



Twelve Months with COVID-19: What Gastroenterologists Need to Know

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Abstract

Corona virus disease-19 (COVID-19) is the latest global pandemic. COVID-19 is mainly transmitted through respiratory droplets and, apart from respiratory symptoms, patients often present with gastrointestinal symptoms and liver involvement. Given the high percentage of COVID-19 patients that present with gastrointestinal symptoms (GIS), in this review, we report a practical up-to-date reference for the physician in their clinical practice with patients affected by chronic gastrointestinal (GI) diseases (inflammatory bowel disease, coeliac disease, chronic liver disease) at the time of COVID-19. First, we summarised data on the origin and pathogenetic mechanism of SARS-CoV-2. Then, we performed a literature search up to December 2020 examining clinical manifestations of GI involvement. Next, we illustrated and summarised the most recent guidelines on how to adhere to GI procedures (endoscopy, liver biopsy, faecal transplantation), maintaining social distance and how to deal with immunosuppressive treatment. Finally, we focussed on some special conditions such as faecal–oral transmission and gut microbiota. The rapid accumulation of information relating to this condition makes it particularly essential to revise the literature to take account of the most recent publications for medical consultation and patient care.

Keywords COVID-19 · SARS-CoV-2 · Gastrointestinal symptoms · Inflammatory bowel disease · Coeliac disease · Liver diseases

Abbreviations

ACL	Acute-on-chronic liver
CLD	Chronic liver disease
ACE-2	Angiotensin-converting enzyme 2
CD	Coeliac disease
COVID-19	Corona virus disease-19
GI	Gastrointestinal
GIS	Gastrointestinal symptoms

IBD	Inflammatory bowel disease
IL	Interleukin
MERS	Middle East respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome

Origin and Pathogenetic Mechanism of SARS-CoV-2

At the end of 2019, a new coronavirus named SARS-CoV-2 (severe acute respiratory syndrome) was isolated and the disease related to it was indicated by the acronym COVID-19 (corona virus disease-19). Human-to-human infection was first reported in the Huanan fish market in Wuhan, and then spread to China, leading to a global pandemic. According to the World Health Organization, as at December 31 2020, the pandemic has caused 95,321,880 infections worldwide and 2,058,227 deaths [1]. SARS-CoV-2 displayed partial similarity to SARS-CoV and MERS-CoV (Middle East respiratory syndrome) in phylogenetic research, clinical manifestations and pathological findings. Based on the genome sequence, SARS-CoV-2 is approximately 89% identical to bat SARS-like-CoV,

Core tip: Gastrointestinal (GI) symptoms and liver involvement are present in about 20% of patients with COVID-19 and, when present, suggest progression towards a more critical illness. SARS-CoV-2 does not worsen the prognosis of pre-existing GI or liver-related diseases, and specific guidelines have been addressed to face the problem. GI procedures must be performed in urgent cases and deferred whenever possible. The more prolonged survival of the virus in the faeces compared to the respiratory tract generates doubts about the appropriateness of the current discharge criteria. The relationship between gut microbiota, ACE-2 expression and the clinical course of COVID-19 still needs to be elucidated.

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82% identical to SARS-CoV human and 50% identical to MERS-CoV. Cases range across all ages, with most patients between 35 and 55 years and fewer cases among children and infants. Males are more susceptible than females (65%) [2]. Symptoms may include fever, cough, sore throat, nausea, myalgia and mild flu-like symptoms; a small percentage evolve towards respiratory failure needing ventilatory support and, in the most severe cases, multi-organ failure and death [3].

Coronavirus spike surface glycoprotein (S-protein of SARS-CoV-2) binds to angiotensin-converting enzyme 2 (ACE-2) to invade host cells. Through genomics studies, researchers have shown that SARS-CoV-2 binds to the same receptor with an affinity which is approximately 10- to 20-fold higher than SARS-CoV [4–6]. Many organs and tissues, besides the respiratory tract, have a high expression of ACE-2: heart, skin, kidney, endothelial cells of small and large vessels and fat. In the gastrointestinal tract, ACE-2 is abundantly expressed at the oesophageal level and in the small and large intestine, particularly in the ileum [7–10]. From an evolutionary point of view, ACE-2 has high structural homology with collectrin, a transmembrane protein with a regulatory function in the expression of neutral amino-acid transporters at the brush border of the proximal renal tubules. The enzyme has a double function: a negative regulation on the renin–angiotensin–aldosterone system and an amino-acid transporter mainly in the small intestine. In the gut, collectrin is not expressed, and its role is performed by ACE-2, which acts as the chaperone for trafficking of an amino-acid transporter on cell membranes, B0AT1, which mediates uptake of neutral amino-acids into intestinal cells. Some studies have shown that ACE-2 knock-out mice do not express B0AT1 in the gut and have low levels of the amino-acids tryptophan, valine, threonine and tyrosine, resulting in severe intestinal inflammation and microbial imbalance. Structural modelling has suggested that the ACE2–B0AT1 complex can bind the S-protein of SARS-Cov-2 and that ACE-2 might be the viral entry point for SARS-CoV-2 in the gut [11].

This systematic review summarises a 1-year experience in dealing with patients with COVID-19 and gastrointestinal symptoms (GIS) before the vaccination programme. We aim to highlight the prevalence and clinical significance of GIS in patients with COVID-19 and to report up-to-date, brief and practical information for gastroenterologists dealing with chronic gastrointestinal diseases (inflammatory bowel disease, coeliac disease, chronic liver disease) at the time of COVID-19.

