INTRODUCTION

The coronavirus disease 2019 (COVID-19) initially described at the beginning of December 2019 in Wuhan, Hubei Province of China, has spread all over the world. As of September 28, 2020, the World Health Organization reported more than 32 million cases and 995 thousands deaths from 235 countries related to this pandemic. The clinical course of SARS-CoV-2 infection can span a wide range from asymptomatic to a rapidly progressing and life-threatening disease, most commonly associated with a variety of symptoms, such as fever, cough, dyspnea, pneumonia, acute respiratory distress syndrome, systemic inflammatory response syndrome, and multiple...
organ failure. Like many other coronaviruses, SARS-CoV-2 infects the gastrointestinal tract. Accordingly, in COVID-19 patients, beside respiratory manifestations, some patients complain of symptoms originating from the gastrointestinal tract, including nausea, vomiting, abdominal pain, and diarrhea. Although the preferential route of infection of SARS-CoV-2 is through exhaled droplets, increasing evidence suggests that SARS-CoV-2 may be also transmitted by a fecal-oral route. Taken together, this evidence provides a rational basis for interpreting the common occurrence of gastrointestinal symptoms reported by COVID-19 infected patients. We aimed at summarizing the current evidence on the pathophysiology of gastrointestinal SARS-CoV-2 infection, fecal-oral route of virus transmission, the involvement of the enteric nervous system, clinical manifestations, treatments, and outcomes of patients with COVID-19.

2 | SARS-COV-2 AND THE GASTROINTESTINAL TRACT

2.1 | Gastrointestinal life cycle

SARS-CoV-2 is a novel single-stranded β-coronavirus, the seventh coronavirus so far described infecting humans, with a genome similarity up to 80% to other highly infective coronaviruses like those of the acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 interacts with the host through its envelope spike glycoprotein which binds the ACE2 receptor of the host (Figure 1A). The spike glycoprotein is composed of two subunits, namely S1 and S2, which favor, respectively, the binding of the virus to the cells and the fusion between the two cellular membranes. This process is independent from the activity of the ACE enzyme since SARS-CoV-2 shows a high binding affinity to ACE2 receptors, reported to be comparable to that of SARS-CoV. After viral binding to ACE2 receptors, the transmembrane protease serine (TMPRSS)2 mediates the cleavage of spike glycoprotein, regulating the virus internalization into the host cell. After internalization, the virus starts its replication using the cellular replication processes, which ends with new viral assemblies, viral secretion, and release of cytokine which contribute to symptom generation.

ACE2 receptors have been reported to be highly expressed in several organs of the human body beyond the lungs, such as endothelial cells, renal tubular epithelium, testes, kidneys, brain, heart, and liver. However, the highest expression of ACE2 in the human body occurs in the brush border of intestinal enterocytes. ACE2 receptors and TMPRSS2 are abundantly expressed in gastric and intestinal epithelial cells and on the cilia of glandular epithelial cells, but not in esophageal squamous epithelial cells. In addition, it appeared that SARS-CoV-2 was not able to infect goblet cells across culture conditions. In other seminal experiments, human or bat intestinal tissues exposed to nasopharyngeal secretions obtained from COVID-19 patients were associated with rapid virus replication and a cytopathic response. Viral nucleocapsid proteins have been detected in the cytoplasm of gastric, duodenal, and rectal cells, but not in esophageal cells from a COVID-19–infected patient with SARS-CoV-2 fecal shedding. The affinity of SARS-CoV-2 for the gastrointestinal tract is highlighted by the fact that between 10% and 20% of COVID-19 patients experience diarrhea as their first symptom before the onset of respiratory symptoms. Furthermore, in a series of COVID-19 patients from the United States, 48 out of 206 patients presented digestive symptoms alone without signs of systemic or respiratory involvement. Taken together, these results support the hypothesis that SARS-CoV-2 can infect and damage human gastrointestinal epithelial cells in vivo and that the gastrointestinal tract could be the primary site of SARS-CoV-2 infection in a subset of patients.

