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# PREVALENCE AND IMPACT OF GASTROINTESTINAL MANIFESTATIONS IN COVID-19 PATIENTS: A SYSTEMATIC REVIEW


## Authors

Bassam Hossain, Shoreh Qazi, Sumair Ahmad, Atif Saleem, Amanke Oranu, and Fahad Malik

# Prevalence and Impact of Gastrointestinal Manifestations in COVID-19 Patients: A Systematic Review

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## Abstract

*Background and objective*: **The aim of this study is to systematically analyze and summarize the implications of COVID-19 on the digestive system by quantitatively evaluating the prevalence of gastrointestinal symptoms such as nausea, vomiting, abdominal pain, constipation, diarrhea, anorexia. reported in COVID-19 cases. We simultaneously investigated other variables to determine the association of such symptoms in COVID-19 patients which can potentially influence the disease prognosis and outcome. This systematic review presents an updated literature on the issue as it requires more scientific discussion in order to better inform the medical community and authorities so that appropriate measures can be taken to control the virus outbreak.**

*Methods*: **MEDLINE database was searched to identify relevant articles. Data was analyzed and synthesized from the 16 eligible studies which exclusively reported GI symptoms in COVID-19 patients along with the disease prognosis. A meta-analysis of studies having adequate information regarding the prevalence of specific GI symptoms in association with other relevant independent variables was performed.**

*Results*: **From the search strategy, we identified 16 articles which fit our eligibility criteria comprising of 10 cross-sectional studies, 2 cohort study, 1 RCT and 3 observational studies. From these pooled studies, 6 articles exclusively talked about COVID-19 patients in which GI symptoms were reported and adequately discussed. In a total of 3646 patients, GI symptoms were documented in (16.2%−10.1%) patients. The most prevalent GI symptom was diarrhea (47%) but the most common clinical manifestation reported was fever (77.4%). Among the adult patients, hypertension (11.6%) was the most frequently reported comorbidity. Presence of viral RNA in stool sample was noted in 16.7% patients with GI symptom. In patients who complained of having GI symptoms, an abnormal liver function was largely observed, with an elevated ALT level in (10.9%) and an elevated AST in (8.8%) of the patients. Evidence of vertical transmission (14.2%) was reported in one study which highlights the extent and mode of viral transmission. It was observed that a great majority of the patients in the 6 studies reporting specifically on patients with GI symptoms were on antiviral therapy (68.6%) as the standard disease management protocol but the eventual disease outcome as in this case died (8.4%), discharged (45.6%) was not linked to just one therapeutic factor but other indicators of disease severity such as positive chest CT findings (87.82%) have led to a poor disease prognosis which was noted in (28.9%) severe patients with GI symptoms compared to (71.1%) non-severe COVID-19 patients with GI symptom.**

*Conclusion*: **Presence of GI symptoms in COVID-19 patients has shown to have a positive association with the poor disease prognosis likely as a result of direct viral toxicity. It is important for the physicians to recognize digestive symptoms as an important characteristic in COVID-19 patients. Hence, precise and targeted documentation of GI symptoms and viral stool sample investigations should be performed in order to understand the rapidly evolving disease symptomology.**

*Keywords:* 2019 novel coronavirus, COVID-19, SARS-CoV-2, Novel coronavirus, Coronavirus disease 2019 virus, 2019-nCoV, COVID19, SARS2, Severe acute respiratory syndrome coronavirus 2, Gastrointestinal, Diarrhea, Digestive, Vomiting, Abdominal pain, Abdominal discomfort, Anorexia, Nausea

