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Features of Gastroenterological Diseases in the Post-Covid Period

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Abstract: The article provides an overview of studies on gastroenterological manifestations in the post-pregnancy period. It has been shown that in addition to the traditional symptoms, patients with SARS-CoV-2 most often experience symptoms such as diarrhea, nausea and vomiting. It has been shown that the dysfunction of the gastrointestinal tract occurs both due to direct exposure to the virus and due to impaired tissue and organ function under the influence of the immune response.

Keywords: post-COVID syndrome, intestines, diarrhea, gastrointestinal diseases

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The global and regional consequences of the SARS-CoV-2 pandemic remain a matter of serious concern. Although the availability of vaccines against the SARS-CoV-2 virus has partially reduced anxiety in some parts of the world, it continues to be a prevailing global public health crisis. Factors that aggravate this problem include viral mutations and the variability of clinical presentations. Typical manifestations of COVID-19 include fever, dry cough, shortness of breath, fatigue, and a sensation of heaviness in the chest. At disease onset, myalgia, confusion, headache, and tachycardia may be present [1]. Early publications reported gastrointestinal symptoms in 1% to 3.8% of cases [2]. Later studies indicated a higher prevalence of gastroenterological symptoms, including diarrhea and nausea in 10.1% of cases and vomiting in 3.6% [3]. The most common gastroenterological symptom is diarrhea. For example, during the SARS outbreak in Hong Kong in 2003, caused by a coronavirus, every fifth patient had stool disturbances [4,5]. The duration of diarrhea typically lasted three to four days and most often resolved spontaneously [5]. Among patients with another coronavirus (MERS), gastrointestinal manifestations such as diarrhea, abdominal pain, nausea, and vomiting were reported in 11.5–32% of cases [6].

Several researchers described gastroenterological symptoms in SARS-CoV-2 infection accompanied by the detection of the virus in feces. Two large clinical studies in China focused on gastrointestinal manifestations and the presence of the virus in fecal samples [7]. In one study, Jin X. et al. examined 74 patients infected with SARS-CoV-2 who presented with diarrhea, nausea, and vomiting. Up to 28% of those with gastrointestinal symptoms had no respiratory symptoms. The study demonstrated that these

patients, compared with those who had no gastrointestinal symptoms (n=577), generally had more severe or critical disease, body temperature above 38.5°C, and elevated aminotransferases. Among all examined patients (n=651), 11.4% had symptoms of liver or intestinal injury [7,8]. In another study, Lin L. et al. analyzed 95 patients infected with SARS-CoV-2, of whom 61.1% had gastrointestinal symptoms. The most significant symptoms were diarrhea (24.2%), nausea (17.9%), vomiting (4.2%), and liver dysfunction (32.6%). Notably, SARS-CoV-2 was detected in biopsy samples obtained during esophagogastroduodenoscopy in three out of six individuals. In two patients, the virus was found in the esophagus, stomach, duodenum, and rectum, confirming its presence throughout the gastrointestinal tract. Viral RNA was detected in 52.4% (n=22) of fecal samples [9]. Thus, these publications highlight the prevalence of gastrointestinal symptoms in patients with COVID-19.

Xiao F. et al. examined medical records of 73 hospitalized patients with SARS-CoV-2 infection in China. Of them, 53.4% had positive fecal tests between days 1 and 12 of infection [10]. Notably, more than 20% of infected patients continued to test positive for the virus in feces even after respiratory samples turned negative. A similar study from Singapore reported that 50% of COVID-19 patients had detectable virus in feces, although only about half of them reported diarrhea [11]. In some cases, diarrhea may be the primary symptom. Y. Song et al. described a 22-year-old patient hospitalized with complaints of frequent watery stools (3–4 times a day) and low-grade fever, without any other symptoms. Imaging revealed bilateral pneumonia, and SARS-CoV-2 RNA was detected in a nasopharyngeal swab. After antiviral treatment (lopinavir and ritonavir), diarrhea resolved alongside improvement in lung findings [12]. There is accumulating evidence showing that gastrointestinal symptoms are common and that SARS-CoV-2 is detected in feces in approximately 50% of infected individuals; however, no clear correlation has been established between gastrointestinal symptoms and fecal viral presence.

What remains unclear is why SARS-CoV-2 causes gastroenterological symptoms and whether the virus can be transmitted through the digestive tract in addition to the respiratory route. A prerequisite for infection is viral entry into host cells. Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter host cells, and ACE2 is an important regulator of intestinal inflammation [13]. A striking discovery was that ACE2 expression is significantly higher in enterocytes of the ileum and colon compared with the lungs [14]. It remains unknown whether intestinal inflammation increases ACE2 expression and consequently raises the risk for patients with inflammatory bowel disease. Detection of SARS-CoV-2 in feces and intestinal mucosa in approximately 50% of cases suggests that intestinal symptoms may be caused by viral invasion of ACE2-expressing enterocytes. Thus, the gastrointestinal tract may serve as an alternative route of infection. In more than half of patients, fecal samples remained positive for an average of 11 days after the virus was cleared from respiratory samples [15].

