella* spp.; *Shigella* spp. ***Stool parasitic exam – *Ancylostoma duodenale*; *Ascaris lumbricoides*; *Blastocystis hominis*; *Diphyllobothrium latum*; *Entamoeba coli*; *Entamoeba histolytica*; *Enterobius vermicularis*; *Fasciola hepatica*; *Giardia lamblia*; *Hymenolepis diminuta*; *Hymenolepis nana*; *Strongyloides stercoralis*; *Taenia* spp.; *Trichuris trichiura*.

Figure 1 – ***Chest–abdomen–pelvis computed tomography (CT) performed on 24.01.2021 in a 74-year-old patient, coronavirus disease 2019 (COVID-19).***

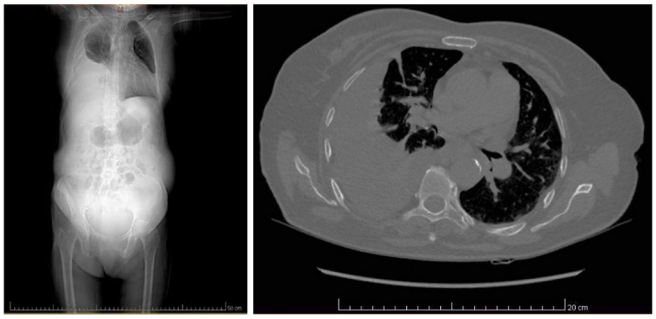

Figure 2 – ***Chest CT: right pleural fluid in large quantities, located apical postero- and latero-basal, with secondary collapse of the adjacent lung parenchyma and mass effect on the mediastinum, shifted to the left.***

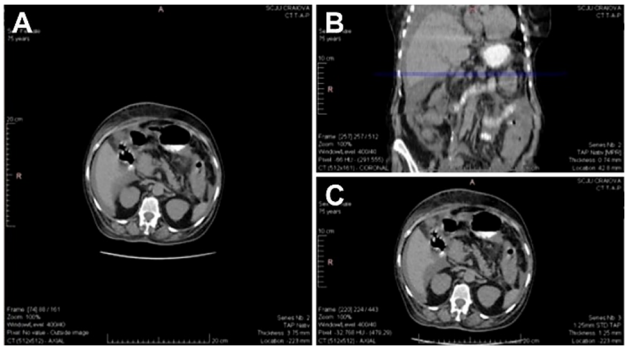

Figure 3 – ***(A–C) Abdominal CT: peritoneal fluid in moderate amount, perihepatic, perisplenic display.***

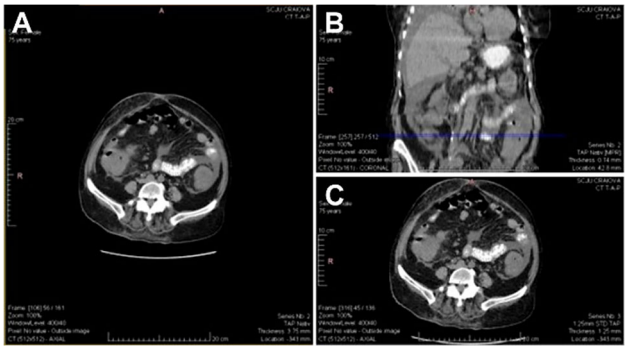

Figure 4 – ***(A–C) Abdominal CT: colic frame with diffuse thickened walls, with edematous appearance, irregular, with asymmetric narrowing of the intestinal lumen, appearance found in the cecum-ascending colon-transverse colon-descending colon-sigmoid-rectum, with hypertrophic mucosal folds, infiltration, and edematous substrate at the level of pericolic fatty areas.***

The indication for surgery was established in two patients with clinical signs of acute surgical abdomen, in which radiological examination and tomography showed pneumoperitoneum. Surgical examination found peritonitis due to segmental jejunal necrosis or segmental necrosis of the sigmoid colon (ischemic colitis). In the first case, a

segmental enterectomy with entero-enteral anastomosis was performed, and the evolution was unfavorable by *exitus* 24 hours postoperatively due to pulmonary complications, and in the second case, a Hartmann-type segmental colectomy was performed (Figure 5), with a slowly favorable postoperative evolution. Although 11 patients showed clinical signs of acute abdomen, the decision to perform the surgery was established after completing the diagnosis with imaging examinations. In a patient whose acute surgical abdomen was excluded, specific anti-COVID-19 therapy (tested positive), and rebalancing therapy were required.