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## 1. Introduction

Since the 2019 novel coronavirus first emerged, it grabbed global attention due to its similarity to the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which were responsible for outbreaks in 2002 and 2012 respectively, infecting a total of more than 10,000 people.[1] Just like SARS-CoV and MERS-CoV, the 2019 novel coronavirus, now named as the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), belongs to the beta genus of family Coronaviridae that comes under the order "Nidovirales". It is an enveloped positive-stranded RNA virus. SARS-COV-2 shares 79% of its genetic makeup with SARS-COV and utilizes the same entry point, angiotensin-converting enzyme II (ACE2) receptor, for infection.[10] Despite a lower mortality rate than SARS-CoV and MERS-CoV, it has spread much more rapidly,[1] being declared a pandemic on March 11, 2020 in a situation report by the World Health Organization (WHO).[2] As of May 10, 2020, it has infected a total of 3,917,366 people; claiming a total of 274,361 lives.[4] The initial cases of COVID-19, the disease caused by SARS-Cov-2, were linked to a seafood and wet animal wholesale market in Wuhan, China, but it later became apparent that person to person transmission was also occurring, mainly through droplets or direct contact.[3] Concern for the possibility of fecal-oral transmission was raised after the stool sample of the first confirmed COVID-19 case in the United Stated tested positive for SARS-CoV-2 by real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) assay after some episodes of loose stool.[5] Furthermore, in a study to examine the presence of viral RNA in feces of patients infected with SARS-CoV-2, 39 of the 73 hospitalized patients tested positive for it, the age of patients with positive results ranging from 10 months to 78 years old.[6] While fever, cough and shortness of breath are the most common presenting symptoms of COVID-19, GI related symptoms such as diarrhea, nausea, vomiting and abdominal pain are being increasingly reported. In a study describing clinical characteristics of 204 COVID-19 patients, 103 were found to have presented with one or more digestive symptoms, 6 of which reported digestive symptoms without any respiratory symptoms. Patients with digestive symptoms were also found to have a longer time from onset of symptoms to hospital admission than those without GI symptoms.[11] Presence of GI symptoms may also be associated with a higher likelihood of being tested positive.[7] Atypical COVID-19 symptoms, such as GI symptoms, should be considered for the detection and better management of such cases. Besides other GI manifestations, liver injury has also been noticed in some patients. According to the American College of Gastroenterology, abnormal liver enzymes were seen in 20–30% of patients with COVID-19 infections.[8] Since the most common presenting symptoms of COVID-19 are related to the respiratory system, clinicians may overlook the possible diagnosis of COVID-19 in patients with an atypical presentation with GI symptoms, which in some cases may precede fever and respiratory symptoms or rarely may even be the only presenting symptom. In addition to this, it is also necessary to highlight the possibility of fecal-oral transmission, such as during procedures like colonoscopies or in areas of poor sanitation, considering stool samples may remain positive even after respiratory samples are tested negative and patients are asymptomatic.[9] This could pose a great challenge for control and prevention, increasing the burden on an already overwhelmed health care system. We conducted a systematic review to summarize the existing data on GI manifestations of COVID-19 and the temporal pattern of fecal shedding of SARS-CoV-2 and to quantitatively evaluate the prevalence of GI symptoms reported in COVID-19 cases, to assist in the management of affected patients and lessen transmission.

## 2. Methods

The systematic review was conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

### 2.1. Inclusion & exclusion criteria

a. Inclusion criteria
- Studies reporting COVID-19 confirmed patients with GI symptoms
- Original articles
- Studies that have been published or accepted in peer-reviewed journals

b . Exclusion criteria
- Studies with COVID-19 confirmed patients that did not report any GI symptoms
- Reviews, meta-analyses, systematic reviews, editorials, comments, communications, case reports, case series, correspondences, letters
- Articles not published in the English language

### 2.2. Search strategy

The MEDLINE database was used to identify epidemiological studies reporting on COVID-19 patients with GI symptoms published between 01 December 2019 to 10 May 2020. A broad combination of keywords for COVID- 19 and GI symptoms were used, which were combined with Boolean operators, to form a comprehensive search query in order to ensure maximum studies were found. The search strategy is described in Annexure 1.