Some studies demonstrated SARS-CoV-2 RNA in anal swabs and stool samples in 29–80% of patients. Other studies reported that the virus can persist in feces for up to 49 days after disease onset [16]. This raises important questions: *Is the virus alive, and if so, in what concentration?* A recent study found that 8 out of 10 infected children had persistently positive rectal swabs even after nasopharyngeal tests became negative [17]. Meanwhile, Wölfel et al. detected SARS-CoV-2 RNA in nasopharyngeal samples but were unable to isolate viable virus from feces [18]. There are reports of viable virus detected in feces even in the absence of diarrhea [19,20], supporting the possibility of fecal-oral transmission. Zhang et al. emphasized that live SARS-CoV-2 can be isolated from stool and can infect and replicate in VERO monkey kidney cells. The authors concluded that “live virus in feces may be an important source of infection, potentially leading to spread in areas with poor sanitation” [21].

Analysis of the literature suggests that gastroenterological manifestations of the new coronavirus infection are initiated both by the direct effect of the virus and by tissue injury caused by the immune response.

The most studied mechanisms include:

1. **Viral tropism for the digestive tract**, manifesting as liver and intestinal injury.
2. **Cytokine storm**, involving lymphocyte activation, increased activity of pro-inflammatory cytokines, and systemic inflammation affecting the gastrointestinal tract [22].
3. **Adverse effects of medications** including prolonged use of antibiotics, antivirals, enteral nutrition, and glucocorticosteroids [23].

Six meta-analyses involving over 53,000 patients with COVID-19 were reviewed.

Table 1 Meta-analysis of COVID-19 Patients with Gastrointestinal Symptoms

Number of COVID-19 patients	Gastrointestinal symptoms	Diarrhea	Nausea/Vomiting	Abdominal pain	Number of studies	Reference
2,477	13%	7.8%	5.5%	2.7%	17	[24]
4,243	17.6%	12.5%	10.2%	9.2%	60	[25]
4,805	Not reported	7.4%	4.6%	Not reported	29	[26]
5,601	9.8%	10.4%	7.7%	6.9%	37	[27]
17,776	20%	13%	8%	4%	108	[28]

The analysis revealed no significant correlation between the presence or absence of gastrointestinal symptoms and COVID-19 overall severity [30–32]. However, another study reported significant differences in the prevalence of abdominal pain and anorexia across severity groups [33]. Further studies, including regional analyses with larger sample sizes, are needed for definitive conclusions [34–39].

The initial step of SARS-CoV-2 infection is the interaction of the spike protein with ACE2 receptors, which are expressed on alveolocytes, cardiomyocytes, hepatocytes, cholangiocytes, endothelial cells, renal tubular cells, and neuroglia. The highest concentrations occur in the mucosa of the ileum and colon [40,41]. ACE2 is crucial for maintaining epithelial barrier integrity and normal gut microbiota composition [42]. Studies have shown reductions in normal intestinal flora and increases in conditional pathogens in COVID-19 patients, regardless of medication intake [43]. Decreases were noted in beneficial anaerobic bacteria such as **Faecalibacterium prausnitzii**, **Eubacterium rectale**, and **Bifidobacteria**, persisting for 1–3 months after viral elimination [44]. Patients with moderate and severe COVID-19 had higher levels of conditional pathogens including **Collinsella aerofaciens**, **Collinsella tanakaei**, **Morganella morganii**, **Streptococcus infantis** [45]. Microbiota alterations are associated with increased intestinal inflammation and elevated fecal calprotectin levels in COVID-19 patients with diarrhea [46]. There is debate about whether the cytokine storm contributes to intestinal dysfunction and worsens disease progression [47].

Patients with gastrointestinal symptoms generally have a less favorable prognosis than those without such manifestations [48]. A meta-analysis of 26 clinical studies (nearly 6000 individuals) reported nausea and vomiting in 7.8% of cases. Studies from the USA, Netherlands, Germany, Australia, and Singapore showed even higher prevalence — 14.9%, three times higher than in Chinese studies [22]. Another meta-analysis of 43 studies and over 10,500 patients found diarrhea in 7.7% of cases [23]. Treatment of diarrhea included symptomatic therapy such as dioctahedral smectite and loperamide; microbiota-regulating agents (probiotics) when needed; and antispasmodics for abdominal pain. Electrolyte imbalance was corrected with rehydration therapy [32].

Conclusion

The conducted research provides new insights into the prevalence, etiology, and potential mechanisms of COVID-19 in the gastrointestinal tract, which are crucial for prevention, clinical management, and treatment strategies.

Unanswered questions remain:

- Why is SARS-CoV-2 found in rectal swabs of asymptomatic individuals?
- Is ACE2 truly the main mediator of viral entry into the GI tract?
- How does the virus survive the extreme pH environment of the digestive system?

Prolonged fecal viral shedding even after respiratory clearance suggests that stool testing and appropriate infection-control precautions should be considered. Further research is needed to determine the viability and pathogenicity of SARS-CoV-2 in feces, especially for preventing transmission by asymptomatic carriers. Patients with gastrointestinal symptoms may be admitted to therapeutic (non-infectious) departments, which may contribute to further viral spread and complicate timely diagnosis. Thus, clinicians should remain alert to COVID-19 in patients presenting with gastrointestinal symptoms and ensure timely correction of identified abnormalities.

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