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REVIEW ARTICLE

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# Gastrointestinal manifestations and possible mechanisms of COVID-19 in different periods

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a pandemic worldwide. Although COVID-19 mainly affects the respiratory system, gastrointestinal (GI) manifestations have been frequently reported in such cases, even as initial symptoms. There have been several studies on different GI manifestations in patients with mild and severe disease or in remission. In this review article we summarized different GI manifestations of COVID-19 at various disease stages and the possible mechanisms based on published literatures, as well as the significance of GI manifestations in systemic inflammatory injury.

**KEYWORDS**
COVID-19, gastrointestinal manifestation, mechanism, SARS-CoV-2, systemic inflammatory injury

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a life-threatening condition caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which was first discovered in Wuhan, Hubei Province in December 2019, and has quickly become a pandemic worldwide. COVID-19 mainly affects the respiratory system, presenting as symptoms including fever, cough and dyspnea,[1] which are the principal clinical manifestations used to recognize COVID-19 at the beginning of the pandemic. However, as the number of confirmed cases has surged, extrapulmonary manifestations, specifically gastrointestinal (GI) symptoms, have been frequently described. Some patients present with GI symptoms even without typical respiratory symptoms. Therefore, GI symptoms should not be neglected in the identification of COVID-19. Moreover, there have been several studies on different GI manifestations of patients with mild or severe COVID-19 and those in remission,[2–4] from which we may conclude that GI symptoms may have distinct features at different stages of the disease. Therefore, overall understanding of GI symptoms in COVID-19 may help identify potentially infected patients effectively and predict disease progression. In this article we summarized GI manifestations and possible mechanisms at different COVID-19 stages by reviewing the recently published literatures, trying to explain the significance of GI manifestations in the systemic inflammatory response.

## 2 | EPIDEMIOLOGY OF GI SYMPTOMS IN COVID-19

It has been proposed that SARS-CoV-2 may be transmitted to human beings by bats through other animals as the intermediate hosts. According to the recent reports that inspect the trend of confirmed cases in China, most new-onset patients used to have a history of

exposure to the seafood market, and SARS-CoV-2 can be detected in their fecal samples. Additionally, cases of familial clustering of COVID-19 characterized by having only GI symptoms have been reported,[5] indicating that the virus may also be found in the GI tract, resulted in a possible fecal–oral transmission. A possibility that the GI tract is the first site to be invaded by SARS-CoV-2 cannot be excluded. Moreover, animal experiment has shown that both intranasal or intragastric inoculation with SARS-CoV-2 can lead to infection.[6] Humans are generally susceptible to SARS-CoV-2, especially elderly individuals or those with chronic comorbidities, and are inclined to progress to the severe or critical type of disease.[3] At present, there is no evidence that whether patients with underlying GI disease have an increased incidence of COVID-19.[7]

The incubation period of the disease in patients with GI symptoms is roughly the same as that of the general population, and the infection period may be longer because SARS-CoV-2 can still be detected from the fecal sample even after GI symptoms disappear.

Until August 2021, the number of cumulative confirmed cases of COVID-19 has exceeded 200 million worldwide. Due to various sample sizes, primary end-points and definition of symptoms, together with potential bias in retrospective studies, the proportion of patients with GI manifestations differs in published studies. A meta-analysis involving 78 studies showed that up to 20% of COVID-19 cases presented with GI symptoms, mainly including diarrhea, anorexia, nausea and vomiting.[8] We arrived at roughly similar results by summarizing the recent literatures (Table 1), showing that the incidence of GI symptoms in Chinese patients with COVID-19 was approximately 11.2%-40.1%, which is slightly lower than that in United States (22.4%-74.0%) and European countries (12.5%-72.6%). One study reported that the incidence of diarrhea in 305 patients in Wuhan was 49.5%, whereas 29.4% and 15.9% patients, respectively, reported nausea and vomiting.[9] Moreover, about 16% patients manifest only GI symptoms.[10] In an American study of 164 cases approximately half reported one or more GI symptoms, which were more common among adolescents and hospitalized patients than non-hospitalized adult individuals.[11] In this study, diarrhea was the most frequent (38%) GI symptom, and patients with three or more GI symptoms accounted for 10%, while these manifestations were the only clinical performance in four patients. Given the rapidly evolving nature of the COVID-19 pandemic, the variants of SARS-CoV-2 are continuously changing and its GI characteristics are also dynamic, which partly explains the differences among studies.[12]

## 3 | GI MANIFESTATIONS AND POTENTIAL MECHANISMS IN COVID-19 AT DIFFERENT STAGES

GI symptoms can occur at any stage of COVID-19, not only as the initial symptoms, but may emerge during the entire course of the disease as well. However, GI performance may differ during different disease stages.