### 2.3. Study selection

Two reviewers (S.Q & O.A.P) independently identified the primary articles by reviewing the titles and abstracts of the search results. Full text screening was then carried out, independently, by four reviewers (S.Q, O.A.P, S.S, M.N) to identify eligible studies in accordance to the inclusion and exclusion criteria. Any discrepancy among the reviewers was resolved by discussion and mutual agreement. The literature search and selection process is represented in Fig. 1 (PRISMA Flowchart).

### 2.4. Data extraction

Two reviewers (S.Q & O.A.P) extracted data from the eligible literature. Studies that did not distinguish COVID- 19 patients with GI symptoms from patients without GI symptoms, the following variables were extracted: first author, country, study design, total number of patients included in study, age, gender, GI symptoms and non-GI symptoms. The extracted data is represented in Table 1.

Studies that distinguished COVID-19 patients with GI symptoms from patients without GI symptoms, the following additional variables were extracted: first author, number of patients with GI symptoms, population type, comorbidities, presence of COVID-19 RNA in stool sample, laboratory findings, treatment, disease severity and outcome. The extracted data is represented in Table 2.

### 2.5. Definitions

#### 2.5.1. Population type

Patients were classified into 3 stratifications: pediatric, adult and pregnant women. Patients younger than 15yrs were classified as pediatric while patients older than 15yrs were classified as adult.

#### 2.5.2. Disease severity

Patients were classified into 2 stratifications: Non-severe and Severe. Patients with mild or moderate symptoms were classified as Non-severe whereas patients with severe or critical symptoms were classified as Severe. Studies that pre-categorized patients into Mild, Moderate, Severe and Critical were recategorized as Non-Severe and Severe respectively. Studies which provided individual patient data, the patients were classified as Mild, Moderate, Critical and Severe in accordance with definitions stated in the National Chinese Health Commission (seventh edition)[13] and then recategorized as Non-severe and Severe respectively.

### 2.6. Data analysis

SPSS (Version 21.0) was used for analysis of data. Normality tests were performed using Shapiro–Wilk. The p-value of Shapiro–Wilk was found to be less than 0.05 therefore we concluded that the data does not follow normal distribution. Correlations were tested using the *Spearsman's* correlation test. The test was two sided and a p-value of less than 0.05 was considered significant unless otherwise stated. The studies included in this systematic review were at a low risk of bias.

## 3. Results

### 3.1. Study selection and data collection

A total of 163 studies were identified through MEDLINE in this systematic review keeping in mind the Preferred Reporting Items for Systematic Review (PRISMA).[12] Mainly observational studies which reported GI symptoms in diagnosed COVID-19 patients were included. After screening the studies via titles and abstract review, 57 studies were subjected to full text reviews, out of which 16 studies were chosen for qualitative analysis and 16 were included in the final review. 14 out of 16 said studies originated from Mainland China, 1 study originated from Korea while 1 study originated from Taiwan. Mode of data collection in most of the studies was EMR, with majority retrospectively reporting data from hospitalized patients with one study reporting data from the nation data base (Taiwan). We included 16 studies in which there were a total of 3646 patients. The studies covered a time span of 12/1/2019 to 5/10/2019. The mean ages and genders affected are discussed in Table 1. The Newcastle–Ottawa scale was applied to assess the quality of the studies, which resulted in an average

