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Stay (GI) Healthy: COVID-19 and Gastrointestinal Manifestations

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ABSTRACT

SARS-CoV-2 is the virus responsible for COVID-19, whose clinical spectrum ranges widely, both in terms of severity and multi-organicity. SARS-CoV-2 mainly involves the respiratory tract, causing from a flu-like syndrome to interstitial pneumonia and acute respiratory distress syndrome. Although its entry receptor, angiotensin-converting-enzyme 2, is typically expressed in epithelial cells of the airways, extra-pulmonary involvement has been consistently demonstrated since the beginning of the outbreak. Gastrointestinal manifestations in COVID-19 may be explained by the abundant expression of ACE2 in the digestive tract. Moreover, not only COVID-19 patients often present with GI symptoms (diarrhea, nausea/vomiting, abdominal pain) and liver tests abnormalities, but there are also data showing active viral replication in the GI tract and possible fecal-oral transmission. Aim of this review is to summarize the evidence regarding prevalence and clinical significance of GI involvement and liver abnormalities in patients with COVID-19, providing the reader with evidence-based recommendations on the management of these conditions.

Keywords: COVID-19; Liver injury; Gastrointestinal; Symptoms; Digestive; Hepatitis; Diarrhea.

Introduction

The coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which has infected more than 70 million people worldwide, is the cause of COVID-19 (coronavirus disease 2019), a condition including both asymptomatic or pauci-symptomatic forms and rapidly progressive deadly forms. SARS-CoV-2 is spread and transmitted mainly through direct or indirect droplets exposure, as the virus has marked tropism for the respiratory tract: its entry receptor, ACE2, is highly expressed in epithelial cells of the upper airways.[1] Pulmonary diseases caused by SARS-CoV-2 include both interstitial pneumonia and acute respiratory distress syndrome (ARDS), the leading cause of hospitalization, ICU admission, and death among infected patients.[2,3] It is now common knowledge that COVID-19 patients may also develop signs or symptoms of injury in other organs, which require prompt recognition and expert management.[4] These extra-pulmonary manifestations of COVID-19 maybe be explained both by the ubiquitous presence of ACE2 receptor, which is abundantly found in the gastrointestinal tract, liver and bile ducts, pancreas, kidney and vascular endothelial cells[5,6] (Figure 1). Specifically, the digestive system appears to be a sensitive target for SARS-CoV-2, with patients often reporting symptoms and signs of GI and liver involvement;[7,8] a role may also be played by in-hospital administration of antiviral medications whose efficacy and safety is still unclear. In this review we will analyze the currently available literature to assess the prevalence and clinical significance of GI involvement and liver tests abnormalities in patients with COVID-19, the possibility of active replication in the digestive system and fecal-oral transmission, with the aim of providing the reader with evidence-based recommendations on the management of these conditions.

COVID-19 and the gastrointestinal tract

Rationale for GI involvement in COVID-19

Coronaviruses are commonly responsible for upper respiratory and gastrointestinal infections in human and other mammals. SARS-CoV-2 share genetic similarities to previously studied coronaviruses, such as SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV), which belong to the genus Betacoronavirus in the family Coronaviridae.[9]

Thanks to past knowledge regarding the entry process of SARS-CoV into human cells, it has been demonstrated that SARS-CoV-2 shares the same cellular entry receptor, angiotensin-converting enzyme 2 (ACE2).[10,11] ACE2 in

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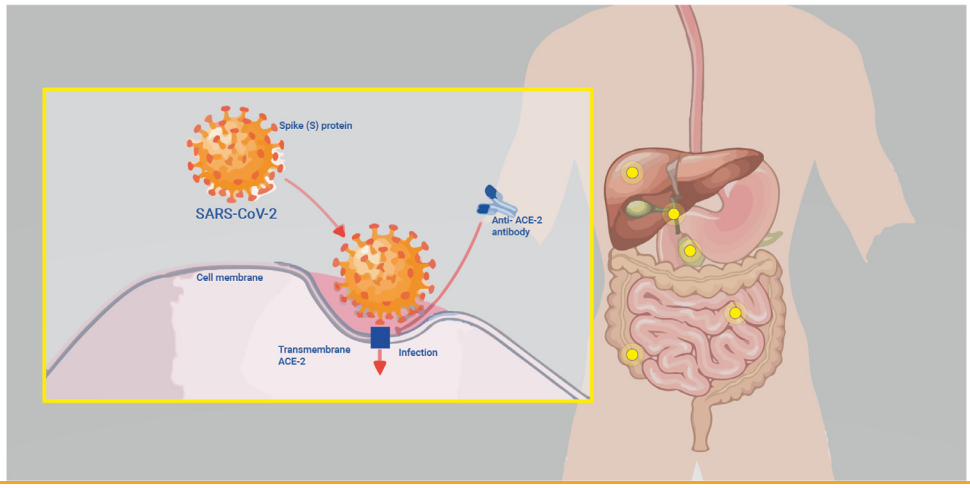