### 3.1 | GI symptoms at disease onset

Time length from the onset of the disease to the appearance of GI symptoms in COVID-19 varies among studies. In some patients GI symptoms appear initially prior to or even without respiratory symptoms or fever, although in most patients GI manifestations occur within 3-10 days of illness.[13] Most patients present with diarrhea, nausea, and vomiting, either alone or simultaneously. Diarrhea and loss of appetite are the two most common symptoms and may be related to the severity of the disease.[14–16] The proportion of patients with COVID-19 having diarrhea has been reported to be 3.7%-12.4%.[17,18] Most patients had mild symptoms that last for 1-7 days, such as watery yellow stool without mucus, pus or blood, often in the absence of obvious dehydration. Stool routine test is usually normal.[19–21] Clinicians should be alerted when diarrhea occurs so as to diagnose COVID-19 at an early stage and to control possible fecal–oral transmission. Diarrhea may also serve as an indicator of poor prognosis in these patients due to their increased risks of secondary infection and multisystem involvement.[14,15,22,23] In addition, almost half these patients have taste disorder as a coexisting or sole clinical manifestation.[24,25] The possible mechanism may be that angiotensin converting enzyme 2 (ACE2), one of the receptors for SARS-CoV-2, distributes in not only pulmonary alveolar cells but also GI epithelial cells, including oral mucosa.[26,27] The spike protein on the surface of SARS-CoV-2 may directly damage GI epithelial cells by binding to ACE2, causing loss of the normal function of ACE2, leading to disturbed intestinal amino acid metabolism and gut dysbiosis, and eventually induces intestinal inflammation and immune disorders.[23,28]

Although abdominal pain in COVID-19 is relatively rare, it must always be carefully differentiated from acute abdominal diseases, especially when it is not accompanied by any other manifestation except for GI symptoms. Several COVID-19 cases have been reported to experience abdominal pain of different degree at disease onset, either diffuse or limited, with or without diarrhea and vomiting.[29–31] Some of the patients present with abdominal tenderness and tension, although there are no signs of peritonitis or appendicitis on their abdominal computed tomography (CT) scan. A real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 nucleic acid detection may sometimes be negative, and does not always conform to the patient's clinical manifestations. Therefore, there is a need for repeated SARS-CoV-2 nucleic acid detections or to make diagnosis until respiratory symptoms and/or characteristic chest CT scan features appear.[18,32]

Viral infections usually lead to a prodrome of non-specific GI symptoms, which makes the diagnosis of GI involvement in COVID-19 challenging at the early stage. However, given its acute and severe onset, the prodromal symptoms are usually mild.[33] In such cases, an epidemiological investigation needs to be considered. For those who are suspected to have COVID-19, SARS-CoV-2 testing and radiological examination are urgently needed. A SARS-CoV-2 fecal test may help differentiate the prodrome and GI involvement as well. In terms of their duration and severity, prodromal symptoms tend to be transient and self-limiting, while in most COVID-19 cases GI symptoms