2.2 | Fecal-oral route of transmission

COVID-19 is an infection with a predominant airborne route of transmission through salivary droplets. Nonetheless, the possibility that SARS-CoV-2 could be transmitted via a fecal-oral route was hypothesized early on after the description of the first cases of COVID-19 reported in visitors of the Seafood Market in Wuhan. Accordingly, it was hypothesized that SARS-CoV-2 gained access via the gastrointestinal tract and subsequently infected the organism following the consumption of meat of illegally traded bats and pangolins. In enterocyte organoids infected with SARS-CoV-2, the virus was primarily secreted apically. If the same occurs in vivo, the virus could be excreted in the lumen of the intestine and eliminated with the feces. In support of the fecal-oral route of transmission of SARS-CoV-2 and in line with the abovementioned gastrointestinal involvement in COVID-19, viral RNA was found in the stool of up to 50% of patients with at
concentrations ranging from $10^3$ to $10^5$ copies/mL, up to 12 days from the initial assessment and even after nasopharyngeal swab became negative.\textsuperscript{16} Several other reports described the detection of SARS-CoV-2 RNA in stool samples.\textsuperscript{22,24} A comprehensive meta-analysis\textsuperscript{25} included 95 studies and 2149 patients. The authors\textsuperscript{25} found that 934 patients (43\%) had one or more SARS-CoV-2-positive sampling sites (stool or anal swab). Although viral RNA was detected in a mean of 25 days after symptom onset, patients may show fecal shedding up to 70 days after symptom onset,\textsuperscript{26} even after viral clearance from the respiratory tract\textsuperscript{16} and respiratory symptoms disappearance.\textsuperscript{27}

Taken together, this evidence suggests that a fecal-oral route of viral transmission is plausible; however, there are still some concerns. First, the detection of SARS-CoV-2 in the feces is based on RT-PCR techniques that may not be able to distinguish between viral fragments and a viable replicating virus. Indeed, while SARS-CoV-2 virus with infective potential was isolated from lungs or throat of COVID-19 patients, in the feces they were either not found\textsuperscript{28} or isolated only in a small proportion of patients (35\%).\textsuperscript{25} Second, even if SARS-CoV-2 RNA has been detected in gastrointestinal specimens from most patients with digestive symptoms, this association was not statistically significant.\textsuperscript{25}

2.3 | The enteric nervous system as a potential entry route of SARS-CoV-2

Growing evidence indicates that SARS-CoV-2 infection is associated with neurological symptoms in a subgroup of patients with COVID-19 and that neurological involvement can aggravate the course of the disease.\textsuperscript{29,30} In both animal studies and in patients with neurological symptoms, coronaviruses show the ability to penetrate the cerebrospinal fluid\textsuperscript{31} and damage the structure and function of the nervous system.\textsuperscript{32} The mechanisms through which SARS-CoV2 enters the central nervous system remain unknown.\textsuperscript{33} The most plausible route of invasion is through the blood-brain barrier.\textsuperscript{31} Alternatively, it has been suggested that coronaviruses can migrate to the brain through sensory or motor nerve endings, achieving retrograde or anterograde neuronal transport through dynein and kinesin motor proteins.\textsuperscript{34} Recently, Esposito et al\textsuperscript{35} suggested that the enteric nervous system (ENS) could act as an entry route of SARS-CoV2 to the brain and the virus would gain access to the brain via vagal and/or splanchnic nerves. A comparable mechanism of neurogenic transmission to the CNS was previously shown for herpes\textsuperscript{36} and influenza viruses.\textsuperscript{37} Previous reports showed that gastrointestinal inoculation of MERS-CoV in mice, another β-coronavirus sharing
similarity with SARS-CoV-2, was associated with brain infection. A recent histochemical study on small and large intestinal specimens and choroid plexus, and adjacent brain parenchyma obtained post-mortem in COVID-19 patients, supports the anatomical plausibility for SARS-CoV-2 neuro-invasion through the ENS. Indeed, ACE2 and TMPRSS2 were abundantly expressed in the perikarya of enteric neurons and glial cells, both in the myenteric and submucous plexus. Enteric neurons showed different levels of ACE2 staining intensity, suggesting a differential expression between neuronal subtypes (Figure 2).

3 | PATHOGENESIS

3.1 | Epithelial cell damage

Intestinal mucosal biopsies obtained during endoscopy from one COVID-19 symptomatic patient revealed normal macroscopic findings, except for mild lymphocyte and plasma cell infiltration and interstitial edema. If confirmed in larger series, this evidence would suggest that SARS-CoV-2 infection is not associated with gross pathology detectable with routine diagnostic techniques.