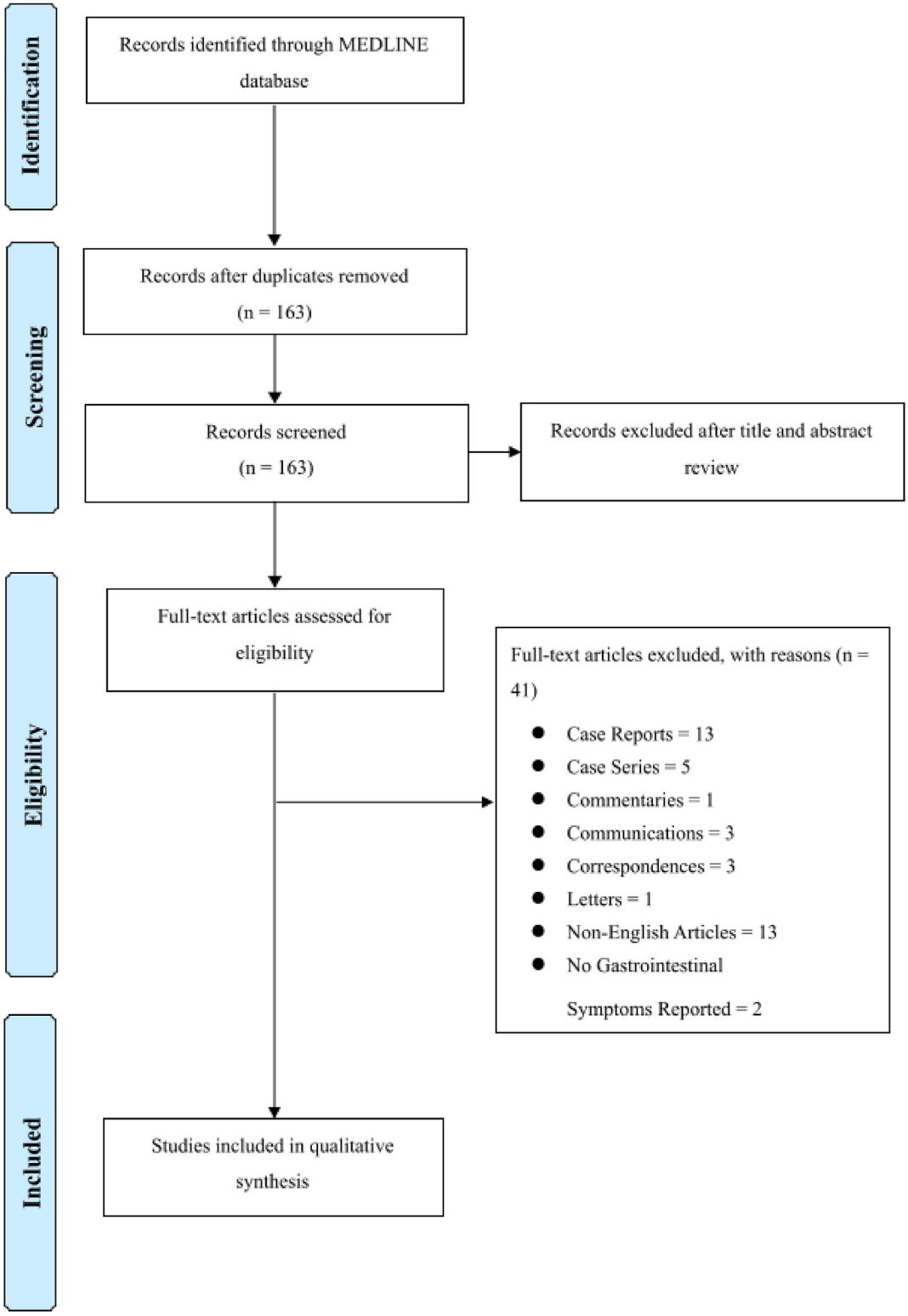



*Fig. 1. Prisma chart.*

*Table 1. Two reviewers (S.Q & O.A.P) extracted data from the eligible literature. Studies that did not distinguish COVID- 19 patients with GI symptoms from patients without GI symptoms, the following variables were extracted: first author, country, study design, total number of patients included in study, age, gender, GI symptoms and non-GI symptoms. The extracted data is represented in Table 1.*