Clinical Studies Collection and Deriving Strategies

We performed a literature search in December 2020, focusing on articles published from January 1 2020, examining data on clinical manifestations of gastrointestinal

involvement. For this purpose, we performed an electronic search of the literature using the online databases Cochrane Library, PubMed, Scopus and Web of Science, entering the query terms ("SARS-CoV-2" OR "COVID-19") AND ("intestine*" OR "gastr*" OR "pancr*" OR "esopha*" OR "colon*" OR "rectum," OR "nausea" OR "vomit" OR "diarrhoea" OR "abdominal pain" OR "anorexia"). We eliminated a priori all experimental studies and limited our literature search to articles published in English in peer-reviewed journals. Further relevant articles were hand-searched using the references of the selected studies. Eligibility criteria were evaluations of in-patients with gastrointestinal symptoms.

Gastrointestinal Involvement in Covid-19

Gastrointestinal Symptoms in Adults

Due to the presence and function of ACE-2 at the intestinal level, many authors have hypothesised that the virus may present a tropism for the enteric epithelium, causing GIS. Although initial studies indicated that GIS was not frequent in COVID-19, recent evidence has shown that this is not the case. In Table 1 and Table S1, respectively, all studies with more than 100 and less than 100 patients found by our systematic literature search are reported, describing the most frequent GIS: anorexia, diarrhoea, nausea, vomiting and abdominal pain [12–125]. A possible reason for the relatively high prevalence of diarrhoea compared to other GIS is that gut epithelial cells (especially in the ileum) have a significantly high ACE-2 expression. GIS might predispose to electrolyte disruptions, hyponatremia, which could exacerbate the disease.

A total of 318 patients with confirmed COVID-19 were included in a US multicentre cohort study. Overall, 61% of patients reported at least one GIS on admission, most specifically anorexia (35%), diarrhoea (34%) and nausea (26%). In addition, patients with GIS reported higher levels of fatigue, myalgia and odour or taste loss. In this experience, there were no variations in clinical deterioration rates between patients with and without GIS when comparing admission to intensive care unit (ICU), mechanical ventilation needs or overall mortality possibly due to the absence of ICU rooms/ventilators at the participating hospitals [25]. A recent paper reported a correlation between the presence of GIS and the severity of respiratory symptoms, the need for ventilatory support and ICU admission [126]. COVID-19 patients with GIS experience worse respiratory symptoms (higher rates of fever, shortness of breath and headache). Moreover, severe cases of COVID-19 occur frequently in patients with GIS, as compared to those without (23% vs. 8%), consistent with the possibility that an intestinal localization might increase the release of pro-inflammatory cytokines with an impact

Table 1 Studies with more than 100 cases reporting gastrointestinal in COVID-19 patients

Author	Patients (<i>n</i>)	Age (years)	Disease severity	Gastrointestinal symptoms (%)			
				Anorexia	Diarrhoea	Nausea/vomiting	Abdominal pain
Wang et al. [12]	138	56 (22–92)	36 ICU; 102 non-ICU	66.7 ICU 30.4 non-ICU	16.7 ICU 7.8 non-ICU	8.3 ICU 2.0 non-ICU	8.3 ICU 0 non-ICU
Han et al. [13]	108	45 (21–90)	Mild	–	14	–	–
Pan et al. [14]	204	52.9 ± 16	Mild to severe	40	17	–/2	1
Cholankeril et al. [15]	116	50 (35–67)	Mild to severe	25.3	14.6	14.6	8.8
Guan et al. [16]	1099	47 (35–58)	Mild to severe	–	3.8	5	–
Zhang et al. [17]	115	49.5 ± 17.1	Mild to severe	–	–	–	–
Wang et al. [18]	1012	50 (39–58)	Mild to severe	–	15	3.6	3.7
Chen et al. [19]	249	51 (36–64)	22 ICU; 227 non-ICU	–; 3.2	–; 3.2	–	–
Liu et al. [20]	137	55 ± 16	–	–	8	–	–
Zhou et al. [21]	191	56 (46–67)	–	–	5	4	–
Zhou et al. [22]	254	50 (36–65)	Mild to severe	–	18.1	5.9/8.3	1.2
Guo et al. [23]	174	59 (49–67)	Moderate to severe	–	12.1	9.8	–
Shi et al. [24]	416	45 (22–90)	Moderate to severe	–	3.8	–	–
Redd et al. [25]	318	63.4 ± 16.6	Mild to severe	34.8	33.7	26.4/15.4	14.5
Jin et al. [26]	651	46.14 ± 14.19	Moderate to severe	–	8.14	2.6/2.7	–
Nobel et al. [27]	278	–	–	–	20.1	22.7	–
Klopfenstein et al. [28]	114	56 (± 18) (group of patients with diarrhoea)	–	–	48	32.45/9.64	22.8
Cholankeril et al. [29]	207	49 (34–65)	–	–	10.8	10.8	7.1
Moura et al. [30]	400	56.40 (16.07)	Moderate to severe	11.5	17.25	13.75/7.50	6.00
Rao et al. [31]	240	48 (23–87)	Moderate to severe	–	8.5	6.3	–
Du et al. [32]	345	63.0 (50.0–68.0)	Mild to critical	–	21.2	7.0/5.2	3.8
Jalali et al. [33]	2322	–	–	2.1	3.6	5.2/3.5	2.5
Khalil et al. [34]	226	41.6 ± 14.8	–	44.7	35	22.6/	–
Elmunzer et al. [35]	1992	60.1 ± 16.3	–	–	34	27/16	11
Laszkowska et al. [36]	2804	63.4 ± 18.4	–	–	23.4	23.2	11.9
Kang et al. [37]	118	61.0 (50–70)	–	–	45.8	–	–
Sulaiman et al. [38]	140	44.99 ± 16.81	Mild to critical	28.57	29.28	22.14	30
Livanos et al. [39]	634	64 ± 16	Mild to severe	–	39	25/13	–
Renelus et al. [40]	734	66.1 ± 15.6	–	–	20.3	14.9/8.45	9.26
Bannaga et al. [41]	321	73 (56.0–82.0)	–	–	4	4.6	4.6
Lei et al. [42]	115	66 (60–70)	Mild to critical	7.83	12.17	7.83	–
Ianiro et al. [43]	420	61	–	–	37	19/–	14
Hajifathalian et al. [44]	1059	61.1 ± 18.3	–	22.7	22.1	15.9/ 8.6	6.8
Zhang et al. [45]	505	51.2 ± 17.2	Mild to severe	18.4	12.3	5.3/2.6	3.4
Aghemo et al. [46]	292	65.0 ± 14.1	–	–	27.1	–/4.0	–

