

Digestive involvement in the Long-COVID syndrome



GASTROENTEROLOGY

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Abstract

Background and aim. The SARS-CoV-2 infection which caused a worldwide epidemic was considered first a lung disease. Later on, it was found that the disease caused by this virus, SARS-CoV-2, can affect most organs, including the digestive system. The long-term effects of this infection are now progressively detected and called Long-COVID. This review aims is to present the updated knowledge of the digestive sequelae after SARS-CoV-2 infection.

Methods. A search was performed in the main medical literature databases. The following search terms were used: long-covid, gastrointestinal or gastric sequelae SARS-CoV-2 and COVID-19. Data on gastrointestinal symptoms after 12 weeks were collected and presented. Observational studies were included. Studies that focus only on acute COVID-19 infection (<4 weeks) were excluded.

Results. The main symptoms that can occur in the long term are: diarrhea, nausea, vomiting, abdominal pain, along with increased liver enzymes. Patients with chronic diseases have a higher risk of developing long-term sequelae, but it is not documented that digestive sequelae are influenced by the presence of chronic diseases.

Conclusions. The SARS-CoV-2 virus can affect any part of the digestive system not only in the acute infection phase but also for longer time, leaving long-term sequelae.

Keywords: COVID-19, digestive diseases, SARS-Cov-2 infection, gastrointestinal tract, liver diseases, long-Covid, sequelae

Introduction

Since spring 2020, population has suffered the dramatic experience of the pandemic caused by the new coronavirus SARS-CoV-2. This special situation has led to an unprecedented explosion of research and despite all the efforts of health professionals, at a distance of several weeks we can observe the persistence of many sequelae [1]. At the beginning, COVID-19 was considered an acute infectious disease with respiratory and sometimes non-respiratory symptoms [2], but the number of people with long-term symptoms is increasing [3]. As such, the identification, understanding and classification of long-term sequelae is an important step in the proper healing of patients [4].

A literature search was undertaken in main data bases of medical publications (PubMed, UpToDate) using the search terms: digestive, gastrointestinal, gastric, SARS-CoV-2, COVID-19, Coronavirus, sequelae and long term. Data on symptoms of gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal pain) which appeared 12 weeks after this viral condition were collected and presented.

Definition

COVID-19 infection can affect almost any organ system. The main disorders caused by this infection include respiratory disorders, nervous and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal

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disorders, and general malaise, fatigue, musculoskeletal pain and anemia [5]. A wide range of symptoms are frequently considered, including fatigue, headache, shortness of breath, anosmia (loss of smell), parosmia (distorted smell), muscle weakness, low-grade fever and cognitive dysfunction [6].

Long-COVID can be defined as a condition characterized by long-term sequelae appearing or persisting after the typical convalescence period of COVID-19 infection [6].

There are several names proposed for long-term symptoms lasting after the typical period of convalescence, as presented below:

1. Post-acute sequelae of COVID-19 (PASC)
2. Chronic COVID syndrome (CCS)
3. Long-COVID

Long-COVID is a term used for people who have been cured of COVID-19 infection but have long-term symptoms, even after 12 weeks after the infection [7].

It is currently accepted that acute SARS-CoV-2 infection lasts about 2-3 weeks, so the first question one should answer is: when can we confirm that a patient has been cured of SARS-CoV-2 infection and therefore, when can we consider the presence of post-COVID symptoms?

SARS-CoV-2 is detectable up to 30 days after the disappearance of symptoms in 10-15% of people diagnosed, but apparently without potential clinical relevance. Nevertheless, it was proposed that this prolonged exposure to SARS-CoV-2 virus may be one of the underlying mechanisms of long-term post-COVID symptoms [7]. At the same time, another dilemma in defining this syndrome is that post-COVID symptoms caused by COVID-19

infection should occur after a positive diagnosis of SARS-CoV-2 infection, but millions of people can be also infected with COVID-19 and never receive a positive diagnosis of infection with this virus [8].