**TABLE 1** Characteristics of included studies about COVID-19 with gastrointestinal symptoms

| First author (publication year) | Country or region | Manuscript type | Study period (2020) | Patients (n) | Age, y (mean ± SD or median [IQR]) | Male sex, % or n (%) | Patients with GI symptoms, n (%) | Diarrhea, % or n (%) | Nausea n (%) | Vomiting n (%) | Abdominal pain n (%) | Anorexia n (%) | Duration of GI symptoms (d) Mean ± SD or median (IQR) | Follow-up (d) | Time end-point | Hospitalization, n (%) | ICU stay, n (%) | Death, % or n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Papa[86] (2020) | Italy | Case-control | 15/3-14/4 | 34* 71# | 71 (64-82)* 74 (59.5-81)# | 22* 43# | 3* 44# | – | – | – | – | – | – | – | Discharge | Case-control | 15/3-14/4 | 34* 71# |
| Aghemo[87] (2020) | Italy | Retrospective | 22/2/-30/3 | 292 | 65 ± 14.1 | 199 (68.2) | 69/245 (28.2) | 69/255 (27.1) | – | 11/274 (4.0) | – | – | – | – | Discharge, death or to ICU | Retrospective | 22/2/-30/3 | 292 |
| Ahmad[88] (2021) | Pakistan | Retrospective | 16/3-14/4 | 194 | 34 (27-48) | 157 (80.9) | 20 (10.31) | – | 8 (4.12) | – | – | 5 (2.58) | – | – | 2020-4-14 | Retrospective | 16/3-14/4 | 194 |
| An[89] (2020) | China | Retrospective | 16/1-30/3 | 205 | 54 (22-77) | 122 (59.5) | 79 (38.5) | 20 (9.8) | 12 (5.9) | 6 (2.9) | 4 (2.0) | 59 (28.8) | – | – | Discharge | Retrospective | 16/1-30/3 | 205 |
| Aumpan[90] (2020) | Thailand | Retrospective | 1/1-30/4 | 40 (30&; 10†) | 30.5 ± 9.2 | 18 (45) | 12 (30) | 15 (2/30& 4/10†) | 5 (0/30& 2/10†) | | 5 (1/30&, 1/10†) | 17.5 (5/30&; 2/10†) | – | – | Discharge | Retrospective | 1/1-30/4 | 40 (30&; 10†) |
| Bishehsari[91] (2021) | USA | Retrospective | 12/3-3/4 | 921 | 47.6 (16.0)€ 52.4 (17.1)‡ | 409 (44.4) | 206 (22.4) | 144 (15.6) | 127 (13.8) | | 52 (5.6) | – | – | – | – | Retrospective | 12/3-3/4 | 921 |
| Burke[11] (2020) | USA | Retrospective | 19/1-3/6 | 164 | 50 | 56 | 97 (59) | 38 | – | 13 | – | – | – | – | – | Retrospective | 19/1-3/6 | 164 |
| Cao[92] (2020) | China | Retrospective | – | 63‡; 94€ | 51.9 ± 14.9‡, 47.5 ± 14.0€ | 24 (38.1)‡; 50 (53.2)€ | 63 (40.1) | 25/63 (39.7) | 21/63 (33.3) | – | – | 47/63 (74.6) | 10.7 ± 4.5‡, 9.1 ± 5.2€ | 16.0 ± 4.9 | Discharge | Retrospective | – | 63‡; 94€ |
| Carvalho-Schneider[93] (2021) | France | Retrospective | 17/3-3/6 | 150a; 150b; 130c | 49 ± 15 | 66 (44) | 48 (33.1)a 26 (17.3)b 15 (11.5)c | 44 (29.3)a, 13 (8.7)b 5 (3.8)c | – | – | – | – | – | 60 | – | Retrospective | 17/3-3/6 | 150a; 150b; 130c |
| Chen[94] (2020) | USA | Case-control | 9/3-15/4 | 101* 239# | 48.3 ± 14.7*; 46.3 ± 15.6# | 41 (41)*; 55 (23)# | 75 (74)*; 126 (53)# | 51 (50)*; 72 (30)# | 30 (30)*; 62 (26)# | 14 (14)*; 29 (12)# | 26 (26)*; 46 (19)# | 54 (53)*; 63 (26)# | – | 4 (4)*; 4 (5)# | Prevalence of GI symptoms | Case-control | 9/3-15/4 | 101* 239# |
| Chen[95] (2020) | China | Retrospective | 25/1-21/3 | 1077 | 59.0 (47.0-68.0) | 550 (49.4) | 359 (33.3) | 208 (57.9) | 71 (19.8) | | 38 (10.6) | – | – | – | Discharge | Retrospective | 25/1-21/3 | 1077 |
| Chen[18] (2020) | China | Retrospective | 20/1-9/2 | 42 | 51 (42.8-62) | 15 (35.7) | 8 (19.1) | 7 (16.7) | 4 (9.5) | 3 (7.1) | 5 (11.9) | – | – | – | Discharge | Retrospective | 20/1-9/2 | 42 |
| Cholankeril[96] (2020) | USA | Retrospective | 9/3-7/4 | 207 | 49 (34-65) | 104 (50.2) | 70 (34.5) | 22 (10.8) | – | – | 14 (7.1) | – | 1 (0-4) | – | At presentation | Retrospective | 9/3-7/4 | 207 |
| Deng[97] (2020) | China | Retrospective | 24/1-10/3 | 61d | 54.8 (12.9) | 25 (41) | – | 3 (4.9) | – | – | – | – | – | 10 (7-13) | – | Retrospective | 24/1-10/3 | 61d |
| Duque[98] (2021) | Portugal | Retrospective | Before 1/4 | 2031 | 50 ± 19.8 | 973 (47) | – | 290 (14.3) | 202 (10) | | 134 (6.6) | – | – | – | – | Retrospective | Before 1/4 | 2031 |
| Elmunzer[99] (2020) | North America | Retrospective | 15/4-5/6 | 1992 | 51 (41-68) | 1128 (56.6) | 1052 (53) | 34 | 27 | 16 | 11 | – | – | – | June 5, 2020 | Retrospective | 15/4-5/6 | 1992 |
| Fallouh[100] (2021) | USA | Retrospective | 24/2-21/5 | 382 | 62.2 ± 16.8 | 203 (53.1) | 202 (52.9) | 28.8 | 22 | 17 | 11.8 | 24.9 | – | – | – | Retrospective | 24/2-21/5 | 382 |
| Ferm[101] (2020) | USA | Retrospective | 14/3-1/4 | 892 | 59 (47-72) | 534 (59.9) | 219 (24.6) | 177 (19.8) | 148 (16.6) | 91 (10.2) | 70 (7.8) | 105 (11.8) | 4 (3-7) | – | April 1, 2020 | Retrospective | 14/3-1/4 | 892 |

(Continues)