Figure 1. Gastrointestinal target organs for SARS-CoV-2.

lungs is mainly expressed in alveolar epithelial type II cells and ciliated cells, but it also expressed in digestive tract epithelial cells, especially in colonic enterocytes, where can be found with up to 100-fold higher concentration than in the respiratory tract.[5,6,12] The digestive system may therefore be considered as a plausible entry route of SARS-CoV-2 into the organism, as well as a target organ due to the high expression of viral receptors.

Besides the frequent reporting of GI symptoms in patients with COVID-19, the hypothesis of digestive involvement by SARS-CoV-2 was supported by several biological observations: a series of histopathological reports that showed viral presence directly in digestive tract cells, endoscopic abnormalities in patients with COVID-19 as well as the consistent finding of viral RNA in stool samples. In 2 different studies, gastrointestinal endoscopy has been performed in patients with COVID-19, with biopsy specimens obtained from esophagus, stomach, duodenum, and rectum: immunohistochemistry showed the presence of SARS-CoV-2 RNA and nucleocapsid proteins in epithelial glandular cells.[7,13] In a patient undergoing surgery for rectal adenocarcinoma with co-existing COVID-19, quantitative reverse-transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 RNA presence in the rectal surgical specimens obtained from resection and in the intestinal mucosa of ileostomy.[14] These findings have been recently corroborated by an experimental model based on human small intestinal organoids, where enterocyte infection by SARS-CoV-2 was demonstrated after performing confocal and electron microscopy.[15] Moreover, in a recent series of 38 COVID-19 patients undergoing upper and lower gastrointestinal endoscopy, abnormalities were found in most examinations: of note, in 25% of the cases endoscopic and histological signs of ischemic injury were reported.[16] Other reports confirmed ischemic bowel damage in COVID-19 patients.[17,18] Although these findings may be interpreted as thromboembolic complications due to the hypercoagulability status typical of COVID-19, diffuse endothelial inflammation in the submucosal vessels of the small bowel has been reported as well as mesenteric ischemia, supporting a direct role of SARS-CoV-2 in causing intestinal micro-vascular injury.[19]

Gastrointestinal symptoms: clinical spectrum and prevalence

Since the early phases of the pandemic, GI symptoms (mainly diarrhea, vomiting, nausea, loss of appetite, loss of taste, and abdominal pain), along with fever and respiratory symptoms (cough, dyspnea), have been increasingly reported as a distinctive feature of COVID-19 (Table 1).

The prevalence of GI symptoms at diagnosis varies across studies, ranging widely from 2% to 57%. In a meta-analysis of 35 studies from China, mainly carried out in the first phase of the outbreak (January to March 2020), clinical characteristics of 6686 COVID-19 patients have been analyzed, finding a pooled prevalence of GI symptoms of 15%. More specifically, the pooled prevalence of diarrhea was 9%, nausea/vomiting 7%, and abdominal pain 3%.[8] A limitation of this meta-analysis is that studies included were mostly carried out in the early phases of COVID-19 outbreak. Moreover, only Chinese patients were included in the analysis regarding prevalence of GI symptoms. Only few months ago little was known about extra-intestinal manifestations of the disease; furthermore, it is reasonable to think that electronic medical records (which most of the studies rely on) were rapidly filled out, mainly in emergency settings as most hospitals faced sudden increases in admissions. The hypothesis of an underlying bias is confirmed by an increasing trend

Table 1. Summary of GI manifestations in hospitalized COVID-19 patients.

GI manifestation	Prevalence
Diarrhea	9%-34%[8,20,21]
Nausea/vomiting	7%-16%[8,20,21]
Abdominal pain	3%-11%[8,20,21]
Abnormal LFTs	14.8%-53%[68]

showed in another meta-analysis that included more recent Western studies: estimated pooled prevalence of GI symptoms was nearly doubled (diarrhea 18.3%, nausea/vomiting 14.9%, abdominal pain 5.3%).[20] A recent multicentric series from US reported that a remarkable 53% of hospitalized patients experienced at least one GI symptom, although most of them (74%) were defined as mild:[21] specifically, diarrhea was reported in 34% of patients, vomiting in 16%, abdominal pain 11%. We can infer that the annotation of GI symptoms could initially be overlooked, as knowledge regarding the clinical spectrum of COVID-19 was still scarce, and the actual prevalence result underestimated in early studies as compared to higher rates reported in recent Western series. An increased susceptibility to develop GI symptoms in Western populations may also explain this finding and cannot be excluded, but further studies are needed to confirm this hypothesis.