**FIGURE 2** Panel 1: ACE2 expression in the human ENS of the large intestine. (A) Overview of the entire gut wall of a colon segment with immunofluorescence stainings for ACE2 (red), the glial marker S100b (green), and with the nuclear marker DAPI (blue). The white rectangles indicate the location of the high-power magnification micrographs below showing a representative submucous and myenteric ganglion. (B, C) Show representative submucous and myenteric ganglia stained for ACE2 (red), DAPI (blue), and the neuronal markers PGP9.5 (B, red) or HuC/D (C, red). The ACE2 staining can be found in neurons and glial cells and is considerably stronger in the colon compared to the small intestine. The overview is a standard epifluorescence image; details are maximum intensity projections of optical sections by structured illumination. Scale bars: overview 250 mm; details 50 mm. Panel 2: TMPRSS2 expression in the human ENS. (A) Overview of the entire gut wall of a colon segment with immunofluorescence stainings for TMPRSS2 (red), the neuronal marker HuC/D (green), and the nuclear marker DAPI (blue). (B, C) Show representative large intestinal myenteric ganglia stained for TMPRSS2 (red), DAPI (blue), and the neuronal markers HuC/D (B, red) or PGP9.5 (C, red). (D) Representative myenteric ganglion in the small intestine stained for TMPRSS2 (red), the glial marker S100b (green), and the nuclear marker DAPI (blue). Note that TMPRSS2 stainings were markedly stronger in enteric ganglia in the colon (A–C) than in the small intestine (D). The overview is a standard epifluorescence image; details are maximum intensity projections of optical sections by structured illumination. Scale bars: (A) 250 mm; (B–D) 50 mm. Figure adapted with permission from Deffner F et al. Front Neuroanat 2020; 14:596439; Copyright © 2020 Deffner, Scharf, Klingenstein, Klingenstein, Milazzo, Scherer, Wagner, Hirt, Mack and Neckel.
but may require more sophisticated assessment of tissue damage and dysfunction. A direct consequence of SARS-CoV-2 infection may be the reduction in the epithelial cell functional mass. In line with this, epithelial cell damage has been shown in both bat and human enteroids which developed progressive cytopathic effect after SARS-CoV-2 inoculation. In addition, Uzzan et al. assessed plasma concentrations of the amino acid citrulline, a surrogate marker of enterocyte mass and function. Compared to COVID-19 patients without gastrointestinal symptoms, those with symptoms (i.e., nausea, vomiting, and loss of appetite) had lower plasma citrulline levels and low plasma citrulline was inversely correlated with inflammatory markers, including C-reactive protein and ferritin.

### 3.2 Inflammation

SARS-CoV-2 infection is associated with innate and adaptive immune cell responses in the infected host. These include the release of interleukin (IL)-2, IL-7, tumor necrosis factor (TNF)-α, macrophage and monocyte products, such as granulocyte colony-stimulating factor, interferon (IFN)-γ-inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1-α. In the intestinal tract, this may lead to tissue inflammation, malabsorption, and diarrhea (Figure 1). To date, there are limited data on gastrointestinal inflammation in COVID-19 patients. However, cytokine production at this level is plausible since SARS-CoV-2 infection of enterocyte organoids engages a strong IFN response along with a milder induction of IP-10/CXCL10 and other cytokine genes. In addition, the finding of increased fecal calprotectin levels in COVID-19 patients provides indirect evidence of gut inflammation. Effenerger et al. reported higher concentrations of fecal calprotectin in patients with diarrhea compared to those with previous diarrhea or without this manifestation. Interestingly, fecal calprotectin concentrations significantly correlated with serum interleukin 6, suggesting that gastrointestinal involvement in SARS-CoV-2 may contribute to systemic inflammation. However, the same authors found that gastrointestinal inflammation did not correlate with SARS-CoV-2 RNA stool shedding, thus weakening the hypothesis of direct cause-effect mechanism.

### 3.3 Enteric nervous system dysfunction

Evidence is accumulating to support the biological plausibility for a direct or indirect involvement of the ENS in SARS-CoV-2 infection. Indeed, coronaviruses have a strong neuro-invasive potential as shown in previous studies after the outbreak of SARS-CoV-1. These studies showed that viral particles could be detected in the brain, where they were located almost exclusively in neurons. It has been suggested that SARS-CoV-2 infection of the central nervous system could occur via neuronal, pericellular, hematogenous, lymphatic, and Trojan routes (infecting migrating leukocytes). Studies in human brain organoids showed that SARS-CoV-2 infects neuronal cells within 2 days of exposure. In addition, SARS-CoV-2 exposure altered the distribution of tau from axons to soma, hyperphosphorylation, and apparent neuronal death. Given the ability of SARS-CoV-2 to infect the gastrointestinal tract, the abundant neural network supplying the alimentary canal, and the fact that both ACE2 and TMPRSS2 are abundantly expressed in the enteric nerves (Figure 2), the possibility of a ENS neuro-invasion, dysfunction, and damage should be of great concern.

In addition to a putative direct effect of the virus on enteric nerves, inflammatory and immune activation in the intestine may cause alterations in the ENS, enteroglial cells, and intestinal smooth muscle which may be involved in symptom generation. Concerning nausea, vomiting, and loss of appetite, several other hypotheses beyond the damage and inflammation of the gastrointestinal tract have been postulated such as the presence of the virus in the dorsal vagal complex and in the area postrema which may elicit symptoms at early stages of the infection. The activation of ENS reflexes and secretomotor responses may be viewed as a defense mechanism to expel the pathogen. However, like in many other gastrointestinal infections, the price to be paid for this is represented by symptom development and eventually long-lasting derangements of gut sensory-motor functions in susceptible individuals.