Table 1 (continued)

Author	Patients (n)	Age (years)	Disease severity	Gastrointestinal symptoms (%)			
				Anorexia	Diarrhoea	Nausea/vomiting	Abdominal pain
Chen et al. [47]	101	48.32 ± 14.74	Mild to moderate	53	50	30/14	26
Zhao et al. [48]	401	47 (33–60) ^b	Mild to critical	–	6.2	0.2	–
Ferm et al. [49]	892	59 (47–72)	–	11.8	19.8	16.6/10.2	7.8
Sierpiński et al. [50]	1942	50	Mild to moderate	47	24.2	–/–	–
Cao et al. [51]	157	49.3 (14.5)	Severe: 26.1%	29.9	15.9	13.4/–	–
Annweiler et al. [52]	353	84.7 ± 7.0	–	–	21.8	6.2	–
Zhang et al. [53]	107 patients With cancer	66 (36–98)	Mild to severe	–	14.0	–	–
Zhang et al. [54]	409	65 (56–71)	Severe	–	22.2	12.2/10.3	6.8
Khan et al. [55]	122	49	Mild to severe	–	4.92	1.64/–	–
Zheng et al. [56]	1320	50 (40–57)	Mild and common type	4.7	8.1	4.3	1.0
Luo et al. [57]	1411	Initial gastrointestinal symptoms: 53.8 Respiratory syndrome and fever: 56.2	–	12.8	4.8	9.5/8.4	4.6
Kaafarani et al. [58]	141	57 (47–70)	Severe	–	29.8	22.0	14.9
Zhan et al. [59]	405	56 (17–95)	Non-severe to severe	42	27.7	18.8	10.1
Díaz et al. [60]	7016	39.79 ± 20.6	ICU 28.4%	–	7.3	–	3.7
Bhayana et al. [61]	412	57 (18–90)	ICU 33%	–	4.8	7.1	33
García-Azorín et al. [62]	104 with headache	56.7 (11.2)	Mild to severe	–	47.1	10.6	–
Sadeghi et al. [63]	102	55.13 ± 17.02	Non-ICU	–	18.5	–	–
Chen et al. [64]	369	61.0 (50.0–70.0)	Mild to severe	–	57.9	19.8	10.6
Elimian et al. [65] ^c	10,517	35.6	Mild to severe	–	3.1	3/2	0.3
Kim et al. [66]	540	36 (26–47)	Mild to severe	12.5	5.8	5.3/3.9	6.6
An et al. [67]	205	54 (22–77)	Mild to death	28.8	9.8	5.9/2.9	2
Ganz-Lord et al. [68]	1698	43.91	Mild to death	–	36.7	–	–
Alizadehsani et al. [69]	319	45.48 ± 18.50	Mild to severe	8.1	–	–	–
Jiang et al. [70]	215	68 ± 64.72	Mild to death	26	12.6	5.1	–
	66	84 ± 81.85		43.9	3	9.1	
Jiang et al. [71]	495	42.24 ± 16:99	Mild to severe	1.4	7.07	5.85	2

Age expressed as mean ± standard deviation or median (range) or range

^aFive paediatric cases

^b30 paediatric cases

^c1268 paediatric cases

on clinical outcome [49]. Wang et al. reported that, in ICU patients, the proportion of GIS, especially anorexia and abdominal pain, was higher than in non-ICU patients (anorexia 66.7% vs. 30.4%; abdominal pain 8.3% vs. 0%) [12].

Abdominal pain, although less frequent, has been associated with severe disease [127].

A recent meta-analysis showed that the prevalence of nausea and vomiting was 7% (95% CI 0.04–0.09), diarrhea was

8% (95% CI 0.06–0.11), abdominal pain was 3% (95% CI 0.01–0.05) and anorexia was 17% (95% CI 0.06–0.27) [128]. Thus, reevaluation of GIS by SARS-COV-2 was lower than by SARS and MERS [129, 130]. Finally, with regard to GI involvement, critical intestinal ischemia has been recorded in 2–5% of patients with COVID-19, compared to no cases in ill patients with non-COVID-19 [58, 131].