In defining long-COVID syndrome, the primary aspect that needs to be clarified is the time frame used to define post-COVID symptoms. It has been proposed that symptoms occurring after more than 3 weeks after the SARS-CoV-2 infection can be considered prolonged or persistent [7]. In other publications, the terms post-acute COVID (symptoms over 3 weeks) and long-term post-COVID or persistent chronic post-COVID (symptoms over 12 weeks) have been proposed [8]. The NICE (National Institute for Health and Care Excellence) guide proposes the following classification:

- acute COVID-19 (symptoms up to 4 weeks);
- symptomatic COVID in progress (symptoms 4 to 12 weeks);
- post-COVID (symptoms developed during or after an infection and lasting more than 12 weeks) [9].

With these being mentioned, a variety of factors could favor the development of post-COVID symptoms. Also, the temporal classification can be influenced if a patient needed hospitalization or not [7].

- Transition phase: symptoms potentially associated with acute COVID-19: symptoms up to 4-5 weeks;
- Phase 1: Acute post-COVID symptoms: symptoms from week 5 to week 12;
- Phase 2: Long-COVID specific symptoms: symptoms from week 12 to week 24;
- Phase 3: Persistent post-COVID symptoms: symptoms lasting more than 24 weeks [7].

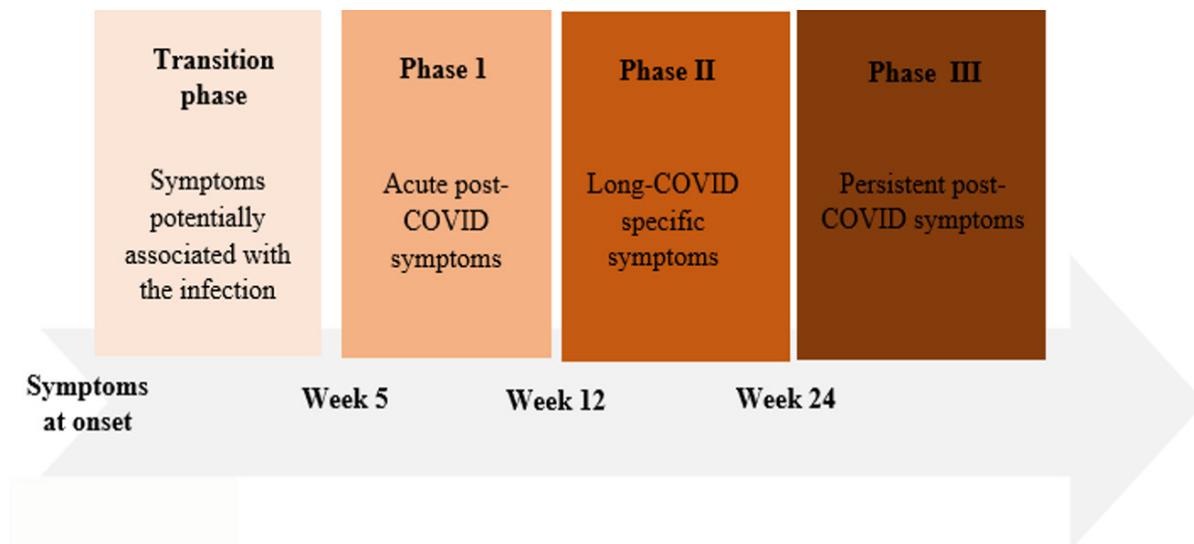


Figure 1. Time frame.

Even though coronavirus disease 2019 (COVID-19) is primarily a respiratory illness, the digestive system has been implicated in this disease. Gastrointestinal symptoms may occur frequently, they may be the only symptoms, or can be present before any respiratory symptoms. The cellular receptor for SARS-CoV-2, ACE2, is highly expressed in the digestive system. Direct functional damage of the gastrointestinal tract by viral interaction with the squamous and columnar epithelium mediated by ACE 2 receptor can occur and can explain the esophagitis caused by SARS-CoV-2 and the diarrhea. Also, the ACE2 is expressed in the liver and pancreas and can explain the associated disorders [2].

In Long-COVID we can observe the persistence of digestive symptoms such as abdominal pain and vomiting or the appearance of digestive sequelae like acid reflux, abdominal distension, belching, vomiting, abdominal pain, rectal bleeding, liver damage and cholangiopathy [9].

Further studies are needed to support the persistence of these sequelae and to improve the management of the long-term effects of this disease.