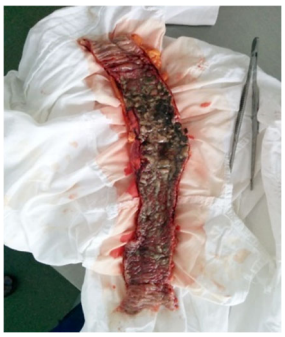

Figure 5 – ***The macroscopic aspect of the colonic resection piece: the ischemic mucosa can be observed in comparison with the (normal) resection margins.***

Diarrhea was present in post-COVID-19 patients, especially in those who followed long-term oral antibiotic treatment (Clarithromycin 500 mg orally at 12 hours or Azithromycin 500 mg daily) or intravenously (Meropenem i.v. 1 g every eight hours). The suspicion of *C. difficile* infection was raised, although four patients in the study received treatment with pre- and probiotics. Thus, following consultations with Departments of Gastroenterology and Infectious Diseases, treatment with Vancomycin was instituted (125 mg every eight hours, orally).

Persistence of diarrhea, negative results in the case of coproculture, coproparasitic examination and toxins A and B produced by *C. difficile*, as well as maintaining the tomographic appearance of enterocolitis, required endoscopic examination of the colon. Colonoscopy found significant edema of the entire large intestine, with areas of stenosis, numerous ulcers, and false membranes, suggestive of pseudomembranous colitis in six patients (Table 2; Figure 6, A–C).

Colonoscopy was performed approximately between days 7–10 after initiation of Vancomycin treatment without favorable clinical response. The macroscopic appearance of pseudomembranous colitis-type colonic lesions raised the suspicion of *C. difficile* infection despite negative fecal toxin tests performed before initiation of Vancomycin therapy. It was thus decided that the patients should follow a "step-down" scheme of treatment with oral Vancomycin in a prolonged scheme with 500 mg every six hours in combination with Metronidazole 500 mg i.v. every eight hours for seven days, then 125 mg Vancomycin at eight hours for seven days. Treatment continued with Vancomycin 125 mg *per os* (*p.o.*) every 12 hours for another five days, then Vancomycin 125 mg *p.o.* per day for five days, and finally two weeks of Vancomycin 125 mg *p.o.* every two days. All cases of pseudomembranous colitis visualized colonoscopically and initially refractory to treatment showed a favorable evolution with remission of symptoms within up to one month. The medication was supplemented by the administration of pre- and probiotics.

From an anatomopathological point of view, in the surgical pieces (colon segment), necrosis of the intestinal mucosa was found, which could be observed microscopically in different degrees in the operated patients with positive COVID-19 (Figure 7, A and B).

Also, the impact that long-term hypoxemia can have on COVID-19 positive patients can be associated with tissue cell necrosis, which can subsequently lead to GI ulceration and bleeding.

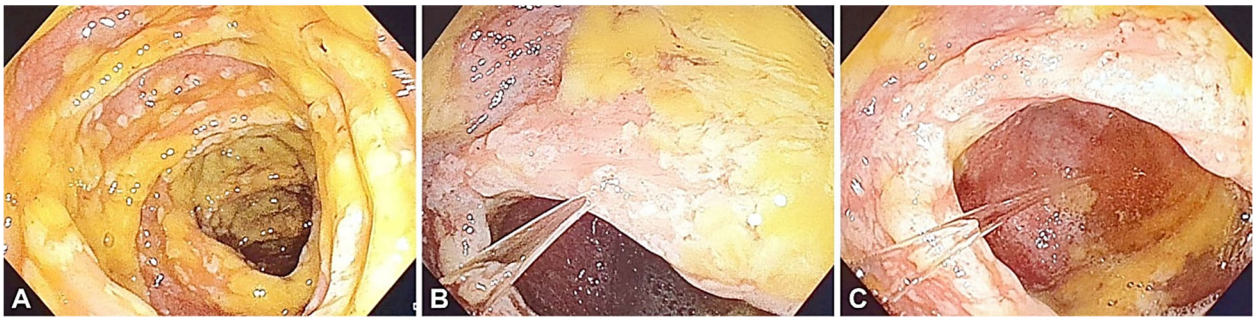

Figure 6 – ***(A–C) Colonoscopy: appearance of pseudomembranous colitis, significant edema and false membranes are observed.***