Gastrointestinal Symptoms in Children

In a recent meta-analysis, data were selected from 32 articles with a total sample size of 759 children [132]. Among the most common clinical manifestations was diarrhoea (19%, 95% CI 9–28%). Another systematic review reported data from 45 paediatric studies on SARS-CoV-2 infection. Paediatric infections were found to be 2% of 44,672 cases in a Chinese paper, 1.2% of 22,512 cases in an Italian study, 5% of 4226 cases in the United States and less than 1% of cases in the United Kingdom. Infections in paediatric patients are therefore a minority; this could be due to active resistance of children to the virus, or an increased frequency of unrecognized asymptomatic cases. The clinical course in the paediatric patient appears to be very mild compared to adults [133]. However, young patients (up to 5 years) have a higher viral RNA load in their nasopharynx than older ones and adults [134]. The most common symptoms in children are fever and cough, but diarrhoea and vomiting have also been reported. Table 2 and Table S2, respectively, show all

studies with more than 100 or less than 100 children found by our search [135–211]. In children, GIS are less common than in H1N1 influenza, which, according to the data, in 2009 caused diarrhoea in more than 20% of children [212]. An essential aspect to consider is that, although children show mild or no symptoms, stool samples and rectal swabs may test positive for viral RNA for several days after infection. In addition, paediatric patients seem to eliminate the virus through faeces for a longer time than adults [213, 214]. Several authors have proposed that the paediatric patient, due to the scarcity of symptoms and the prolonged elimination of the virus with faeces, could be an essential vehicle for transmission. However, the role of children in the spread of the virus has not yet been fully clarified.

Liver Involvement

Patients with COVID-19 may experience liver injury with elevated enzymes in blood tests. ACE-2 is expressed abundantly in hepatocytes and, in particular, on biliary epithelial cells, and this justifies the frequent liver involvement during SARS-COV2 infection. The incidence of liver involvement ranges from 15% to 50% of patients presenting with increased levels of transaminase with a relatively mild elevation in serum bilirubin [12, 14, 15, 77, 78], while, in patients with severe disease, the proportion of liver injury was also higher [12, 16, 79, 213]. A recent meta-analysis calculated that up to 25% of patients would develop liver involvement

Table 2 Studies with more than 100 cases reporting gastrointestinal in COVID-19 patients. Paediatric population

Author	Patients (n)	Age (years)	Disease severity	Gastrointestinal symptoms (%)			
				Anorexia	Diarrhea	Nausea vomiting	Abdominal Pain
Giacomet et al. [135]	127	4.8 (0.3–8.5)	Asymptomatic to critical	–	22	–9.4	6.3
Garazzino et al. [136]	168	5, 2.3 (0.3–9.6)	–	–	13.1	–5.4	–
Du et al. [137]	182	6 (0–15.0)	Asymptomatic to critical	–	4.9	–3.8	3.8
Gaborieau et al. [138]	157	0.5 (0.1–10)	Mild to severe	10.2	15.3	–7.6	–
Guo et al. [139]	341	7 (0–14)	Asymptomatic to critical	–	4.4	2.9	–
Rabha AC et al. [140]	115	0.6–3	Asymptomatic to critical	21.7	13	17.4	8.7
Bayesheva et al. [141]	558	< 19	Asymptomatic to critical	–	2	–	–
Parri et al. [142]	100	3.3 (0–17.5)	Asymptomatic to severe	23	9	10	4
CDC COVID-19 Response Team [143]	291	11 (0–17)	Asymptomatic to severe	–	37	31	17
DeBiasi et al. [144]	177	9.6 (0.1–34.2)	Asymptomatic to severe	–	15	–	–
Lu et al. [145]	171	6.7 (0–15)	Mild to severe	–	8.8	6.4	–
Armann et al. [146]	128	< 18	Mild to severe	17	17	17	17
Wu et al. [147]	148	84 (18–123)	Mild to moderate	–	21.6	21.6	–
Zhen-Dong et al. [148]	406	7	Asymptomatic to death	–	5.4	5.4	–
Feldstein et al. [149]	186	9.1 (4.1–11.7)	Severe to death	–	92	–	–
Godfred-Cato et al. [150]	570	8 (4–12)	Mild to critical	–	53.2	61.8	61.9
Guo et al. [151]	136	7 (0–14)	Asymptomatic to severe	–	4.4	2.9	–

Age expressed as mean \pm standard deviation or median (range) or range

(95% CI 0.16–0.33, $P < 0.0001$) [215]. There are several possible mechanisms of liver damage: (1) immune-mediated hepatitis, (2) direct viral cytopathic effect, (3) drug-induced liver injury secondary to medications used for the treatment of COVID-19 disease (lopinavir, ritonavir, remdesivir, chloroquine, tocilizumab, umifenovir), (4) hypoxia secondary to lung disease enhancing hepatic damage, (5) infection-induced systemic inflammation, (6) hepatic congestion secondary to positive pressure ventilation, and (7) reactivation of pre-existing liver disease [214].