**TABLE 1** (Continued)

| First author (publication year) | Country or region | Manuscript type | Study period (2020) | Patients (n) | Age, y (mean ± SD or median [IQR]) | Male sex, % or n (%) | Patients with GI symptoms, n (%) | Diarrhea, % or n (%) | Nausea n (%) | Vomiting n (%) | Abdominal pain n (%) | Anorexia n (%) | Duration of GI symptoms (d) Mean ± SD or median (IQR) | Follow-up (d) | Time end-point | Hospitalization, n (%) | ICU stay, n (%) | Death, % or n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Graham[102] (2021) | UK | Retrospective | 23/2-23/4 | 478 | 70 (23) | 279 (58.4) | 161 (33.7) | 17.4 | 7.5 | 13 | 7.3 | 13.8 | – | – | – | Retrospective | 23/2-23/4 | 478 |
| Greco[103] (2021) | Italy | Retrospective | Mar-Jul | 495 | 70 ± 17 | 23 (37.1) | 62 (12.5) | – | – | – | – | – | – | – | 100 days | Retrospective | Mar-Jul | 495 |
| Guerra[104] (2020) | Spain | Cross-sectional | 24/4-27/5 | 82[e] | 46 ± 14 | 38 (46.3) | – | 35 (42.7) | – | – | 12 (14.6) | – | – | – | May 27, 2020 | Cross-sectional | 24/4-27/5 | 82[e] |
| Kim[105] (2021) | Korea | Retrospective | 19/2-30/4 | 5253 | – | 1796 (40.4)[&] 380 (47.0)† | – | 375 (8.4)[&] 87 (10.8)[†] | 178(4.0)[&] 62 (7.7)[†] | | – | – | – | – | – | Retrospective | 19/2-30/4 | 5253 |
| Lapostolle[17] (2020) | France | Prospective | 24/3-6/4 | 1487 | 44 (32-57) | 700 (47) | – | 352 (23.7) | 288 (19.4) | 168 (11.3) | – | 305 (20.5) | – | 0.5 | 48h | Prospective | 24/3-6/4 | 1487 |
| Laszkowska[106] (2020) | USA | Retrospective | 11/3-28/4 | 2804 | 63.4 ± 18.4 | 1565 (56) | 1084 (38.7) | 657 (23.4) | 648 (23.2) | – | 334 (11.9) | – | 13.8 | – | Discharge | Retrospective | 11/3-28/4 | 2804 |
| Leal[107] (2021) | Portugal | Retrospective | Mar-Apr | 201 | 71 (26) | 113 (56.2) | 60 (29.9) | 36 (17.9) | 14 (7) | 22 (10.9) | 10 (5) | 60 (29.9) | 9 (12) | – | – | Retrospective | Mar-Apr | 201 |
| Luo[10] (2021) | China | Retrospective | 10/1-29/2 | 183[f]; 1228[g] | 53.8[f]; 56.2[g] | 55.7[f]; 64.5[g] | – | 68 (37.1)[f] | 134 (73.2)[f] | 119 (65.0)[f] | 65 (35.5)[f] | 180 (98.3)[f] | – | – | – | Retrospective | 10/1-29/2 | 183[f]; 1228[g] |
| Mario[108] (2020) | Spain | Retrospective-prospective | 11/3-21/4 | 76 | 45.8 ± 11.4 | 23 (30.3) | 45 (59.2) | 31 (40.8) | 17 (22.4) | 7 (9.2) | 21 (27.6) | 12 (15.8) | – | Up to 2020/04/21 | First negative PCR | Retrospective-prospective | 11/3-21/4 | 76 |
| Martin[46] (2020) | USA | Case-control | 4-23/4 | 41[h] 82[i] | 68.7 ± 15.1[h], 67.6 ± 14.3[i] | 27 (66)[h], 54 (66)[i] | – | 11 (27)[h], 27 (33)[i] | – | – | 1 (2)[h] 8 (10)[i] | 7 (17)[h] 26 (32)[i] | – | – | Discharge | Case-control | 4-23/4 | 41[h] 82[i] |
| Mokarram[109] (2021) | Italy | Retrospective | Mar-Sept | 91 | 51 | 56 (51) | – | 29 (31.8) | 39 (42.8) | 24 (26.3) | 11 (12) | 40 (43.9) | – | – | – | Retrospective | Mar-Sept | 91 |
| O'Keefe[110] (2021) | USA | Retrospective | 24/3-26/5 | 337 (223[&]; 106[¶]; 8[†]) | 45.7 (44.1-47.2) | 108 (32) | – | 62 (28)[&] 48 (45)[¶] 2 (25)[†] | 32 (15)[&] 45 (42)[¶], 5 (63)[†] | – | 27 (12)[&] 25 (24)[¶] 1 (13)[†] | – | 6 (5-8)[j] 7 (6-8)[k], 4 (2-6)[l] | 30 | – | Retrospective | 24/3-26/5 | 337 (223[&]; 106[¶]; 8[†]) |
| Park[111] (2020) | Korea | Prospective | 4-24/4 | 46[&] | 26 (18-57) | 21 (45.6) | 16 (34.7) | 7 (15.2) | 1 (2.1) | 0 | 5 (10.8) | 5 (10.8) | – | 52 (39-61) | 2020/4/24 | Prospective | 4-24/4 | 46[&] |
| Ramachandran[112] (2020) | USA | Case-control | 18-31/3 | 31[‡] 119[€] | 57.6 ± 17.2[‡], 63.3 ± 14.6[€] | 19 (62.3)[‡] 64 (53.8)[€] | – | 15 (48.4)[‡] | – | – | – | – | – | – | Discharge | Case-control | 18-31/3 | 31[‡] 119[€] |
| Remes-Troche[113] (2020) | Mexico | Retrospective | 1/4-5/5 | 112 | 43.72 ± 15 | 81 (72.3) | 23 (20.5) | 20 (17.8) | – | 8 (7.1) | 11 (9.8) | – | – | – | May 5, 2020 | Retrospective | 1/4-5/5 | 112 |
| Renelus[114] (2020) | USA | Retrospective | 10/3-13/4 | 734 | 66.1 ± 15.6 | 379 (51.6) | 231 (31.5) | 149 (20.3) | 109 (14.9) | 62 (8.5) | 68 (9.3) | – | – | | 30/4 2020 | Retrospective | 10/3-13/4 | 734 |
| Saeed[115] (2020) | Norway | Retrospective | 17/3-1/4 | 76 (9*) | 48 (31-81) | – | 76 (100) | 1 (11.1)* | 8 (88.9)* | 5 (55.6)* | 76 (100) | – | – | 14.1 | – | Retrospective | 17/3-1/4 | 76 (9*) |
| Schettino[116] (2020) | Italy | Prospective cohort | 23/3-5/4 | 190 | 64.6 ± 15.4 | 127 (66.8) | 138 (72.6) | 72 (37.9) | 32 (20) | 19 (10) | 6 (3.1) | 97 (51) | – | – | Discharge or death | Prospective cohort | 23/3-5/4 | 190 |