### 3.4 ACE2 receptors

In addition to the well-known activity of ACE2 in the renin-angiotensin system (RAS), this enzyme is also involved in the regulation of intestinal amino acid homeostasis and the expression of antimicrobial peptides which may contribute to the regulation of gut microbiota. The dietary amino acid tryptophan is able to modulate ACE2 function. In laboratory animals, anorexia and malnutrition and reduction in tryptophan intake correlated to ACE2 dysfunction leading to altered expression of gut antimicrobial peptides, followed by gut dysbiosis and intestinal inflammation. Accordingly, ACE2 knockout mice display increased susceptibility to intestinal inflammation induced by epithelial cell damage. As ACE2 receptor downregulation has been reported in previous SARS coronavirus-induced lung injury, ACE2 dysfunction has been postulated to participate to the development of COVID-19–related gastrointestinal symptom generation.

### 3.5 Altered gut microbiota

SARS-CoV-2 has been shown to be associated with an altered microbial community which in turn could participate in the COVID-19 systemic inflammatory response and cytokine storm. Moreover, ACE2 downregulation by SARS-CoV-2 may produce...
itself changes in gut microbiota since this receptor normally acts as regulator of immunity. Previous data in patients with influenza showed changes in gut microbiota, which in turn reduced host immune response leading to greater lung damage. Changes in gut microbiota composition and the potential benefit of microbiota modulation in COVID-19 have been recently investigated. An early report from Hong Kong compared the fecal microbiota of 15 patients with COVID-19 with that of 6 patients with community-acquired pneumonia and 15 healthy individuals. The results showed enrichment of opportunistic pathogens in COVID-19 (ie, Clostridium hathewayi, Actinomyces viscosus, and Bacteroides nordii) along with depletion in commensals (ie, Eubacterium, Faecalibacterium prausnitzii, Roseburia, and Lachnospiraceae taxa). A subsequent study evaluated gut microbiota composition of patients with active replication of SARS-CoV-2. Fecal samples associated with signatures of high SARS-CoV-2 infectivity showed enrichment of Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis, and Morganella morganii, which have been previously linked to opportunistic infections. A further study investigating gut microbiota of COVID-19 patients found an enrichment in Streptococcus, Rothia, Veillonella, Actinomyces, and Erysipelatoclostridium, and all these genera, except the latter, were correlated with C-reactive protein and D-dimer levels suggesting a possible correlation between changes in fecal microbiota and systemic inflammation. Although all these studies suffer from small sample size and lack of appropriate control groups, taken together, these results suggest the presence of an altered gut microbial community in patients with SARS-CoV-2 infection susceptibility and its association with gastrointestinal and systemic inflammation in COVID-19.

3.6 | Liver injury

A possible pathogenic mechanism explaining hepatobiliary manifestations is represented by the entrance of the virus into the hepatocyte mediated by ACE2 receptor, which is expressed in the liver, causing SARS-CoV-2-mediated immunologic injury. Indeed, a number of other mechanisms have been called into question, namely hypoxic injury as a consequence of respiratory failure, the systemic inflammatory response (ie, cytokine storm), the exacerbation of a pre-existent liver disease, and the injury caused by the drugs used for treating the infection and its manifestations (eg, antiviral therapies, antibiotics, monoclonal antibodies, acetaminophen). Some insights into the mechanisms leading to liver damage derive from studies focusing on post-mortem histopathological alterations of the liver. More in depth, liver findings were described in a series of 40 autopsy cases from the United States. Histologically, macro-vesicular steatosis, mild acute hepatitis, and minimal-to-mild portal inflammation were the most common findings. Viral PCR was detected in 11/20 (50%) patients, even if at very low levels in most cases, and its presence was not associated with ALT levels. Taking all these data together, viral-mediated injury seems to be the most plausible mechanism of liver damage.