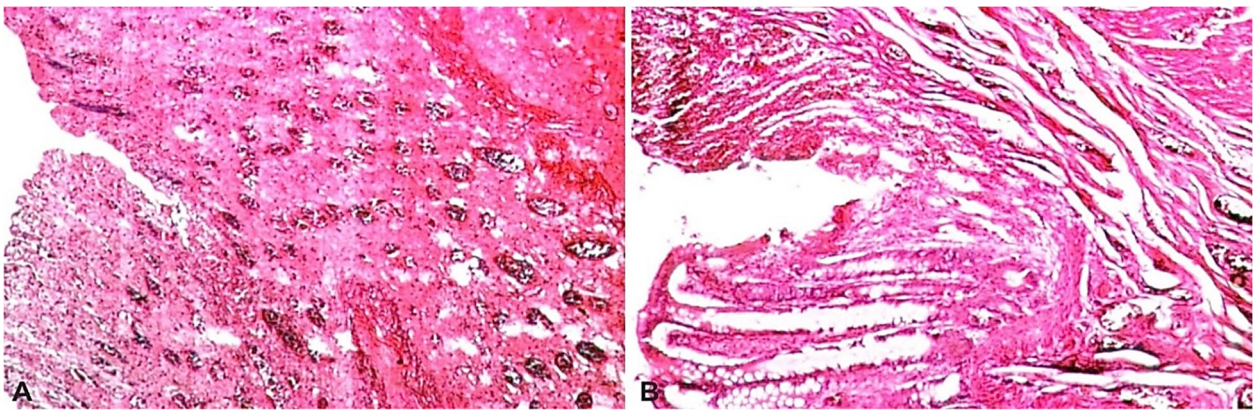

Figure 7 – ***Pathology exam: (A) Colon mucosal necrosis; (B) Colon wall necrosis. Hematoxylin–Eosin (HE) staining: (A and B) ×40.***

Discussions

Diarrhea, defined by the *WHO*, is the presence of more than three stools/day of low consistency. Acute diarrhea is infectious by nature, so we analyzed the patients' feces for the most common bacterial (*E. coli*, *Salmonella* spp., *Shigella* spp. and *C. difficile*) and parasitological causes, which were negative. We evaluated the presence of *C. difficile* in relation to the consumption of antibiotics by some patients, but also the hospitalization of some patients in medical and sanitary units. However, the tests for *C. difficile* were positive in only seven cases. Clinical manifestations associated with acute diarrhea consisted of abdominal pain in all patients, of varying severity. Some patients also reported nausea and vomiting.

GI symptoms in COVID-19 have been frequently reported, the most common being diarrhea, nausea, and vomiting. The SARS-CoV-2 virus is thought to enter the host cell through the interaction of the viral spike protein with the ACE2 present in the host cell, which are present in both the respiratory and intestinal tracts. It has been demonstrated that the virus acts on enterocytes in studies carried out on specimens extracted from the human small intestine, but also on models carried out on primates [8]. Cytopathic effects related to viral infections, altered intestinal permeability leading to malabsorption, cytokine-driven inflammation, and altered intestinal flora are some of the key mechanisms of action of the virus studied. It is interesting that the presence of diarrhea was observed in patients who had symptoms of COVID-19 for more than 10 days [9], and the administration of antivirals (Lopinavir, Ritonavir) also led to the remission of diarrheal episodes, thus supporting the connection between this symptom and disease [10]. Pseudomembranous colitis is an affection of the colon characterized by the appearance of whitish-yellow deposits with a tendency to coalesce and the formation of pseudomembranes in the colonic mucosa. The most common causes are infectious diseases, and *C. difficile* is the main cause of pseudomembranous colitis. Other causes include parasitic, viral (cytomegalovirus), bacterial or other types of colitis [such as inflammatory bowel diseases – ulcerative colitis (UC) or Crohn's disease, collagenous colitis, Behçet's disease]. *C. difficile* infection can often be superimposed. In the case of the presented patients with SARS-CoV-2 infection, with antibiotic treatments and with prolonged hospitalization in the services of infectious diseases and internal medicine, with negative coproparasitic examination and coproculture, it was decided to institute specific treatment for *C. difficile* infection, even if the testing of fecal toxins A and B were negative in most patients, as the specialized literature admits cases of pseudomembranous colitis with ICD (*C. difficile* infection) and negative toxins [10].

The involvement of liver function in COVID-19 is either due to viral toxicity or secondary to dysbiosis. Studies have demonstrated the presence of the SARS-CoV-2 virus in low titers in the liver tissue of positive COVID-19 patients, in contrast to Middle East respiratory syndrome (MERS) patients, in which the virus could not be detected at the liver cellular level [11]. Microvascular thrombosis caused by the disease can lead to hepatic hypoxia, which can subsequently lead to liver dysfunction. An increase in alanine transaminase (ALT) and aspartate transaminase (AST) values was observed in some patients, increasing the importance of the need to evaluate liver function more carefully in the context of the COVID-19 disease, liver destruction being encountered. Patients with chronic liver disease are at increased risk for severe forms of COVID-19 disease.