**TABLE 1** (Continued)

| First author (publication year) | Country or region | Manuscript type | Study period (2020) | Patients (n) | Age, y (mean ± SD or median [IQR]) | Male sex, % or n (%) | Patients with GI symptoms, n (%) | Diarrhea, % or n (%) | Nausea n (%) | Vomiting n (%) | Abdominal pain n (%) | Anorexia n (%) | Duration of GI symptoms (d) Mean ± SD or median (IQR) | Follow-up (d) | Time end-point | Hospitalization, n (%) | ICU stay, n (%) | Death, % or n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shang[13] (2020) | China | Retrospective | 20/1-29/2 | 157[j] | 59 (43-67) | 75 (47.8) | — | 157 (100) | 42 (26.8) | 32 (10.4) | 8 (5.1) | — | 4.5±1.6 | — | Discharge | Retrospective | 20/1-29/2 | 157[j] |
| Sierpinski[117] (2020) | Poland | Cross-sectional | 17-18/4 | 1942 | 50 | 773 (39.8) | 53.60 | 470 (24.2) | — | — | — | 912 (47) | — | — | — | Cross-sectional | 17-18/4 | 1942 |
| Sulaiman[118] (2020) | Iraq | Retrospective | 2/3-1/5 | 140 | 45.0 ± 16.8 | 100 (71.4) | 78 (55.7) 33 (23.6)[f] | 41 (29.3) | — | 31 (22.1) | 42 (30) | 40 (28.6) | — | — | Discharge | Retrospective | 2/3-1/5 | 140 |
| Sun[119] (2021) | China | Retrospective | 20/2-31/3 | 932 (880[&,¶]; 52[†]) | 58 (48-67) | 375 (40.2) | — | 73 (8.3)[&,¶], 7 (13.5)[†] | 31 (3.5)[&,¶]; 1 (1.9)[†] | | — | 178 (20.2)[&,¶]; 25 (48.1)[†] | 5 (4-12) | 90 | — | Retrospective | 20/2-31/3 | 932 (880[&,¶]; 52[†]) |
| Taziki Balajelini[120] (2021) | Iran | Retrospective | Feb-Jul | 599 | 38.3 ± 13.6 | 286 (47.8) | 251 (41.9) | 151 (25.2) | 123 (20.5) | 77 (12.9) | 159 (26.5) | — | — | — | — | Retrospective | Feb-Jul | 599 |
| Tsibouris[121] (2020) | Greece | Retrospective | 6/4-6/5 | 61 | 70 (55-83) | 34 (55.7) | — | 11/61 | 4/61 | | 2/61 | — | — | — | May 6, 2020 | Retrospective | 6/4-6/5 | 61 |
| Xiao[122] (2020) | China | Descriptive | 10/1-17/2 | 90 | 61.0 (48.3-69.0) | 51 (57) | — | 90 (100) | 22 (24) | 15 (17) | 6 (7) | 22 (24) | 5 (2.0-9.3) | — | Discharge | Descriptive | 10/1-17/2 | 90 |
| Xu[123] (2020) | China | Retrospective | 26/1-20/3 | 48 | 41 (18-90) | 25 (52.1) | 12 (25) | 3 | 1 | — | — | 3 | — | — | — | Retrospective | 26/1-20/3 | 48 |
| Yang[124] (2020) | China | Retrospective | 2-13/2 | 50 (23[‡]; 27[ε]) | 44.6 ± 2.8[‡] 42.5 ± 3.3[ε] | 13 (56.5)[‡] 15 (55.6)[ε] | 23 (100)[‡] | — | — | — | — | — | 12.13 ± 2.44[‡] | — | Discharge | Retrospective | 2-13/2 | 50 (23[‡]; 27[ε]) |
| Yoshida[125] (2020) | USA | Retrospective | 27/2-5/7 | 776 | 60.5 (16.1) | 365 (47.3) | 269 (36.6) | 187 (25.4) | 154 (21) | | 65 (8.8) | — | — | — | — | Retrospective | 27/2-5/7 | 776 |
| Zhang[126] (2020) | China | Retrospective | — | 505 | 51.2±17.2 | 228 (45.1) | 164 (32.5) | 62/164 | 27/164 | 13/164 | 17/164 | 93/164 | — | — | — | Retrospective | — | 505 |
| Zhang[69] (2020) | China | Retrospective | 20/1-29/2 | 409 (307[m]; 102[n]) | 65 (range 28-87) | 162 (52.8)[m] 72(70.6)[n] | — | 61 (19.9)[m], 30 (29.4)[n] | 38 (12.4)[m], 12 (11.8)[n] | 33 (12.4)[m], deceased: 9 (8.8)[n] | 23 (7.5)[m], 5 (4.9) | — | 4.2 ± 1.5[m], 4.9 ± 1.5[n] | — | Discharge or death | Retrospective | 20/1-29/2 | 409 (307[m]; 102[n]) |
| Zhang[3] (2020) | China | Retrospective | 17/1-12/2 | 788 (52[&]; 658[¶]; 61[†]; 17[**]) | 37.5 (19.3-45.8)[&] 45.0 (35.0-55.0)[¶] 55.0 (44.0-62.0)[†], 70.0 (55.0-73.0)[**] | 26 (50.0)[&] 329 (50.0)[¶] 39(63.9)[†] 13(76.5)[**] | 7(13.5)[&], 63(9.6)[¶], 12(19.7)[†], 6(35.3)[**] | — | — | — | — | — | — | — | Discharge | Retrospective | 17/1-12/2 | 788 (52[&]; 658[¶]; 61[†]; 17[**]) |
| Zheng[127] (2020) | China | Retrospective | 5/1-9/3 | 1320 (192[‡]; 1128[€]) | 50 (38-56)[‡] 51 (41-58)[€] | 90(46.9)[‡] 489(43.4)[€] | 192 (100)[‡] 0[€] | 107 (55.7)[‡] | — | — | 11 (5.7)[‡] | 62 (32.3)[‡] | — | — | Discharge | Retrospective | 5/1-9/3 | 1320 (192[‡]; 1128[€]) |