Prevalence data

The data found in the medical literature suggest that not every person infected with COVID-19 develops long-term symptoms. A study conducted by the United Kingdom's NICE agency shows that those at the highest risk of developing long-term COVID are: the elderly, women and patients who had five or more symptoms in the first week of illness. In this study, the people most likely to be affected by long-term COVID-19 were white women, aged 40 to 60, with two or more medical conditions, such as a cardiovascular disease, asthma, or type 2 diabetes [10].

The British Office for National Statistics shows that approximately 1 in 5 patients who have tested positive for COVID-19 have symptoms for a period of 5 weeks or more. Also, 1 in 10 patients who have tested positive for COVID-19 have symptoms for a period of 12 weeks or more [5]. Additional studies are needed to provide more accurate data on larger and more diverse patient groups.

The incidence of post-COVID-19 related gastrointestinal symptoms is between 3% and 79%, in various studies. Further studies are required to provide more accurate data [11,12].

Long-term symptoms and clinical manifestations

The researchers have identified two large categories of this syndrome, based on the symptoms presented. One category is mainly represented by respiratory symptoms, such as cough and dyspnea, but also includes fatigue and headache. The second category of symptoms are those that suggest damage of the major organs. For example, cardiovascular conditions like hypertension, cardiac

dysrhythmias, circulatory signs and symptoms, chest pain coronary atherosclerosis, and heart failure, diseases of the nervous system like neurocognitive disorders and headache or damage of the entire digestive system [13].

An observational study shows that the group of patients analyzed have reported a number of symptoms affecting different systems: post-COVID neurocognitive symptoms (concentration disorder, dizziness, loss of attention, confusion), post-COVID autonomic symptoms (chest pain, tachycardia, palpitations), post-COVID gastrointestinal symptoms (diarrhea, abdominal pain, vomiting), post-COVID respiratory symptoms (general fatigue, dyspnea, cough, sore throat), post-COVID musculoskeletal symptoms (myalgias, arthralgias), psychological related symptoms after COVID-19 infection (post-traumatic stress disorder, anxiety, depression, insomnia) and other manifestations (ageusia, anosmia, parosmia, rash). Also, the persistence of symptoms at 8-12 weeks is demonstrated in most patients, even in those hospitalized with a mild form of the disease [14].

A different study which included 430 patients found symptoms after the convalescence from the acute infection with COVID-19 including general, upper, lower respiratory tract, neurological, cutaneous complaints, and symptoms suggesting other systems of the body affected. The mean duration of persistent post-COVID-19 symptoms after recovery was 176 ± 35.1 days. Data obtained showed the most common gastrointestinal symptoms were anorexia (42.6%) and gastritis (32.3%). Also, another important symptom present was abdominal pain 20% [15].

In another observational study, which analyzed the sequelae of COVID-19 infection at 12 weeks after the infection, 44% of the study group reported gastrointestinal symptoms at 12 weeks after discharge, of which 51 patients showed gastrointestinal symptoms after discharge and one had gastrointestinal sequelae that healed by 12 weeks of follow-up. The most common gastrointestinal sequelae found in the analyzed group were: loss of appetite (28 [24%]), nausea (21 [18%]), acid reflux (21 [18%]) and diarrhea (17 [15%]); abdominal distension (16 [14%] patients), belching (12 [10%] patients), vomiting (11 [9%]), abdominal pain (eight [7%]) and rectal bleeding [2%] [9].

None of the 65 patients without gastrointestinal sequelae at 12 weeks showed gastrointestinal symptoms at hospitalization or during hospitalization. Of the 52 patients with gastrointestinal sequelae after discharge, 15 (29%) had gastrointestinal symptoms at hospitalization and during hospitalization, 34 (65%) had symptoms during hospitalization, and three (6%) showed symptoms only after discharge. We can conclude that long-term digestive manifestations were found in patients who had such manifestations also during the acute infection [9].

Comparing general criteria such as age, sex, body mass index and incidence of comorbidities, in patients with gastrointestinal sequelae with those of patients

without gastrointestinal sequelae, similarities were found. For example, 44.2% patients with gastrointestinal sequelae were over 60 years old, 51.9% were men, 48.1% were women, 15.4% had hypertension, 7.7% had diabetes, 3.8% had cardiovascular diseases. Also 46.2% patients without gastrointestinal sequelae were over 60 years old, 58.5% were men, 41.5% were women, 30.8% had hypertension, 9.2% had diabetes and 6.2% had cardiovascular diseases. We can consider that the existence of a predisposing factor in the occurrence of gastrointestinal sequelae cannot be found [9].