4 | CLINICAL FEATURES

4.1 | Common gastrointestinal manifestations

Beside the respiratory and systemic manifestation of COVID-19, such as fever, dyspnea, cough, pneumonia, fatigue, headache, rhinorrhea, anosmia, and dysgeusia, symptoms involving the gastrointestinal tract have been also widely described (Figure 3). Among these symptoms, diarrhea is the most commonly reported, however with a wide prevalence according the published literature ranging from 3% to 96%. Dysgeusia has also been frequently described as an early and sometimes unique symptom of COVID-19 with a prevalence ranging from 71% to 88.8%. A recent meta-analysis including 78 studies with 12797 patients assessing the occurrence of gastrointestinal symptoms in COVID-19 patients concluded that digestive symptoms are seen in up to 1 in 5 infected patients. Among digestive symptoms, the weighted pooled prevalence of diarrhea was 12.4% (95% confidence interval (CI), 8.2% to 17.1%), nausea and/or vomiting 9.0% (95% CI, 5.5% to 12.9%), anorexia 22.3% (95% CI, 11.2% to 34.6%), and abdominal pain 6.2% (95% CI, 2.6% to 10.3%). However, these data need further validation due to high data heterogeneity, diverse study designs, methodology pitfalls, such as the absence of use of validated questionnaires or definitions for symptoms assessment, lack of controls and the lack of evaluation of previous gastrointestinal chronic disease or the influence of concomitant therapies with potential adverse events on the gastrointestinal tract. A previous metaanalysis that adjusted the results for pre-existing gastrointestinal conditions, showed, as expected, a lower rate of digestive symptom occurrence. The adjusted reported pooled prevalence was 8.7% (95% CI, 5.4% to 13.9%) for diarrhea, 8.0% (95% CI, 3.0% to 19.8%) for anorexia, and 5.1% (95% CI, 2.3% to 11.0%) for nausea. Several metanlyses have reported a higher prevalence of gastrointestinal symptoms in severe vs. mild cases of COVID-19 that is, anorexia 31.4% vs. 14.9%, diarrhea 11.1% vs 5.5%, vomiting 5.1% vs 2.5%, and abdominal pain 8.1% vs 1.8%, suggesting that digestive symptoms severity and frequency raise in parallel with advanced stages of the disease.

4.2 | Uncommon gastrointestinal manifestations

Several case reports described a wide range of less frequent gastrointestinal manifestations. Among these, gastrointestinal bleeding has been described in several papers. Little is known on the potential mechanisms involved. These may include inflammation-induced coagulopathy and thrombo-inflammation and a direct damage of the virus on the gastrointestinal mucosa. However, since bleeding occurred mainly during hospitalization a multifactorial etiology has been postulated. A rather high prevalence of peptic ulcer disease complicated by bleeding was noticed in patients with a moderate-to-severe acute respiratory distress syndrome caused by COVID-19. Notably, most patients admitted to hospital were given thromboprophylaxis, which may represent an additional risk
factor for bleeding. COVID-19–induced coagulopathy associated with increased D-dimer and fibrinogen levels may predispose to a high risk of micro- and macro-circulatory thrombosis which may explain the occurrence of another complication, namely ischemic colitis.85 It has been hypothesized that COVID-19–associated immune activation in the gastrointestinal tract may lead to Peyer’s patch hypertrophy and mesenteric lymphadenopathy, which can act as a primary point for intussusception, an event reported in case series of COVID-19 patients.86 Finally, disorders of gastrointestinal motor function up to severe motility derangement and pseudo-obstruction have been reported in the critically-ill COVID-19 patient with high degree of systemic and intestinal inflammation.87

4.3 | Inflammatory bowel disease

Theoretically, patients with inflammatory bowel disease (IBD) may be more susceptible to SARS-CoV-2 infection due to the chronic intestinal inflammatory state and the use of immunosuppressant agents.88 Previous reports showed that compared to controls, patients with IBD showed a sustained higher ACE2 expression in the mucosa of the ileum and colon and higher soluble circulating levels of ACE2, independently of the presence of inflammation,55,89 possibly related to higher expression of IFN-γ which promotes ACE2 expression. Moreover, trypsin-like proteases, which are responsible of S protein cleavage and SARS-CoV-2 internalization, have been reported to be upregulated in IBD patients.90 However, to date there is no evidence supporting an increased susceptibility to SARS-CoV-2 infection due to ACE2 and TMPRSS2 upregulation.88 According to another hypothesis IBD patients could be protected from the infection due to higher levels of circulating ACE2 soluble receptors which bind SARS-CoV-2, thus competing with cell bindings and preventing or limiting the infection.91,92 A large multicentric Western collaborative study reported a cumulative incidence of SARS-CoV-2 infection in patients with IBD of 0.4% (97 out of 23879), comparable to that of the general population (0.4%),93 thus excluding an increased or reduced risk of COVID-19 for these patients. The authors93 also found that corticosteroids increased the risk of hospitalization [odds ratio (OR) 7.6], whereas monoclonal antibodies therapy reduced the risk of pneumonia and hospitalization (OR 0.1 and 0.3, respectively). Taken together, these data suggest that the risk of SARS-CoV-2 infection of patients with IBD seems comparable to that of the general population.

4.4 | Celiac disease

Celiac disease, an autoimmune gluten-related intestinal disease, is associated with increased risk of infections, including influenza94 and pneumonia.95 Based on this evidence, it could be speculated that celiac disease is associated with increased risk of COVID-19. A
recent a cross-sectional large-scale study showed that COVID-19 patients do not have a significant difference in the odds of having a positive test for SARS-CoV-2 as compared with control subjects (9.4% vs. 8.1%; OR 1.18; 95% CI, 0.75–1.84). Furthermore, no differences in the odds of COVID-19 were found in patients with or without histological confirmation of celiac disease, symptomatic or without symptoms, and adopting or not adopting gluten-free diet.96 Similar results were obtained from a recent real-life study of a cohort of celiac disease patients during the SARS-CoV-2 outbreak in Italy.97 All together, these data suggest that subjects with celiac disease are not associated with an increased risk of COVID-19; however, longitudinal prospective studies are needed to better understand whether the risk of contracting COVID-19 changes over time and additional precautions to prevent virus exposure are necessary in these subjects.