A recent large retrospective cohort study, including 2073 Chinese patients with COVID-19, found that increased transaminases and direct bilirubin levels were independent predictors of mortality related to COVID-19 [215]. As far as acute-on-chronic liver (ACL) failure, among 192 hospitalised patients with chronic liver disease (CLD), 38% of the 84 cirrhotics developed ACL disease. However, mortality was not different when comparing CLD patients with or without cirrhosis. Moreover, mortality was similar between the CLD cohort and matched control without CLD [216].

Pancreatic Involvement

Theoretically, pancreatic involvement is based on the evidence that ACE-2 is usually expressed in the pancreas (exocrine glands and islets) of healthy people, indicating that SARS-CoV-2 might also cause pancreatic injury and potentially contribute to islet damage [217]. Wang et al., in a retrospective study of 52 patients with COVID-19, described such pancreatic involvement: 17% of patients showed an abnormality in amylase [115 ± 25 U/L (normal value < 90) or lipase [71 ± 34 U/L (normal value < 70)] and six had elevated levels of blood glucose suggestive of pancreatic islet damage. Patients with pancreatic injury had a higher incidence of anorexia and diarrhoea, more severe illness on admission, lower levels of CD3 + T-cell and CD4 + T-cell and higher levels of AST, GGT, creatinine, LDH and ESR. It is possible that some critically ill patients already had pancreatic damage on admission, and that this had been caused by drugs (NSAIDs and glucocorticoids) [81]. De-Madaria E. et al. replied that the definition of pancreatic injury, as referred by Wang et al., lacks specificity and does not meet Atlanta's criteria. A mild increase in blood levels of pancreatic enzymes within the threefold upper normal limits threshold can be explained by many factors other than direct viral damage, and the authors did not provide data on imaging techniques, which are crucial for diagnosing pancreatitis [218]. In another recent systematic review, cases of acute pancreatic disease associated with SARS-CoV-2 were searched to assess whether there was an association between the two. Six case reports and two retrospective cohort studies were selected but, unfortunately, the etiological factors

and diagnostic criteria applied are not always well described [219].

In conclusion, the risk of pancreatic involvement related to Covid-19 and the subsequent risk of acute pancreatitis exist. However, the clinical relevance of mildly elevated pancreatic enzymes in COVID-19 is unknown.

Covid-19 and Chronic GI and Liver Disorders

Inflammatory Bowel Disease (IBD)

GIS appear to be secondary to intestinal inflammation, as evidenced by a recent study showing a strong correlation between the presence of diarrhoea and the elevation of faecal calprotectin and serum IL-6 [80]. Moreover, the examination of serum inflammatory markers showed elevated levels of procalcitonin, C reactive protein, D-dimer, ferritin tumour necrosis factor, interleukin (IL)-2R, IL-6, IL-8 and IL-10 [220]. These findings raise the question of whether the presence of the virus could be responsible for relapse in patients with inflammatory bowel disease (IBD), especially if requiring immunosuppressive drugs. ACE-2 receptor is highly expressed in inflamed IBD mucosal samples compared to controls. In addition, cytokines expressed in IBD, such as interferon-gamma, can potentially induce ACE-2 expression, consistent with the idea that mucosal inflammation can increase ACE-2 expression. These results indicate that patients with IBD might be especially vulnerable to COVID-19; nevertheless, there is no evidence that this is the case. In a recent systematic review and meta-analysis, data from 11 studies were reported to evaluate the various clinical manifestations of SARS-CoV-2 in patients with IBD [221].

Diarrhoea was the most common GI manifestation in IBD patients (27.26%; 95% CI 19.51–36.69; $I^2 = 87\%$) per 100 persons. The pooled prevalence was 13.08% for abdominal pain (95% CI 9.24–18.19; $I^2 = 69\%$), 10.08% for nausea (95% CI 5.84–16.85; $I^2 = 80\%$) and 8.80% for vomiting (95% CI 4.43–16.70; $I^2 = 85\%$) per 100 persons. A noteworthy finding was the preponderance of abdominal pain in IBD patients, which is not common in the COVID-19-infected general population, as seen in other investigations. The current literature indicates that there is no evidence of increased risk or worsened outcomes in COVID-19 patients with IBD [222].

Covid-19 seems to be more severe in old patients and in those with comorbidities (e.g. coronary heart disease, obesity, diabetes mellitus, malnutrition, cardiovascular disease, obstructive pulmonary disease and hypertension), severe IBD and/or needing surgery [223]. Considering the risk of flare-ups leading to a need for steroids or other potential immunosuppression or hospitalisation, the British Society of Gastroenterology, in a document addressing the

needs of IBD patients, does not recommend interrupting or decreasing medications without first addressing it with the IBD team. Moreover, physicians must consider that immunosuppressive drug effects can persist for several weeks or months following cessation of treatment and that the evidence available indicates that patients with IBD do not have an elevated risk of developing COVID-19. Patients that receive immune suppressants should be closely monitored for symptoms and/or signs that indicate COVID-19. In addition, those patients over 60 years of age and/or with comorbidities who have a higher risk of SARS-CoV-2 induced pneumonia should remain at home and avoid public gatherings [224]. An international adult and paediatric registry (Surveillance Epidemiology of Coronavirus Under Research Exclusion—SECURE-IBD) is available to collect all the cases of COVID-19 in IBD patients at www.covidibd.org. This registry will help to define the impact of COVID-19 in these patients and how factors such as age, severity, comorbidities and IBD treatments impact COVID-19 outcomes. Data on the effects of IBD medications on COVID-19 outcomes extrapolated from the registry have been recently published. The study, which includes 1439 cases from 47 countries, demonstrated that combination therapy and thiopurines may determine a worst COVID-19 outcome, while no differences were observed comparing different classes of biological drugs [225].