Strikingly, GI symptoms may be the only clinical manifestation of COVID-19 or precede other symptoms: in a study of 1141 cases, 16% presented with GI symptoms as only chief complaint;[22] in another study analyzing 138 consecutive hospitalized patients, 14 (10%) patients presented with diarrhea and nausea 1-2 days before the development of fever and dyspnea.[23] In another large western multicentric series, GI symptoms preceded other COVID-19 symptoms in 13% of cases and started concurrently in 44%.[21] This aspect could have serious implications in terms of late recognition of COVID-19 patients who present with GI symptoms only, promoting further viral spread if no preventive measures are applied and delaying appropriate care.

Loss of taste has also emerged as a highly prevalent symptom in COVID-19 patients. According to 2 European multicentric studies, between 74% and 88% of patients with mild-to-moderate disease can report disturbances of taste throughout the disease course; together with smell disturbances, they can represent the first symptom in nearly one third of patients (29.2%).[24,25]

One may also wonder if GI symptoms are specific for COVID-19 or may be also found in negative controls. Answering this question is a case-control study, where characteristics of patients who presented to a tertiary care hospital and underwent nasopharyngeal swab for SARS-CoV-2 were compared, according to a positive (cases) or negative (controls) result. In this study, the prevalence of GI symptoms was high, with significantly higher figures in patients with a positive nasopharyngeal swab (74% vs 53%, $P < 0.001$).[26] Overestimation of GI symptoms may be explained by a recall bias, due to the telephonic survey methodology that was used to obtain clinical information.

Finally, it is not clear which GI symptom may be more specific of COVID-19: nausea and loss of appetite are sometimes only vaguely reported by patients and may also develop in other acute inflammatory or infectious conditions, as part of the cytokine-mediated systemic inflammatory response. According to the biological bases of gastrointestinal damage explained above, we hypothesize that diarrhea is the symptom that may better reflect the intestinal epithelial injury directly mediated by SARS-CoV-2; studies are needed to clarify this issue.

As regards features at GI endoscopy, only Massironi et al described endoscopic findings in a population of 38 hospitalized COVID-19 patients undergoing esophagogastroduodenoscopy and colonoscopy, mostly performed because of GI bleeding.[16] Abnormal findings were frequent (75% of esophagogastroduodenoscopy and 70% of colonoscopies) but heterogeneous: 5 patients were found having duodenal ulcers, 4 erosive gastritis and 2 gastric neoplasms, all of them likely to represent incidental findings, as well as the underlying cause of GI bleeding. More intriguing is the common report of ischemic, histologically confirmed, signs in the colon (20%), as it may represent an intestinal microvascular injury directly mediated by SARS-CoV-2, as explained above.

Gastrointestinal symptoms: the role of medications

Prevalence of GI symptoms changes between time of diagnosis and hospitalization: throughout COVID-19 convalescence, GI symptoms can be reported in up to 74% of patients.[27] It is reasonable to think that medications administered during hospital stay can interact with the digestive system: antibiotics, in particular, are a common cause of diarrhea in hospitalized patients and their use was shown to be independently associated with development of diarrhea in COVID-19 patients also.[13]

A role may also be played by antiviral treatments, which have been extensively administered early in the outbreak, although limited data existed regarding their efficacy and safety. Evidence has since then accumulated, especially from clinical trials, which provide an estimate of the related likelihood of causing GI symptoms. In a randomized trial of hydroxychloroquine in 150 patients with mild-to-moderate COVID-19, 16% of those who received antiviral treatment developed GI symptoms (whereas no patients in the standard of care group did); of note, diarrhea occurred in 10% of the cases, being the most frequent adverse event in the treatment group.[28] Even higher rates are reported in another randomized trial investigating the use of Lopinavir/Ritonavir in 199 patients: GI adverse events occurred in 30% of patients, compared to only 3.1% in the control group.[29] Opposite results have been shown in trials investigating the use of Remdesivir: in a randomized, placebo-controlled trial, prevalence of GI adverse events (diarrhea, nausea, vomiting) was relatively low and no significant difference was shown with the placebo-group (11% vs 9%).[30] Of note, the authors report a remarkable prevalence of constipation (14%), which did not differ between groups and whose development, however, is common in hospitalized patients. Two later RCTs of Remdesivir did not further report prevalence of GI symptoms among treatment-related adverse events.[31,32]