Hepatic manifestations

Liver impairment in patients with COVID-19, defined by the alteration of blood liver enzymes, is a common finding, and it has been reported since the description of the first case series from China.98 Liver test abnormalities (ie, altered transaminases and/or bilirubin) were found to be common in most reports, ranging from 16% to 53% of the series.1,20,74,98,99 In most cases, transaminases were more commonly increased in patients with severe COVID-19, especially those requiring admission to the intensive care unit.1 Also, severe liver alteration was uncommon, and transaminase alterations were not necessarily associated with a worse outcome.99 Later, a systematic review and meta-analysis reported all published data from Asian populations until April 4, including a total of 1948 individuals.100 The pooled prevalence of liver injury was 12%
(18% when considering altered alanine aminotransferase [ALT]), while that of liver comorbidities was 3%. Also, patients displaying gastrointestinal symptoms were more likely to have liver injury, and this corroborates the possible spread of the virus from the gastrointestinal tract to the portal vein, until the liver. Finally, liver injury was more likely to occur in patients with severe COVID-19, as previously hypothesized. Later, more data regarding liver injury emerged (Table 1). According to another retrospective series of 2273 patients who tested positive for SARS-CoV-2, transaminase alterations were common, but mild in most of the cases. In a multivariable analysis, severe acute liver injury was significantly associated with increased blood inflammatory markers (ferritin and interleukin 6). Also, patients with severe liver injury showed higher rates of intensive care unit admission, acute kidney injury, and mortality.

### 4.5.1 COVID-19 and pre-existing liver disease

Data regarding the outcome of COVID-19 in patients with a pre-existing liver disease are still scant. In the largest studies from the United States focusing on this issue, 250/2780 patients (9%) with COVID-19 were affected by a liver disease, and liver cirrhosis was reported in 50 patients. The most commonly reported liver diseases were fatty liver disease and non-alcoholic steatohepatitis. After propensity matching, the risk of death was increased (risk ratio 3.0) compared to patients with no known liver disease, as well as the risk of hospitalization. Given the observational nature of the study, the possible causes of this finding were not further investigated.

### 4.5.2 COVID-19 in liver transplant patients

The magnitude of the impact of COVID-19 in patients with a transplanted liver is yet to be clearly defined. According to a series from an Italian liver transplant center, three out of 111 transplanted patients died from severe COVID-19. All of them were elderly male patients on immunosuppressants seem to have developed a milder course. In these patients, acute kidney injury was also noticed in more than half of the cases, and it might have represented the most important contributor of the unfavorable outcome. Upon admission, liver function tests were within the limit of normal in most cases. Unlike the study by Bhoori et al., Lee et al. are cautious regarding the continuation of immunosuppressants. To conclude, liver function test alterations are very common, and usually mild, in patients with COVID-19. A pre-existent liver disease may predispose to worse outcomes.

### 4.6 Biliary and pancreatic manifestations

Several reports identified the presence of acute acalculous cholecystitis in COVID-19 patients. Unlike the study by Bhoori et al., Lee et al. are cautious regarding the continuation of immunosuppressants. To conclude, liver function test alterations are very common, and usually mild, in patients with COVID-19. A pre-existent liver disease may predispose to worse outcomes.

### 5 DIAGNOSIS

In patients with COVID-19 and gastrointestinal symptoms, careful history should be taken in order to assess whether symptoms developed with COVID infection or were pre-existent. In patients presenting to the clinician with acute onset of gastrointestinal symptoms, particularly diarrhea, information regarding high-risk contact exposure and the presence of other symptoms should be investigated. The onset of gastrointestinal symptoms should be carefully assessed as they may precede respiratory symptoms of a few days. In clinical settings with limited resources, patients with both respiratory and gastrointestinal symptoms should be prioritized for SARS-CoV-2 testing.