Another observational study included a total of 2113 members, 112 hospitalized patients and 2001 non hospitalized patients (confirmed COVID-19, n=345; symptom-based COVID-19, n=882; and suspected COVID-19, n=774). In this study we can observe that even though fatigue and dyspnea were the two most prevalent symptoms, diarrhea (10%) was present at follow up, 12 weeks later [16].

The largest longitudinal cohort study of hospital survivors with COVID-19 published so far presents the health consequences within 12 months after symptom onset. It was found that most patients had a good recovery during follow-up. However, sequelae symptoms, lung diffusion impairment, and radiographic abnormalities persisted to 12 months in some patients, especially in patients who were critically ill. In this study we can observe that 11 (1%) patients still presented diarrhea or vomiting even after 12 months, and 22 patients (2%) visited the outpatient clinic for gastrointestinal symptoms before the 12 months follow-up. As for the outcome, 88% patients had returned to their original work and most of these patients (76%) had returned to their level of work before COVID-19 [17].

In another train of thoughts, knowing that the ACE-2 receptor, the gateway to the cell for SARS-CoV-2 virus, is also expressed in liver cells and bile ducts, some studies have analyzed the enzymes that show liver injury 12 weeks after discharge. Therefore, blood tests showed that alanine aminotransferase was higher in patients with gastrointestinal sequelae suggesting the persistence of long-term liver damage. Liver damage in SARS-CoV-2 infection may be a direct expression of viral infection in the liver but may also be a consequence of the inflammatory response or drug injury due to antipyretic and antiviral medication used during treatment [18,19].

Another retrospective study analyzed the clinical, demographic, and laboratory parameters of recurrent cases of COVID-19 infection. Various concomitant diseases and significantly increased concentrations of liver enzymes suggesting hepatocytolysis (ALAT, ASAT) were observed in recurrent cases of COVID-19 compared to the control cases. The study data showed that elevated levels of ALAT and ASAT may predict the risk of recurrence of COVID-19 infection in the long term and may provide information about prevention and control of COVID-19 infection in the future [20].

In another study it has been described that direct viral damage to cholangiocytes and eventual chronic liver disease can occur. Three cases of a novel severe cholangiopathy arising after more than 12 weeks in recovery from critical COVID-19 with potential for long-term hepatic morbidity were described. Each patient developed marked cholestasis with associated jaundice that persisted long after cardiopulmonary and renal recovery. Laboratory analyses for acute or chronic viral infections and autoimmune serologies were negative and liver imaging showed no evidence of cirrhosis in any patient. Removal of biliary sludge or extraction of small extrahepatic duct stones were performed but did not resolve the jaundice. Percutaneous liver biopsies were performed, and all 3 biopsies exhibited predominant cholangiocyte injury with accompanying microvascular changes. The authors consider that these cases constitute a novel cholangiopathy arising as a long-term hepatic morbidity after critical COVID-19 infection [21].

On the same note, a case of fulminant post-COVID-19 cholangiopathy in a 47-year-old man who recovered from acute respiratory distress syndrome from COVID-19 developed end-stage liver disease from post-COVID-19 cholangiopathy. On day 58 from his initial presentation, his laboratory blood tests included AST of 384 U/L, ALT of 175 U/L, alkaline phosphatase of 1644 U/L, and total bilirubin of 19.0 mg/dL. Initial abdominal ultrasound showed severe fatty liver and innumerable gallstones throughout the gallbladder without biliary dilation or gallbladder wall thickening. After 12 weeks from his initial presentation, the patient was hospitalized for hypotension during hemodialysis. Laboratory tests showed ALT of 130 U/L, AST of 491 U/L, alkaline phosphatase of 2730 U/L, and marked hyperbilirubinemia with total bilirubin of 19 mg/dL. Abdominal ultrasound showed cholelithiasis without evidence of acute cholecystitis, and magnetic resonance cholangiopancreatography demonstrated mild intrahepatic biliary ductal dilatation with multifocal strictures or beading without extrahepatic biliary dilatation. The patient underwent orthotopic liver transplantation (OLT) after being placed on the list for liver transplantation with a Model for End-Stage Liver Disease score of 37. After OLT the patient is doing well and has normal liver tests. In this matter it is important to consider that patients can develop post-COVID-19 cholangiopathy, which can progress to a fulminant course [22].