Impact of gastrointestinal symptoms on clinical outcome

It is still matter of debate if GI symptoms are associated with a different course of COVID-19, as studies have shown conflicting results. In an early study of 651 patients, 74 presented with GI symptoms and showed higher rates of severe course of disease, including need for mechanical ventilation, compared to those without GI symptoms (22.9% vs 8.1%).[33] Another series confirmed that among patients admitted to ICU the prevalence of GI symptoms was higher than in those who did not require intensive support.[23] In nonhospitalized COVID-19 patients, the presence of GI symptoms may predict clinical deterioration, being associated with higher risk of hospital admission.[34] Lastly, a meta-analysis of 3772 patients concluded that those with severe disease were significantly more likely to have GI symptoms (odds ratio 1.60, 95% confidence interval 1.09-2.36).[8]

On the other hand, in a retrospective study of 292 hospitalized patients, we showed that the presence of GI symptoms at diagnosis was a negative predictor of mortality or ICU-admission (adjusted hazard ratio 0.47; 95% confidence interval 0.23-0.97), thus suggesting that a milder disease course may be associated with the digestive involvement.[35] Supporting these findings are 2 recent studies from US, which did not show higher rates of clinical deterioration in patients presenting with GI symptoms.[26,36]

Consistent with the assumption that worse outcomes are not associated with GI involvement is the hypothesis that GI symptoms may instead portend a milder form of COVID-19, which may explain an indolent but longer disease course. Indeed, a significantly longer time from onset to admission in patients presenting with GI symptoms was showed in a multicentric Chinese study (9.0 days vs 7.3 days);[37] a recent US study also demonstrated a longer disease duration.[26]

An explanation for the differences shown between studies may be the heterogeneity of the examined populations: disease course in Chinese patients may be more severe than in Western cohorts; deeply varying median ages are also reported, which may determine differential clinical frailty between groups. Another explanation is the different timing of symptoms onset: some studies analyzed patients who developed symptoms during hospitalization and not only at admission, when biasing by possible in-hospital confounding factors may be less likely.[13]

Management of gastrointestinal symptoms

According to the available evidence, the clinician should consider COVID-19 as a differential diagnosis in patients who present with new-onset GI symptoms (Figure 1). Careful history regarding co-existing GI disorders should also be taken. Level of suspicion should be increased if GI symptoms are accompanied by other typical COVID-19 symptoms (fever, cough, dyspnea, sore throat, and new-onset loss of taste/smell); if such symptoms are not reported, careful monitoring is recommended as GI symptoms may precede their development by few days.[20]

Once COVID-19 diagnosis is made, other causes of GI symptoms should nevertheless be ruled out, according to patient profile: in a young patient complaining of fever, abdominal pain and diarrhea, a flare of IBD is a possible differential diagnosis;[38] in an elderly and comorbid patient, especially if antibiotic treatment has been recently administered, *Clostridioides difficile* may be a likely cause of diarrhea; adverse reactions to other concomitant medications should be checked carefully.

As to COVID-19 specific treatment, we mentioned that GI symptoms may be expression of drug toxicity. With limited regard to hydroxychloroquine and lopinavir/ritonavir, drug withdrawal may be considered if the severity of GI