Recent studies suggest multiple implications of SARS-CoV-2 in the etiopathogenesis of liver failure, either through direct viral cytopathic effect, through systemic inflammatory response syndrome (SIRS), through changes resulting from hypoxia, through liver injury given by drugs or even through vascular changes given by exacerbated coagulopathy. Although ACE2 is involved in facilitating virus entry into the host cell, ACE2 is found in greater quantity in cystic duct epithelial cells and less in hepatocytes and Kupffer cells [12]. ACE2 expression is highly expressed in the epithelial cells of the cystic duct, in approximately the same manner as in the alveolar cells. The renin–angiotensin system (RAS) has an important role in liver inflammation, tissue remodeling and fibrosis. ACE2 is a key regulator of the RAS through its negative effects and limits fibrosis through the degradation of angiotensin II and the formation of angiotensin [1–7]. Upon binding of the SARS-CoV-2 virus, ACE2 undergoes the process of endocytosis, and its levels are thus reduced on the cell surface.

Moderate and severe increases in ALT and AST were observed in patients with COVID-19, these increases being the most common liver abnormalities reported in the literature [13], observed in most patients included in the study. The stress-induced liver injury associated with COVID-19 may be correlated with oxidative stress, intestinal endotoxemia, and increased Kupffer cell reactivity through activation of the sympathetic nervous system. Sepsis, for example, frequently encountered in severe cases of COVID-19, is an immune response given by the alteration of the body to an infection, which can later lead to organic dysfunction, but also psychological stress. The pathophysiology of sepsis associated with liver injury involves hypoxic liver injury due to ischemia and shock, cholestasis, and resultant hepatocellular injury. Also, severe hypoxia and hypovolemia have been cited causes of ischemic/hypoxic liver injury in COVID-19 associated with acute respiratory failure or shock. The injury in this case may be the result of metabolic acidosis with increased calcium levels and changes in mitochondrial membrane permeability [14].

Current studies suggest the contribution of the altered microbiota in the activation of an immune-mediated inflammatory response, of particular importance in COVID-19, determining the subsequent clinical evolution of patients infected with SARS-CoV-2. GI blood supply reaches the liver *via* the portal venous system. Thus, the disruption of the intestinal flora with the alteration of the intestinal barrier can lead to sepsis-induced liver dysfunction [15]. The impact of pre- and probiotics on COVID-19 patients should be studied, as the role of the intestinal microbiota in modulating the immune system is proven, and the digestive aspects of this disease support the need to administer an effective cocktail of probiotics, able to maintain the necessary balance. It is also an important factor to note whether the microbial flora has a role in the susceptibility of the patient to develop a more severe form of the disease and whether the administration of probiotics would have an effective therapeutic effect in the management of this type

of patients. A high level of inflammation reduction is known because of the use of probiotics, and even the usefulness of their consumption in the remission of UC [16]. We found, compared to the cases treated in the two Clinics, an increased number of patients who presented with symptoms of enterocolitis or even with clinical manifestations of acute surgical abdomen, in the context of the COVID-19, either in the disease state phase, or during the convalescence period. Analyzing from a paraclinical, intraoperative and endoscopic point of view, necrosis, areas of ulceration and false membranes were observed, aspects that may be related to the damage at the microvascular level, through microvascular angiopathy, already described at the level of different organs and tissues [17, 18]. Microvascular angiopathy is a consequence of hyperactivation of the host immune response.

Post-mortem studies of patients who died following COVID-19 demonstrated the existence of micro-thrombi at the level of the hepatic vascular bed and ischemic necrosis of the liver tissue [19]. The first autopsy performed on an 85-year-old patient, positive for SARS-CoV-2 infection, showed segmental dilatation and stenosis of the small intestine [20]. The persistence of diarrhea and digestive symptoms under rebalancing therapy, and in the case of positive COVID-19 patients, under specific therapy, benefited from the introduction of Vancomycin treatment. The evolution of the digestive symptoms was favorable with the remission of diarrhea, independent of the respiratory evolution.

Conclusions

In the presented article, the patients were investigated for the most common causes of acute diarrhea, and although related to a small number of patients with the described symptoms, analyzing pre-existing studies, we support the need for the examination and in-depth study of the intestinal level impairment that SARS-CoV-2 affects patients and the introduction of pre- and probiotics into the recommended medication. We observed the correlation of typical digestive symptoms for enterocolitis in positive COVID-19 patients (either in the condition phase or in the convalescence period) with paraclinical examination uncharacteristic of the most common organisms causing this pathology. Negative results for *C. difficile*, *Shigella*, *E. coli*, *Salmonella*, and various parasites ruled out these causes in patients who presented with acute diarrhea and abdominal pain. Considering their status related to the infection with the new coronavirus, we appreciate the need for future investigation of this potential cause as well, as the evolution of these patients may put their lives at risk in the absence of timely treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Cosmin Vasile Obleagă and Rukie Ana Maria Ahmet have the same contribution as the first author.

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