Celiac Disease

To date, no research has shown that patients with celiac disease (CD) are at an elevated risk of severe COVID-19 as compared to patients without CD.

As for IBDs and also for CD patients, an international registry is currently collecting data of patients to monitor and report the outcomes of COVID-19 occurring in patients with celiac disease (SECURE-Celiac). The database encourages clinicians worldwide to report all cases of COVID-19 in celiac patients, regardless of severity (including asymptomatic patients identified through health screening). The database is accessible at <https://covidceliac.org/>.

The CD Foundation Medical Advisory Board reports that patients with CD are not usually considered immunocompromised. A small number of CD patients with extreme malnutrition and weight loss, type 2 refractory CD, immunosuppressive medications or other serious illnesses may be at an elevated risk of severe COVID-19 and should consult with their physicians. CD is a chronic medical condition with a slightly elevated risk of infection, community-acquired pneumonia and worse outcomes with influenza [226] and therefore might benefit from an implementation of a vaccination programme for *Streptococcus* pneumonia and influenza. High-coverage vaccination programmes may help reduce the stress on the national healthcare system: e.g. avoiding being

misled by diseases that can cause influenza-like symptoms in particular during the cold season during a pandemic, and also lower coinfections that could increase potential COVID-19 mortality. It is fair to hypothesise that those with CD, particularly the elderly, maybe at a slightly increased risk of worse infections with this new virus. Recently, Siniscalchi et al. surveyed 276 patients with CD using an ad hoc COVID-19 survey. He found that the lockdown had a small effect on patients' psychological health: CD patients did not think they were at excessive risk of being infected with the Sars-COV-2 virus nor worried about the shortage of gluten-free food. Elderly patients and patients with other comorbidities were the most worried, probably because they knew they were at greater risk of mortality [227]. In another recent survey of 1983 responses, improved adherence to the gluten-free diet was reported for 29% of enrolled adults and children [228].

Based on a retrospective cohort study, another paper has been published on the management of CD in children with antitranglutaminase IgA between 5 and 10 times the upper limit of normal and positive endomysial antibodies during the COVID-19 outbreak.

The authors conclude for the possibility of temporarily reducing the antitranglutaminase IgA threshold for a biopsy-sparing approach, avoiding delayed diagnosis and complications. Certainly, a rigorous follow-up of illness course and serum auto-antibody levels is extremely crucial to confirm diagnoses over time [229].

Chronic Liver Disease

Since the pandemic began, several studies have been conducted to assess a link between underlying liver diseases and the course of SARS-CoV-2 infection. Patients that might be at increased risk of a severe course of COVID-19 are those with chronic hepatitis B and C or cirrhosis, alcohol-associated liver disease, non-alcoholic fatty liver disease or steatohepatitis that may suffer from metabolic comorbidities such as diabetes, hypertension and obesity [230, 231].

According to the World Gastroenterology Organization, patients with chronic liver disease without cirrhosis and/or after liver transplantation are not at an increased risk of severe COVID-19 disease. Some general approaches are strongly recommended: (1) reduce direct exposure and maintain social distance; (2) maintain care according to guidelines; (3) routine testing of liver biochemistry is not recommended for outpatients; (4) exclude viral hepatitis in patients with elevated transaminase; (5) maintain antiviral medications for B or C hepatitis; (6) delay non-urgent procedures of surveillance such as liver ultrasound and screening; (7) maintain immunosuppressive therapy if not differently prescribed; (8) use telemedicine whenever possible; (9) implement vaccination for *Streptococcus*

pneumonia and influenza; (10) limit contact with medical personnel to a minimum; and (11) promote collaboration with local health care providers and primary care facilities. Additional recommendations for patients with decompensated liver disease include that listing for transplantation should be restricted to patients with poor short-term prognosis and that in-hospital liver transplant evaluation programmes should be maintained aiming to shorten hospital stays. A patient with chronic liver disease who results positive to COVID-19 should be admitted for in-patient care in the presence of additional risk factors for a more severe COVID-19 course like hypertension, diabetes, obesity, cirrhosis or a post-transplant status. A patient with chronic liver disease, negative to COVID-19 who needs in-patient care should be admitted to COVID-19-clean hospitals, preferably in private rooms, and specialised centres should provide easily accessible hepatology consultations [232].

At the beginning of the Sars-Cov-2 pandemic, there was much concern about liver-transplanted patients since they were theoretically at higher risk of COVID-19 because of chronic immunosuppression. However, a prior experience of Italian patients found that none of the transplanted patients on highly intensive immunosuppression experienced a more severe disease course [233]. A more recent prospective Spanish nationwide study reported that, although liver transplant patients are chronically immunosuppressed and have an increased risk of acquiring COVID-19, their mortality rate is lower than the matched general population [234].