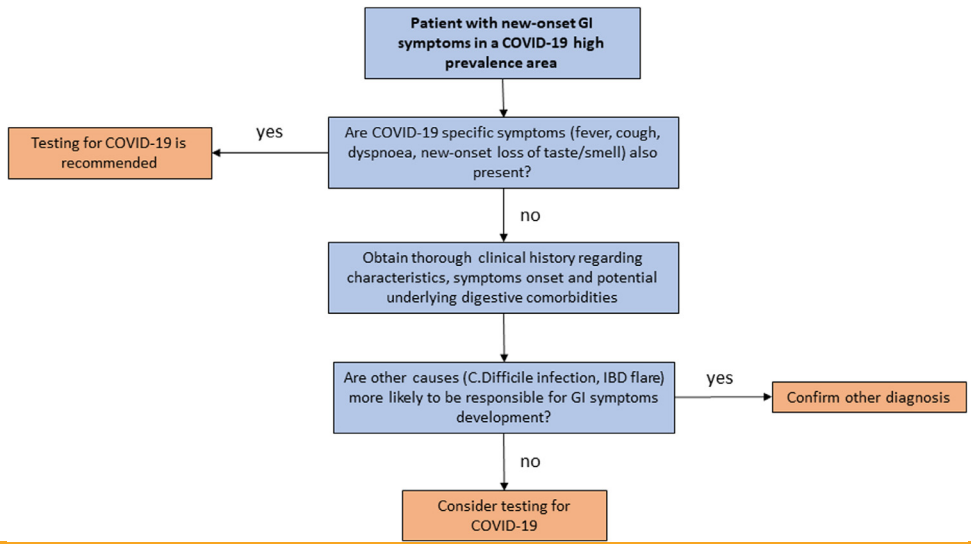

Figure 2. Proposed algorithm for management of suspected COVID-19 patients presenting with GI symptoms. IBD, inflammatory bowel disease.

symptoms (eg, diarrhea-related dehydration) becomes seriously harmful to the patient, as recent results from randomized trials did not show significant clinical benefit associated with their administration and several guidelines do not recommend their use in routine practice.[28,29,39,40] Withdrawal cannot at present be recommended for drugs whose efficacy is still under investigation.

To date, no specific guidelines about treatment of COVID-19 associated GI symptoms have been issued: thus, management is mainly supportive and should not differ from routine care[41]: in case of severe diarrhea, administration of intravenous fluids along with serum electrolytes monitoring are recommended; if C. Difficile is excluded and no blood streaks are present, antidiarrheal agents as loperamide can be used (Figure 2). Severe nausea and vomiting can be treated with parenteral antiemetics (metoclopramide, ondansetron or prochlorperazine).

COVID-19 fecal viral shedding: implications for transmission of the disease

The main routes of transmission of SARS-CoV-2 are through respiratory and direct contact; knowledge about other possible modalities, as fecal–oral transmission, remains limited.[42,43]

Studies published before the COVID-19 pandemic have proved that other coronaviruses can be shed in feces: in the MERS–CoV outbreak in 2012, 14.6% of infected individuals had positive fecal specimens at low viral loads.[44] Similarly, during the 2002-2004 SARS outbreak, that was caused by a virus that shares high level of genetic homology with SARS-CoV-2, fecal shedding was demonstrated in a subgroup of patients.[45]

Current knowledge on SARS-CoV-2 relies on multiple studies that have been conducted with the aim to verify fecal shedding and fecal-oral transmission: RT-PCR was used for detection of viral RNA in stool samples and rectal swabs from infected patients.[46–53] In all these studies, mainly composed of small cohorts of patients, viral RNA has been identified in stool or rectal swabs, with a prevalence ranging between 36% and 53% of all confirmed cases.

Moreover, due to different study designs, the timing of specimen collection is largely heterogeneous among studies and unstandardized. Therefore, it is still challenging to define accurately when fecal viral shedding may start (eg, during the incubation period, upon symptoms occurs or during convalescence) and how long the shedding continues. In some studies, samples were obtained consecutively during hospitalization and viral RNA positivity ranged between 1 day and more than 1 month after symptoms onset.[51,53]

A recent systematic review by Gupta et al, including 26 studies and 824 patients, has demonstrated a high incidence and persistence of positive fecal RT-PCR tests for SARS-CoV-2 after negative nasopharyngeal swabs in patients with COVID-19.[54] Among 199 patients who tested positive for fecal viral RNA, during subsequent follow-up 62.8% of them showed persistent fecal RNA shedding after a negative nasopharyngeal swab. These findings suggest that viral shedding may continue despite no detectability in upper respiratory tract. None of the included studies, however, was planned to detect viable virus in feces except the study by Wang et al: out of 153 stool specimens tested in this study, 44 were PCR positive and replicating virus was detected in 2 of 4 specimens.[46]

Also unclear is the association between viral detection in stools, symptoms or disease severity. According to a meta-analysis, patients who presented with gastrointestinal symptoms (77.1% vs 57.7%) and patients with more severe disease (68.3% vs 34.6%) tended to have a higher fecal detection rate, although statistical significance was not reached.[55] Opposite results come from a recent report, suggesting instead that fecal detection of SARS-CoV-2 RNA is not related to disease activity or digestive symptoms.[47] The finding of viral genetic material in stool may not necessarily imply that virions with infectious potential are present in fecal material and that, consequently, viral spreading is possible through feces. A few studies have directly tried to demonstrate the existence of this route of transmission: Wang et al. cultured stool specimens of 4 patients that had high viral RNA copy numbers and, through electron microscopy, observed replicating virus in 2 of them.[46] Wolfel et al also demonstrated very high concentrations of viral RNA in the stools of 9 COVID-19 patients, but evidence of replication in the GI tract remains unclear, since detection of GI cells containing subgenomic mRNA (a proof of active replication) was only occasional.[56]