(Continues)

**TABLE 1** (Continued)

| First author (publication year) | Country or region | Manuscript type | Study period (2020) | Patients (n) | Age, y (mean ± SD or median [IQR]) | Male sex, % or n (%) | Patients with GI symptoms, n (%) | Diarrhea, % or n (%) | Nausea n (%) | Vomiting n (%) | Abdominal pain n (%) | Anorexia n (%) | Duration of GI symptoms (d) Mean ± SD or median (IQR) | Follow-up (d) | Time end-point | Hospitalization, n (%) | ICU stay, n (%) | Death, % or n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhu[128] (2020) | China | Retrospective | Before Feb 4, | 90[d] | 52 (37.8-59) | 32 (32.7) | — | 8 (8.2)[d] | — | — | — | — | — | 14 | 2 weeks | Retrospective | Before Feb 4, | 90[d] |

*COVID-19 cases group.
#Control group without COVID-19.
&Mild COVID-19.
¶Moderate COVID-19.
†Severe COVID-19.
**Critical COVID-19.
‡COVID-19 with GI symptoms.
[c]COVID-19 without GI symptoms.
[a]Initial onset of COVID-19.
[b]30 days after initial onset of COVID-19.
[c]60 days after initial onset of COVID-19.
[d]COVID-19 patients in recovery stage.
[e]COVID-19 with inflammatory bowel disease.
[f]COVID-19 patients with GI symptom only.
[g]COVID-19 patients with respiratory symptom.
[h]COVID-19 patients with GIB.
[i]COVID-19 patients without GIB.
[j]COVID-19 patients with diarrhea.
[k]COVID-19 patients with nausea.
[l]COVID-19 patients with abdominal pain.
[m]Survived COVID-19 patients.
[n]Deteriorated COVID-19 patients.
Abbreviations: —, not available; GI, gastrointestinal; GIB, gastrointestinal bleeding; ICU, intensive care unit.

persist for about 10 days and may be aggravated with respiratory deterioration. Moreover, other factors such as the patient's prior or current medication and history of GI comorbidities should not be neglected. Microbial agents may affect the gut immune response and gut microbiota and in turn the clearance of the virus from the gut.[34] Therefore, the American Gastroenterological Association Institute has suggested that for patients with COVID-19 who are under medication, treatment-related adverse GI effects should be considered and evaluated.[35]

### 3.2 | GI symptoms at disease progression

The appearance and aggravation of GI symptoms can be used to indicate disease progression. GI symptoms are more commonly seen in severe and critically ill patients compared with those with mild disease, and is related to an increased risk of adverse outcomes (odds ratio [OR] 1.9, $P = 0.047$).[3,19] In addition to non-specific GI symptoms, COVID-19 mainly leads to a variety of GI-related complications during disease progression, including dysfuction of digestion and absorption, GI motility disorder, acute intestinal ischemia, GI bleeding, *Clostridium difficile* (*C. difficile*) infection and pancreatic injury.