No strong evidence is available for supporting routine stool testing for SARS-CoV-2. Commonly used laboratory tests for the management of COVID-19 patients are reported in Table 2. A recent metanalysis including 60 studies showed that SARS-CoV-2 RNA was detected in stool samples from 48.1% patients and, more importantly, viral RNA was found also in stool collected after respiratory samples turned negative. Only 1% had gastrointestinal positivity alone (ie, rectal swabs or fecal assays) in the absence of a positive test from other sites (sputum and oral, nasopharyngeal, or throat swab). These findings suggest that only in rare cases with...
negative nasopharyngeal swabs, would stool and rectal swab testing be of value, particularly in patients with gastrointestinal symptoms, increasing the possibility of obtaining a diagnosis of SARS-CoV-2 infection. Moreover, fecal or rectal testing may be helpful for monitoring the infection and the viral shedding since 49 out of 54 studies (91%) with serial RNA evaluations, reported persistent positivity for SARS-CoV-2 RNA after respiratory testing turned negative, with a mean time of delayed positivity of 12.5 days. However, further validation studies are needed before these tests are included in the clinical algorithm of COVID-19. In addition, although SARS-CoV-2 RNA can be detected in biopsy samples from the esophagus, stomach, duodenum, and rectum taken during endoscopy, to date, there is no indication for invasive assessments in COVID-19 patients complaining of gastrointestinal symptoms.

### 5.1 Liver and pancreatic testing

Despite the absence of established guidelines, there seems to be enough evidence to support monitoring of liver function through serum blood markers. In particular, we would suggest testing, in all hospitalized patients, transaminases, total and fractionated bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase, coagulation, and serum albumin. In those patients showing alterations at baseline, or with a worsening clinical picture, additional testing during hospital stay could be useful as a prognostic marker. The role of diagnostic imaging in this setting has not yet been established, as well as the potential role of a liver biopsy. Pancreatic enzymes (ie, amylase, lipase) should only be tested in case of suspicious of acute pancreatitis.

### Table 2: Non-invasive commonly used biomarkers for gastrointestinal, liver and pancreatic COVID-19 involvement evaluation

| Sample | Parameter | Variation | Meaning |
|--------|-----------|-----------|---------|
| Sputum | SARS-CoV-2 RNA | + | COVID-19 diagnosis Positive rate higher than throat swabs (from 28.6% to 72%) |
| Blood | Blood count and coagulation | | |
| Neutrophils | ↑ | Associated with diarrhea and deaths |
| Lymphocyte | ↑ | Associated with diarrhea and deaths |
| Hemoglobin | ↓ | GI bleeding |
| D-dimer | ↑ | Associated with ischemic colitis |
| Inflammatory markers | | |
| C-reactive protein | ↑ | Associated with GI symptoms |
| Interleukin-6 | ↑ | Associated with diarrhea and death Correlation with fecal calprotectin |
| Interleukin-10 | ↑ | Associated with diarrhea and death |
| Tumor necrosis factor-α | ↑ | Associated with diarrhea and death |
| Ferritin | ↑ | Associated with severe clinical course and thrombotic complications |
| Interferon-γ | ↑ | Stimulate the production of inflammatory cytokines. Enhance hyper-inflammation and exacerbates the severity of the disease |
| Hepato-biliopancreatic tests | | |
| Alanine aminotransferase | ↑ | In 19% of patients, associated with severe clinical course |
| Aspartate aminotransferase | ↑ | In 32.7% of patients. Associated with liver injury, longer hospital stay, intensive care unit admission |
| Gamma-glutamyltransferase | ↑ | In 12.1% of patients, no association with poor outcomes or symptoms Case reports on acute pancreatitis |
| Alkaline Phosphatase | ↑ | Associated with severe clinical course |
| Lactate dehydrogenase | ↑ | Associated with GI symptoms and severe/critical clinical course |
| Bilirubin | ↑ | Associated with severe clinical course |
| Albumin | ↓ | Associated with GI symptoms |
| Lipase | ↑ | Associated with systemic inflammation and GI symptoms |
| Glucose | ↑ | Associated with severe/critical clinical course |
| Intestinal cells integrity tests | | |
| Citrulline | ↓ | Associated with systemic inflammation and GI symptoms |
| Feces | SARS-CoV-2 RNA | + | From 29% to 58.1% of patients; pooled results: 43.7% |
| Fecal calprotectin | ↑ | Associated with diarrhea |
| Fecal occult blood | + | In 38% of patients with GI symptoms |
6 | OUTCOME AND PROGNOSIS

6.1 | Association of symptoms with severity and mortality

Since gastrointestinal symptoms mainly occur before respiratory and systemic involvement,124,125 several authors evaluated whether digestive symptoms occurrence represents an unfavorable prognostic factor.76,100,124 In a pivotal metaanalysis on 4 studies, Gul et al127 concluded that COVID-19 patients with gastrointestinal symptoms had a higher risk of acute respiratory distress syndrome, but not mortality.127 Accordingly, pooled data from various studies confirmed that COVID-19 mortality in patients with gastrointestinal symptoms was comparable to the overall COVID-19 mortality, accounting for 0.4% (95% CI, 0% to 1.1%).76,100,126 On the other hand, the occurrence of gastrointestinal symptoms may be useful in predicting nasopharyngeal swab positivity (OR 1.7).73

7 | SHOULD WE EXPECT A WAVE OF POST–SARS-COV-2 FUNCTIONAL GASTROINTESTINAL DISORDERS?