As results are based on very small group of individuals, new studies conducted on larger cohorts are necessary to confirm what is the possibility of infectious virions to be detectable in patients' stool, what is their actual infective potential and how long for. Results are essential to clarify the attitude of SARS-CoV-2 to spread through fecal-oral transmission and, in turn, to apply appropriate preventive measures.

COVID-19 and the liver

In the context of COVID-19, liver injury has been reported as a risk factor for worse outcomes and death, in line with previous evidence in SARS and MERS infection.[57,58] Transient elevation of serum aminotransferases and impaired markers of liver function and bilirubin have been observed in up to 58% of patients with severe COVID-19, but the underlying mechanisms and possible complications are still poorly understood.[23,59–61] Since the beginning of the pandemic, several studies set in large Chinese cohorts of patients showed that liver involvement is common, with a prevalence secondary only to the respiratory system.[62–64] Considering its crucial role in defense against pathogens, liver injury may be due to several factors such as systemic inflammatory response and direct virus-related liver toxicity, but also drug toxicity, microbiome alterations, impairment of gut barrier and

progression of pre-existing chronic liver disease. Despite many hypotheses, the exact etiology of abnormal liver tests and their main features and clinical significance remain unclear. Moreover, whether COVID 19 infection is associated with poor prognosis in patients with underlying chronic liver disease is still debated; solid data supporting specific management strategies are also lacking (Figure 3).

Mechanisms of liver injury

One of the key mechanisms suggested to explain liver injury secondary to COVID-19 include direct viral toxicity, which represents a specific mechanism adding to endothelial dysfunction and release of inflammatory cytokines commonly observed in sepsis. Viral entry through ACE2 can occur directly in the hepato-biliary system.[11] Studies on gene expression revealed a significant enrichment of ACE2 in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6%).[65] Thus, several authors suggested a major role of bile duct cells in liver injury, considering them as crucial player in dysregulation of liver immune response. In the attempt to explain mechanisms of liver damage, Guan et al proposed up-regulation of ACE 2 expression due to compensatory proliferation of hepatocyte induced by bile duct cells.[66] Another mechanism of liver damage may be the dysregulation of innate immune response against the virus and consequent production on inflammatory cytokines. Several case series found that lymphopenia ($<1.1 \times 10^9$/L) and elevated CRP (> 20 mg/L) were independent risk factors for liver injury and mortality.[67] However, whether inflammatory cytokine storm results in liver damage remains to be elucidated. When considering drug induced liver injury, current therapeutic strategies in COVID-19 are mostly experimental; steroids, antiviral agents, biologic therapies, and alternative drugs are widely used in clinical trials worldwide. However, mild liver test alterations are often observed at baseline prior to the start of any specific medication. Hepatotoxicity caused by chloroquine or hydroxychloroquine has not been reported so far, and the same holds true for Remdesivir. Fan et al have recently found an association between abnormal liver function and administration of lopinavir/ritonavir[68]: the authors hypothesized a iatrogenic etiology considering that 23.7% of discharged patients developed elevated liver function tests during hospitalization, which was found to be associated with prolonged length of stay. Of note, 47.3% of the discharged patients showed impaired liver exams at baseline. Tocilizumab, an IL-6 antagonist, is known to be associated to transient mild elevation of aminotransferases in previous clinical trials, with resolution of the biochemical alteration in 2-6 weeks without any major clinical impact.[69] Mechanisms such as hepatic congestion in mechanical ventilated patients and hypoxic hepatitis have been also proposed but are not supported elsewhere in the literature.[70] Transaminases elevation could also reflect extra hepatic viral damage such as muscle damage similar to myositis as observed in severe influenza infection. Supporting the role of drug induced liver injury as the cause of transaminases elevation are the findings derived from liver biopsy performed in COVID-19 patients: liver specimens revealed a pattern of histological injury consistent with drug-induced liver injury (DILI) with moderate microvesicular steatosis, mild lobular and portal activity.[71]