In another study about the organ impairment in low-risk individuals with post-COVID-19 we can observe that after a median of 141 days organ impairment was more common in post-COVID-19 than in healthy controls. Impairment was present in the liver in 28% (12% inflammation, 21% ectopic fat, 10% hepatomegaly), pancreas in 40% (15% inflammation, 38% ectopic fat) and other organs like the heart, lungs and spleen. Of the patients, 70% had impairment in at least one organ and 29% had multiorgan impairment, with overlap across

multiple organs. Impairment in the liver, with further organ impairment was reported in 63% of patients [23].

Alteration of the intestinal microbiome has been reported in other studies [24,25]. It is recognized the role of the intestinal microbiome both in maintaining health and in the occurrence of various pathologies such as: digestive (irritable bowel syndrome, inflammatory bowel disease, celiac disease), hepatic (non-alcoholic steatohepatitis), neuropsychiatric disorders, metabolic disorders (obesity, diabetes), autoimmune and last but not least, oncological disorders. In this regard, strong evidence has been provided about the fact that changes in the composition and function of the intestinal microbiome (dysbiosis) can cause changes in the immune response, intestinal permeability, digestive motility, thus inducing a long-term proinflammatory status.

Another aspect of the damage following COVID-19 infection is the risk of *Clostridium Difficile* colitis. *Clostridium difficile* colitis is one of the most common hospital-acquired infections. Significant risk factors associated with *Clostridium difficile* infection are: antibiotic exposure, old age, and hospitalization. Therapeutic recommendations include the administration of broad-spectrum antibiotics to all patients with bilateral pneumonia associated with SARS-CoV-2 but these antibiotics are strongly associated with *Clostridium difficile* infection [25]. A case of severe colitis caused by *Clostridium difficile* has been reported in one patient after completion of treatment for acute viral infection. For this case, an emergency pancolectomy was necessary due to the poor response to conservative treatment. Subsequent developments were slowly favourable until recovery. Even though this case is considered to be part of the phase 1: acute post-COVID symptoms, it is important to be mentioned as an important digestive alteration in patients diagnosed and treated for COVID-19 that should alert clinicians [26].

Table I. Main gastrointestinal symptoms/alteration in Long-COVID.

SITE	SEQUELS
Digestive tract	<ul style="list-style-type: none"> • acid reflux • belching • gastritis • nausea • vomiting • diarrhea • abdominal distension • abdominal pain • rectal bleeding • alteration of the intestinal microbiome
Liver	<ul style="list-style-type: none"> • hepatocytolysis • cholangiopathy
Pancreas	<ul style="list-style-type: none"> • persistent inflammation

On another note, another negative impact of this pandemic, with long-term effects, is delaying endoscopy in patients with inflammatory bowel diseases. Endoscopy is useful not only to monitor the efficacy of therapy but also to screen for dysplasia and colorectal cancer. A prolonged period without endoscopy could have long-term implications for these patients such as increased risk of high-grade dysplasia, colorectal cancer, and early post-operative recurrence in patients with Crohn's disease after ileocolonic surgery. Despite the fact that all endoscopies can generate aerosol droplets and pose a risk of transmission of SARS-CoV-2, postponing the endoscopy can cause many long-term effects by missing various diagnoses [27].

Finally, most published studies to date on post-COVID symptoms have found that 50-70% of hospitalized patients have many post-COVID symptoms up to 3 months after discharge from hospital. The absence of evidence-based clinical practice guidelines for the management of long COVID-19 requires further studies.

Conclusions

Long-COVID is another major impact of the pandemic. Undoubtedly, the importance of chronic conditions, are underlined as risk factors for hospitalization and mortality in COVID-19 infection, but their presence has not been confirmed as a risk factor for long-term digestive symptoms.

It is currently known that COVID-19 can affect any part of the digestive system. The most common digestive symptoms in Long-COVID are: diarrhea, nausea, vomiting, abdominal pain, along with increased liver enzymes.

Long-term sequelae of the digestive system in COVID-19 infection should be further explored in future related studies.

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