Dysfunction of digestion and absorption, which mainly manifests as intolerance of enteral nutrition and worsening of diarrhea, results in the lack of nutrients and malnutrition, thus a deterioration of the overall condition. Nutrition plays a vital role in the recovery process of these patients. Monitoring of stool weight can be used to assess the nutritional status of patients with severe disease, which can also be regarded as an indicator for their tolerance to enteral nutrition.[36]

Half of the critically ill patients are reported to have severe GI motility disorder.[37] Gastric retention is common, as enteral nutrition is usually given to these patients through a nasogastric tube. Some patients have typical manifestations of intestinal obstruction that may develop into intestinal necrosis and require emergency surgery. Local or extensive ischemia may be related to factors such as small intestinal vascular thrombosis, enteric nerve dysfunction caused by viral infection, and systemic metabolic and acid-base imbalance.[38]

Many studies have reported that patients with COVID-19 may have acute abdominal pain and bloody stool that might conform to the diagnosis of ischemic bowel disease. One report[39] confirmed the presence of non-occlusive mesenteric ischemia on abdominal CT scan in these patients. This can further be confirmed histopathologically when the necrotic bowel has to be surgically removed.[40,41] COVID-19-related hypercoagulability status has been confirmed to be associated with a poor prognosis.[42,43] Based on this hypercoagulable tendency coupled with the induction of systemic inflammatory response and cytokine storm, disease progression is often difficult to control and almost always related to death.

GI bleeding can also be observed in patients with COVID-19, with a prevalence of approximately 3.04%.[44,45] The common reasons include peptic ulcer, esophagitis and rectal ulcer.[46] Possible mechanisms include GI mucosal damage caused by viral invasion, long-term hypoxemia, and multiorgan failure with coagulation disorders. In addition, use of glucocorticoids, oral nonsteroidal anti-inflammatory drugs or anticoagulants, which are usually used to treat comorbidities, can cause GI bleeding as well.[47]

Destruction of the intestinal mucosal barrier by SARS-CoV-2 increases the risk of co-infection with other pathogens. There are few reports of positive bacterial culture in fecal sample of patients with COVID-19, but most hospitals use antibiotics empirically to lower a possibility of gut-derived bacteremia. However, due to the widespread use of antibiotics, the incidence of *C. difficile* infection has been gradually increasing. Data from the Detroit Medical Center in the United States[22] shows that from March to April 2020 the incidence of *C. difficile* infection is 3.6/10 000 patient-days, which is higher than that during January and February (3.32/10 000 patient-days). *C. difficile* infection can appear at the same time as respiratory symptoms present or within 1 week after COVID-19 is diagnosed. Patients with *C. difficile* infection are more severely ill and have a higher mortality rate compared with those without *C. difficile* infection. Similarly, COVID-19 patients can infect with cytomegalovirus, which is thought to be related to the function of T lymphocytes and elevated interleukin (IL)-6 levels.[48,49]

Pancreatic involvement has been reported in some patients with COVID-19, including pancreatic enzyme changes, acute pancreatitis and subsequent metabolic disorders.[50–52] One systematic review[53] revealed that 11.7% of patients presented with hyperlipasemia, ranging from an upper limit of around 50-60 U/L to a lipase level of over 300 U/L. Unlike the obvious pancreatic impairment in acute pancreatitis, hyperlipasemia in patients with COVID-19 may be occult with unclear etiology. However, hyperlipasemia may be used to recognize disease progression at the early stage and serum lipase levels may be a marker of disease severity. High serum lipase levels usually predict pancreatic damage and are significantly associated with an increased need for intensive care unit (ICU) admission.[54,55] The potential mechanisms may include a high ACE2 expression in the pancreas, which suggests that SARS-CoV-2 can also attack the pancreas, leading to direct pancreatic injury and inflammatory response.[53,56] Additionally, secondary damage from systematic cytokine storm and drug-related pancreatic injury may be involved as well.[57,58]

Other GI complications in COVID-19, such as bowel obstruction or perforation, have been rarely reported. Possible causes may be direct bowel damage by SARS-CoV-2 infection, and local ischemia or necrosis due to the inflammatory response and hypercoagulable state.[59,60]