GI Procedures During Covid-19 Pandemic

Endoscopic Procedures

At the beginning of the pandemic, multi-society guidelines recommended the postponement of non-emergency endoscopic procedures in adults and children [235–237]. Nowadays, the recommendations for diagnostic procedures are a dynamic process that needs to be updated regularly. It remains a good rule to screen with a COVID-19 questionnaire about the presence of symptoms, the history of potential exposure to infected individuals, travel to/from the containment zone and vaccination. Another suggestion is to use pre-endoscopy viral testing, although these are not routinely available everywhere. In the latter case, viral testing should be reserved for those patients at high risk of having COVID-19 infection after the questionnaire. Digestive endoscopy in COVID patients with GI symptoms showed variable results: oedema of the lamina propria (reported in two of three studies) and the presence of the virus in various levels of the GI tract [72, 78, 238].

Liver Biopsy

Recommendations can be examined based on individual risk–benefit considerations. Routine liver biopsy is not recommended in COVID-19 patients with liver test abnormalities. Liver biopsy should be deferred whenever possible in the event of non-alcoholic fatty liver disease or chronic viral hepatitis grading/staging and when the clinical indication is not urgent such as in the case of mildly elevated transaminases of unknown aetiology. Even in cases of autoimmune liver disease the biopsy should be postponed and an empiric therapy recommended. Liver biopsy should not be delayed in the event of liver masses suspected of malignancy [232].

Faecal Transplantation

An international panel of experts in faecal microbiota transplantation and stool banking recommends updating the screening of stool donors, as the risk of faecal transplantation of SARS-CoV-2 may be high [239]. Faecal microbiota transplantation is not regulated in the same way worldwide: some countries control it as a drug (USA, UK, France) and some as a tissue (Italy). In contrast, others do not provide for precise regulation (Australia) [240], and this complicates the situation, possibly leading to the spread of the infection. A more troubling concern is the unauthorised practice of homemade faecal microbiota transplantation, which is common among patients who would like to seek this treatment for reasons outside treatment protocols or clinical trials. The authors propose the screening of donors for the existence of risk factors for COVID-19: symptoms, travel history, and interaction within the previous 30 days with individuals with confirmed or suspected dangerous infections. The RT-PCR assay should be considered in all donors in endemic countries. In addition, donor stools should be processed and quarantined 30 days before use and released if symptoms do not appear in the donor. According to other authors, to ensure secure and efficient FMT to critically ill patients with persistent and refractory *C. difficile* infection, enhanced donor screening and validated stool tests for SARS-CoV-2 are needed [241]. However, faecal microbiota transplantation for these patients should be postponed until the pandemic is better under controlled conditions [242].

Covid-19 and Special Conditions

SARS-CoV-2 and Faecal-Oral Transmission

SARS-CoV-2 belongs to viruses with intermediate respiratory and faecal–oral transmission capacity. The finding of viral RNA in faeces and anal and rectal swabs, reported in several studies, suggests the possibility of faecal–oral

transmission. In the 2002–2003 SARS outbreak, SARS-CoV RNA was found in stools only after the fifth day of disease, and the proportion of stool-positive specimens steadily increased, peaking on day 11, with viral RNA still present for up to a month. It would also appear that the survival of the virus in the faeces is longer than in the respiratory tract. If this is also confirmed for SARS-CoV-2, doubts about the appropriateness of the current discharge criteria, based on the negative detection of the virus in two respiratory samples obtained 24 h apart, might arise. Table 3 reports the studies evaluating the presence of the SARS-CoV-2 in faecal specimens [60, 72–75, 78, 80, 91, 94, 96, 114, 119, 154, 155, 158, 171, 207, 210, 243–281]. No relationship has been reported between the persistence of the virus in the faeces, the severity of disease and the presence of GIS. In a recent meta-analysis, it was shown that positive faecal samples from 64% of patients remained positive for SARS-CoV-2 for an average of 12.5 days, up to a maximum of 33 days, after respiratory samples became negative for SARS-CoV-2, making faecal–oral transmission plausible [282].

This finding is different from what has been reported with MERS, where the derangement of the gut epithelium was related to the subsequent development of pneumonia and severe disease [91]. In the United States, SARS-CoV-2 was first identified in stool samples. The possible faecal–oral transmission supports the necessity of strict measures while handling the stools of coronavirus-infected patients as well as adequate disinfection of hospital wastewater.

Covid-19 and Gut Microbiota

The lung and the gut are linked by a continuous two-way dialogue, each influencing the conditions of the other. Although the connection between these two systems is not yet fully understood, we know that the gut plays a central role, both because a break in the mucosal barrier may lead to the passage of endotoxins, bacterial metabolites and hormones in the body, and because gut microbiota are in constant communication with the immune system. During acute pulmonary disease, bacteria of intestinal origin can be found in the lungs secondary to bacterial translocation. Recent research has shown that the mucosal surfaces of the gastrointestinal and respiratory tract comprise distinct microbial species, both with overt and indirect effects on host defences against viral lung infections. Moreover, antiviral immune responses caused by acute respiratory infections, such as influenza, are associated with changes in respiratory and gastrointestinal microbiota (dysbiosis), which may affect the resulting function of the immune system [283]. As mentioned above, ACE-2 is crucial for the expression in the small intestine of some amino acid transporters, and, through this, ACE-2 can regulate intestinal microbiome composition [11]. In

addition, gut microbiota could influence the action or change the expression of ACE-2.