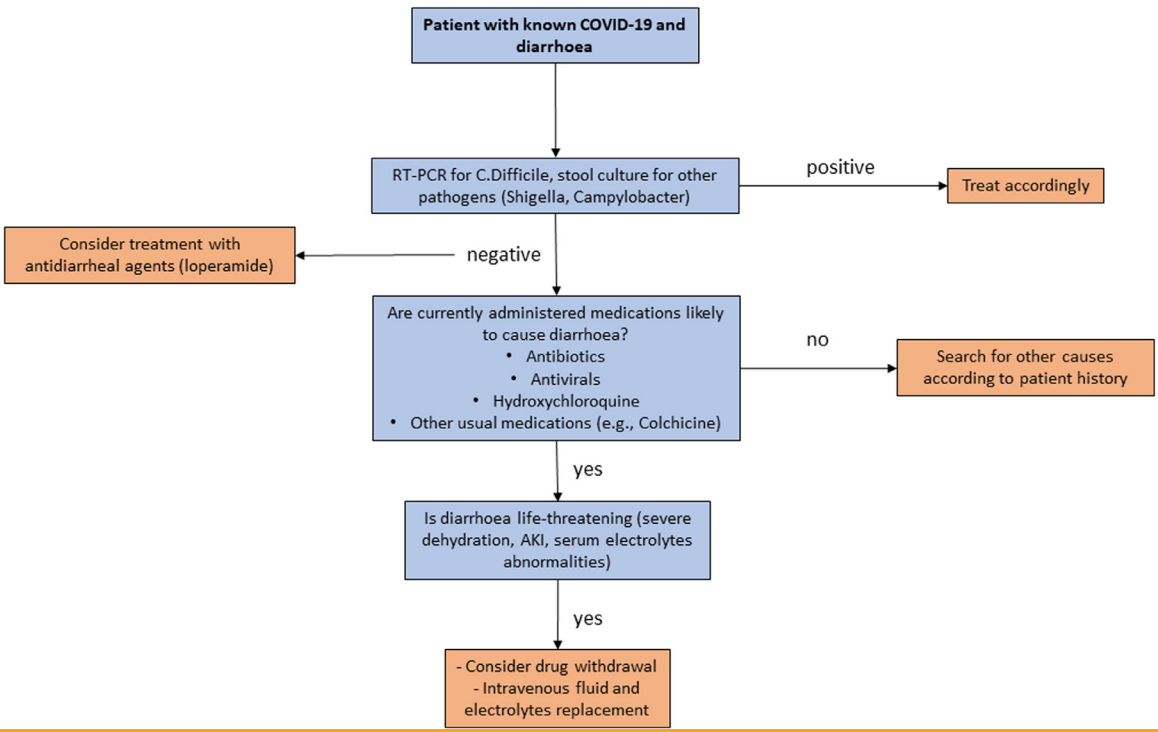

Figure 3. Proposed algorithm for management of diarrhea in COVID-19 patients. RT-PCR, reverse transcriptase-polymerase chain reaction; AKI, acute kidney injury.

Prevalence and severity of abnormal liver tests in COVID-19

Definition of abnormal liver test has been quite ambiguous in studies conducted in COVID-19 cohorts. Some studies considered any elevation of liver function parameter above the upper limit of normal, while others did consider only elevation higher the 2 or 3 times the upper limit of normal; others did not specifically quantify the alteration.[72] No standardized timing of assessment has been considered either. Incidence of liver injury in COVID 19 ranges from 14.8% to 53%, and the most common pattern observed was hepatocellular damage, with mild to moderate elevation of AST and/or ALT during the early stage of the disease.[60,68,73–75] Decreased serum albumin and increased serum bilirubin levels have also been observed, in severe cases; Chen et al reported abnormal levels of albumin in 98% of patients.[61] Severe cases of COVID-19 pneumonia without pre-existing chronic liver disease were characterized by higher rate and extent of livery injury that nonsevere ones.[74] This finding is consistent with previous reports of higher levels of transaminases, bilirubin, LDH and PT in patients admitted to ICU when compared with patients nonrequiring ICU management.[73] Liver failure has been rarely reported, with a single case of increase of AST and ALT up to 7590 U/L and 1445 U/L being described[61]: elevation of aminotransferases is usually characterized by peak values lower than 5 times the upper limit of normal. As stated before, abundant expression of ACE2 on bile duct cells explains the alteration of cholestatic markers that is observed in several cases series including COVID 19. However, while elevation of GGT has been reported in up to 54% of patients, only 1.8% of them did have elevation of ALP levels.[76,77]

Studies reported a correlation between the degree of liver dysfunction and the severity of liver disease. Although a recent meta-analysis including 20 studies with 3428 COVID-19 patients evidenced that higher levels of serum transaminases and total bilirubin were associated with severe clinical outcome,[78] there is contrasting evidence on these findings, with other studies from Western countries not supporting this observation.[79,80]

In most patients, impaired liver tests do not require additional diagnostic tests, on the other hand, patients receiving investigational product such as antivirals (lopinavir/ritonavir, remdesivir) and immunosuppressive drugs with slight elevation of aminotransferases should be monitored, with no absolute contraindication to continue treatment (Figure 4).