Compared with patients with severe disease, critically ill patients with COVID-19 are at an increased risk of serious complications.[61] GI dysfunction is closely related to poor prognosis.[62,63] The potential mechanism mainly involves direct viral invasion through ACE2 and the aggravation of systemic inflammation. The involvement of the digestive system is most likely due to ACE2 in the GI tract. One study[64] has revealed that plasma ACE2 activity is elevated in patients after COVID-19 infection and is associated with its severe form. During disease progression, GI damage caused by lung injury and systematic inflammation play a dominant role. The gut–lung axis may impair

pulmonary and GI functions through microbial metabolites and an abnormal immune response. Levels of lung-derived abnormal cytokines and T cells are elevated after a viral infection, which promotes interaction with receptors in the GI tract and activates intense responses in the gut, leading to intestinal immune damage and disturbance of intestinal flora.[65] In return, bacterial imbalance and inflammatory molecules from the gut can act on the pulmonary alveolar cells through the bloodstream, further aggravating the inflammation.[66,67] Several studies have found that levels of inflammatory indicators generally arise at 1-2 weeks after the disease onset and gradually increase along with disease progression.[68,69] Patients with diarrhea have much higher peripheral levels of IL-6, IL-10 and tumor necrosis factor (TNF)-α than those without diarrhea.[69]

### 3.3 | GI symptoms at treatment intervention and remission

The main therapeutic interventions for COVID-19 are symptomatic support, and antiviral and anti-inflammatory therapies. Non-specific GI symptoms such as diarrhea and abdominal pain in patients with mild disease are often self-limiting.[5,19] In the remission stage, symptoms and levels of inflammatory indicators may gradually improve within a few days, but the detection of viral nucleic acid by real-time RT-PCR may remain positive until up to 1 month after the disappearance of symptoms. The fecal nucleic acid detection of SARS-CoV-2 may convert to negative results later than that of a nasopharyngeal swab, perhaps owing to the aggregation and colonization of the virus in the GI tract.[30,70] Early administration of enteric nutrition, use of glucocorticoids and human γ-globulin can be considered for severe and critically ill patients.[71,72] Recent evidence suggests that glucocorticoids can reduce IL-6 levels by activating ACE2 and counteract the systemic inflammatory response to reduce lung injury in patients with severe COVID-19.[73,74] However, whether use of glucocorticoids can improve GI function needs further investigation. Other treatments such as interferon, lopinavir and ritonavir, antibacterial drugs and intestinal microecological modulators have been widely used in clinical practice, without evidence from rigorous large-scale clinical trials.[75] Specific antibodies are not produced after recovery from COVID-19. Four weeks after their discharge, 15.4% of the patients were negative for SARS-CoV-2 immunoglobulin G (IgG) and IgM antibodies, while one case has been reinfected in the convalescent phase.[76]

## 4 | IMPACTS OF COVID-19 ON PATIENTS WITH DIGESTIVE COMORBIDITIES

Of COVID-19 cases with pre-existing chronic GI disorders, cancer and inflammatory bowel disease (IBD) are the most commonly studied. Several studies have indicated that compared with those without GI malignancies, patients with GI malignancies are more susceptible to COVID-19 and were more likely to manifest in a severe form, which may result from higher expressions of *ACE2* and *TMPRSS2*.[77,78] Although patients with IBD seem to have no increased risk of contracting COVID-19, medications for IBD may affect the disease course. Roy et al have reported that ulcerative colitis and the use of 5-aminosalicylates are related to an increased mortality in COVID-19.[79] Anti-TNF therapy may attenuate serological responses to a SARS-CoV-2 vaccination.[80]

Endoscopic assessment is generally performed for the diagnosis and treatment in patients with GI symptoms. Unfortunately, during the COVID-19 pandemic the performance of endoscopic procedures has been restricted and delayed because of the excess burden on respiratory function and an increased risk of viral transmission during the procedures.[81] To resolve this dilemma, the need for endoscopic procedure should be fully evaluated and a risk stratification of GI disease and COVID-19 should be performed.[82,83] For example, it is inevitable that patients with acute or recurrent persistent GI bleeding shall undergo endoscopy. Thus, intra- or post-procedure risk management should be further implemented as the statement of the European Society of Gastrointestinal Endoscopy and the European Society of Gastroenterology and Endoscopy Nurses and Associates.[82] Moreover, some invasive procedures can be considered as a safe alterative for disease screening to minimize the unnecessary exposure to SARS-CoV-2 caused by fecal and radiological tests or capsule endoscopy in both patients and healthcare staff.[84,85]

## 5 | SUMMARY

GI manifestations can be used as an auxiliary index to assess disease severity and predict patient outcome in COVID-19, in combination with other vital signs and supplementary examinations. There are, however, limitations about the relationship between GI manifestations and COVID-19. There are no strict standards to detect these manifestations and it is sometimes difficult to distinguish GI manifestations at different stages of the disease because of specific individual conditions and an overlapping nature of the symptoms. Different GI symptoms are valuable in offering some clues to assess the severity of COVID-19. The combination of GI manifestations with pulmonary or systematic conditions is extremely essential for the assessment of COVID-19 severity. Besides, as the lack of strong specificity, many potential factors are required to be summarized as well, including GI comorbidities, medications, mental status, and functional GI diseases. The long-term impact of COVID-19 on the GI tract needs to be evaluated during the follow-up period. Further studies are needed to thoroughly identify the role of GI manifestations in the pathogenesis or progression of COVID-19 and to treat patients with COVID-19 in this worldwide pandemic.

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## CONFLICT OF INTEREST

The authors have no conflict of interest.

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