In a recent study, Gu et al. reported a significant decrease in microbial diversity in intestinal microbiota specimens collected from COVID-19 patients in comparison with those collected from healthy controls [284]. Furthermore, they observed typical signs of dysbiosis: an increase of opportunistic pathogens and a decrease in the abundance of beneficial microbes, including microbial bacteria belonging to the Ruminococcaceae and Lachnospiraceae families. Zuo et al. showed significant alterations in the gut microbiome in COVID-19 patients [285], and demonstrated an inverse correlation between the abundance of *Faecalibacterium prausnitzii*, considered a beneficial intestinal species, and SARS-COV-2 severity. Sufficient data are not yet available on the influence of the microbiota on the clinical course of COVID-19 and the onset of GI symptoms nor on the effect of COVID-19 on the integrity of the intestinal barrier or the onset of dysbiosis.

Conclusions

We have provided an update on the prevalence of gastrointestinal symptoms and liver injury in COVID-19 patients, showing that digestive symptoms and liver injury are not uncommon in COVID-19 patients, in particular in severe ones. Children with COVID-19 seem to have a milder course of GI and liver involvement as compared to adults. Patients with GI tract involvement as initial symptoms may have a delayed diagnosis of COVID-19. Moreover, those with digestive involvement tend to progress towards severe or critical illness and an unfortunate course of the disease. More attention should be paid to early identification of these patients. SARS-CoV-2 does not increase the risk of aggravation of disease among patients with pre-existing GI or liver-related comorbidities. However, these patients might benefit from an implementation of vaccination programmes, reducing possible direct exposure to the virus and maintaining social distance and care according to guidelines possibly through telemedicine without the need for reducing/stopping immunosuppressive treatment.

Nonetheless, limitations should be reported. First of all, the central core of researches has been written in other languages, particularly in Chinese. Then, GISs seem to be underreported because some symptoms were not taken into account or they were not considered as relevant or even more not categorised. In summary, the fast-evolving literature on this new pathological entity makes the gathering of new information highly relevant, since a better understanding and up-to-date knowledge of all available information might be useful, not only for scientific purposes but also for

Table 3 Presence of SARS-CoV-2 viral RNA in specimens from GI tract

Study	Patients (n)	Sample	Positivity rate (%)
Xiao et al. [72]	73	Stool	53.4
Lo et al. [73]	10	Stool	100
To et al. [74]	15	Rectal swabs	27
Wu et al. [75]	74	Stool	55
Lin et al. [78]	65	Stool	47.7
Effenberger et al. [80]	40	Stool	30
Cheung et al. [94]	59	Stool	15.3
Chen et al. [243]	28	Anal swabs	39.28
Zhang et al. [244]	14	Stool	37.5
Chen et al. [96]	42	Stool	66.67
Zhang et al. [245]	16	Anal swabs	62.5
Tan et al. [154]	10	Stool	30
Zheng et al. [91]	96	Stool	59
Xu et al. [155]	10	Rectal swabs	80
Wu et al. [246]	132	Stool/Anal swabs	9.83/10
Wang et al. [247]	153	Stool	29
Zhao et al. [119]	401	Rectal swabs	20
Xiong et al. [158]	105	Stool	37.1
Zuo et al. [114]	15	Stool	46.7
Díaz et al. [60]	12	Stool	50
Lei et al. [248]	217	Anal swabs	21.2
Peng et al. [249]	38	Anal swabs	Disease onset: 14.9 Recovery: 29.8
Liu et al. [250]	47	Anal swabs	Morning: 2.5 Afternoon: 5
Huang et al. [251]	19	Anal swabs	21.1
Li et al. [252]	100	Anal swabs	20.2
Peng et al. [253]	9	Anal swabs	22
Novazzi et al. [254]	107	Rectal swabs	10.3
Zhang et al. [255]	61	Stool	9.83
Wu et al. [256]	91	Stool	86.8
De Ioris et al. [210]	22	Stool	68
Chen et al. [257]	97	Faecal/perianal swabs	53.61
He et al. [258]	20	Stool	55
Lu et al. [259]	73	Stool	54.8
Wang et al. [260]	69	Stool	28.99
Shi et al. [261]	99	Stool	21.2
Deng et al. [262]	61	Stool	27.9
Lei et al. [263]	7	Stool	57.1
Lu et al. [264]	28	Stool	40.74
Shang et al. [265]	564	Stool	Patients with diarrhoea: 63.9 Respiratory only: 14.3
Han et al. [266]	12	Stool	92
Xu et al. [267]	23	Stool	69.6
Han et al. [268]	206	Stool	Digestive symptoms: 73.3 Respiratory only: 14.3
Lin et al. [269]	217	Anal swabs	21.2
Wei et al. [270]	84	Stool	With diarrhoea: 69 Without diarrhoea: 17
Ling et al. [271]	66	Stool	16.7
Turriziani et al. [272]	134	Stool	19.4

Table 3 (continued)

Study	Patients (n)	Sample	Positivity rate (%)
Jiehao et al. [273]	6	Stool	83.3
Yin et al. [274]	33	Stool	24.2
COVID-19 Investigation Team [275]	10	Stool	70
Hua et al. [207]	35	Stool	91.4
Sun et al. [276]	49	Stool	44.12
Kim et al. [277]	74	Stool	10.1
Young et al. [278]	8	Stool	50
Wu et al. [171]	74	Stool	13.51
Mesoraca et al. [279]	15	Stool	33
Du et al. [280]	10	Stool	70
Zhou et al. [281]	42	Anal swabs	14.3

the practical implications so as to provide the best care for our patients.

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Declarations

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

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