COVID-19 and pre-existing liver disease

Data concerning COVID-19 infection in patients with chronic liver disease (CLD) are rapidly accumulating. Regarding the prevalence of chronic liver disease in COVID 19 patients, a meta-analysis of 11 studies, pooling data of 2034 patients predominantly from China, showed that only 3% had an underlying liver disease, with no mention of etiology or severity.[81] Chronic liver disease,[82–84] and in particular cirrhosis,[85–87] has been consistently associated with disease severity and increased

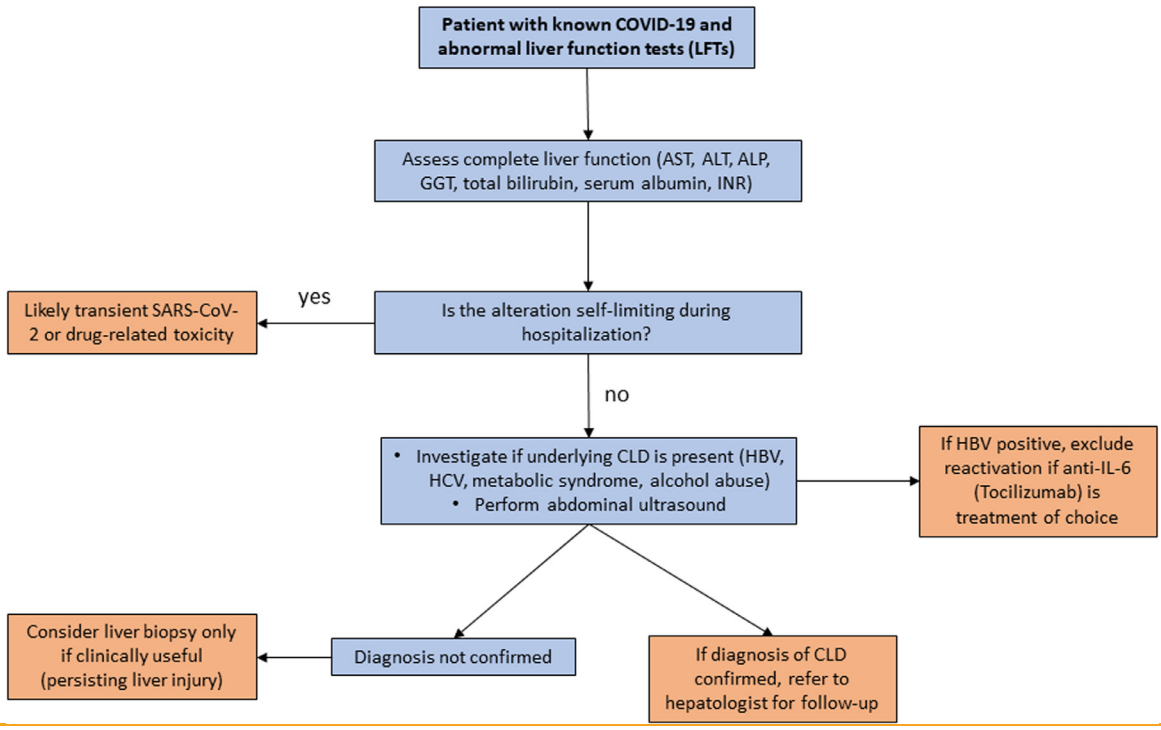

Figure 4. Proposed algorithm for management of liver tests abnormalities in COVID-19 patients. LFTs, liver function tests; AST, aspartate amino-transferase; ALT, alanine amino-transferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl-transpeptidase; INR, international normalized ratio; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IL-6, interleukin-6.

mortality in COVID-19: specific attention must be given to this subgroup of patients, both presenting as outpatients or inpatients, as they may be at risk of rapid clinical deterioration.

Authors' contributions

Conception and design of the work: Vespa, Aghemo.

Drafting and critical revising of the work: Vespa, Pugliese, Colapietro, Aghemo.

Final approval of the version to be published: All authors.

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Conflicts of Interest
The authors disclose no conflicts.