Acute infection gastroenteritis of bacterial, protozoan, and viral nature is currently the strongest known risk factor for the development of irritable bowel syndrome (IBS) and functional dyspepsia.54 A systematic review and meta-analysis showed that >10% of patients with infectious enteritis develop IBS.128 A recent large community survey suggests that viral gastroenteritis could be one of the most frequent form of post-infection IBS.129 Risk factors for post-infection functional syndromes included female gender, severe enteritis, the presence of psychological distress, and the use of antibiotics during the infection.128

Given the ability of SARS-CoV-2 to infect the gastrointestinal tract, leading to tissue damage and inflammation, and based on the large use of antibiotics in COVID-19 patients, it seems reasonable to speculate that this combination would lead to a wave of post-COVID-19 functional gastrointestinal disorders, including IBS.130 Other factors support this hypothesis: first, COVID-19 course has a median length of about 12 days,131 thus hypothetically conferring more than a 10-fold increase in the risk of post-infectious IBS.132 Second, COVID-19 is associated with psychological impairment, including anxiety and depression,133 which may contribute to the development of functional gastrointestinal disorders.

Putative pathophysiological mechanisms underlying long-term gut dysfunction and symptom generation after SARS-CoV-2 infection of the gastrointestinal tract may include the persistence of gut dysbiosis seen in post–COVID-19 (see above) which, in turn, could contribute to maintain a chronic state of intestinal low-grade inflammation, increased permeability, and bile acid malabsorption. In addition, SARS-CoV-2 infection is associated with T helper cell 17 and mast cell activation contributing to COVID-19–related cytokine storm,134 which resembles that observed in septic complications of intestinal bacterial translocation.135 Mast cell activation could be a direct effect of viral entrance into the cell as mast cells express ACE2 and TMPRSS2 required for SARS-CoV-2 life cycle.134 Previous studies demonstrated that mast cell infiltration and mediator release in proximity to mucosal innervation may contribute to abdominal pain perception in IBS patients.136,137 Although these data suggest that mast cells could play a role in gastrointestinal symptom development in COVID-19, further studies are now needed to confirm this hypothesis. Taken together, these data suggest that a sequence of events, including SARS-CoV-2 infection of epithelial cells, inflammatory cells, and enteric neurons may lead to long-lasting changes in gastrointestinal function, leading to symptom generation including nausea, vomiting, diarrhea, and abdominal pain in susceptible individuals.

8 | MANAGEMENT

To date, no specific drugs have been reported for the treatment of gastrointestinal symptoms in COVID-19 patients. However, since the pathophysiological mechanisms underlying digestive symptoms are similar to those reported for respiratory symptoms, it may be reasonable thinking about a beneficial effect of these drugs for the gastrointestinal tract. For example, several monoclonal antibodies inhibit ACE2 receptors, creating an interference for virus binding,138 whereas other molecules act on virus internalization mechanisms.7 On this line, it has been reported an amelioration of diarrhea after antiviral treatment.139 It is worth noticing that several drugs currently used for COVID-19 treatment may also cause gastrointestinal symptoms.122 Indeed, chloroquine, hydroxychloroquine, and lopinavir/ritonavir may induce nausea, vomiting, abdominal pain, and diarrhea in up to 30% of patients.140–142 Moreover, antibiotics and antivirals used for COVID-19 treatment may cause dysbiosis and diarrhea. The China National Health Commission has been among the first to recommend probiotics in severe COVID-19 patients to ameliorate gut microbial homeostasis, to prevent bacterial infections, and to likely obtain antiviral effect.143 Indeed, probiotics may favor the innate and adaptive immune response, interfere with virus lifecycle through the production of antiviral metabolites.144 Thus, symptomatic treatments for each gastrointestinal symptom may be advised,122 in addition to specific nutritional recommendations and micronutrients supplementation.145 No specific treatment for treating liver injury exists.122

9 | CONCLUSIONS AND FUTURE PERSPECTIVES

Although gastrointestinal manifestations represent a tangible and important phenotypic expression of SARS-CoV2 infection, several aspects still need to be clearly defined, including (1) a transmission via the fecal-oral route; (2) a contribution of gut microbiota to severity and progression of the disease; (3) the long-term
consequences of the infection on digestive functions; (4) the role of gastrointestinal symptoms as predictors of severity; and (5) efficacy of therapies directed to gastrointestinal and liver manifestations. Understanding the relative importance of each of these factors and their interactions is needed to better understand the complex pathophysiology and management of gastrointestinal symptoms in COVID-19.

CONFLICT OF INTERESTS
The authors have no competing interests.

AUTHOR CONTRIBUTIONS
GM, VS, ADS, and GB designed the review; GM, MVL, CC, MRB, and GB performed literature search and drafted the manuscript; and all authors critically revised and approved the final version of the manuscript.

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