| Study/author | Country | Multicentre / Single- centre | No. of patients | Age (mean) | Gender | | Gastrointestinal (GI) Symptoms | | | | | Non − GI Symptoms |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Male | Female | Abdominal Pain | Diarrhea | Anorexia | Nausea/ Vomiting | Other GI Symptoms | |
| Huang et al.[14] | China | Single-centre | 41 | 49.3[a] | 30 (73%) | 11 (27%) | NA | 1 (3%) | NA | NA | NA | Fever [40 (98%)]<br>Cough [31 (76%)]<br>Myalgia/fatigue [18 (44%)]<br>Sputum production [11 (28%)]<br>Headache [3 (8%)]<br>Haemoptysis [2 (5%)]<br>Dyspnoea [22 (55%)] |
| Chen et al.[15] | China | Single-centre | 99 | 55.5 | 67 (67.7%) | 32 (32.2%) | NA | 2 (2%) | NA | 1 (1%) | NA | Fever [82 (83%)]<br>Cough [81 (82%)]<br>Shortness of breath [31 (31%)]<br>Muscle ache [11 (11%]<br>Confusion [9 (9%)]<br>Headache [8 (8%)]<br>Sore throat [5 (5%)]<br>Rhinorrhoea [4 (4%)]<br>Chest pain [2 (2%)] |
| Liu et al.[16] | China | Multicentre | 137 | 55.0 | 61 (44.5%) | 76 (55.5%) | NA | 11 (8%) | NA | NA | NA | Fever (112 (81.8%)]<br>Cough [66 (48.2%)]<br>Myalgia or fatigue [44 (32.1%)]<br>Expectoration [6 (4.4%)]<br>Hemoptysis [7 (5.1%)]<br>Headache [13 (9.5%)]<br>Heart palpitations [10 (7.3%)]<br>Dyspnea [26 (19%)] |
| Jin et al.[17] | China | Multicentre | 651 | 45.2[b] | 331 (50.8%) | 320 (49.2%) | NA | 56 (8.6%) | NA | Nausea [17 (2.6%]<br>Vomiting [18 (2.8%)] | NA | Fever [545 (83.7%)]<br>Cough [435 (66.8%)]<br>Sputum production [227 (34.9%)]<br>Haemoptysis [11 (1.7%)]<br>Sore throat [99 (15.2%)]<br>Nasal obstruction [37 (5.7%)]<br>Muscle ache [71 (10.9%)]<br>Fatigue [119 (18.3%)]<br>Shortness of breath [27 (4.1%)]<br>Headache [67 (10.3%)] |
| Lin et al.[18] | China | Single-centre | 95 | 45.3 | 45 (47.4%) | 50 (52.6%) | NA | 23 (24.2%) | 17 (17.9%) | Nausea [17 (17.9%)]<br>Vomiting [4 (4.2%)] | Acid reflux [2 (2.1%)]<br>Epigastric discomfort [2 (2.1%)] | NA |

(*continued on next page*)

*Table 1. (continued)*

| Study/author | Country | Multicentre / Single- centre | No. of patients | Age (mean) | Gender | | Gastrointestinal (GI) Symptoms | | | | | Non − GI Symptoms |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Male | Female | Abdominal Pain | Diarrhea | Anorexia | Nausea/ Vomiting | Other GI Symptoms | |
| | | | | | | | | | | | Upper GI haemorrhage [2 (2.1%)] | |
| Kim et al.[19] | Republic of Korea | Multicentre | 28 | 42.6 | 15 (53.6%) | 13 (46.4%) | 1 (3.6%) | 3 (10.7%) | NA | NA | NA | Cough [8 (28.6)]<br>Sputum [6 (21.4)]<br>Sore throat [8 (28.6)]<br>Rhinorrhea [2 (7.1)]<br>Myalgia [7 (25.0)]<br>Fatigue [3 (10.7)]<br>Shortness of breath [1 (3.6)]<br>Headache [7 (25.0)] |
| Lo et al.[20] | China | Single-centre | 10 | 48.3[a] | 3 (30%) | 7 (70%) | 2 (20% | 8 (80%) | NA | Nausea [5 (50%)] | NA | Fever [8 (80%)]<br>Cough [5 (50%)]<br>Dyspnea [5 (50%)<br>Sore throat [5 (50%)]<br>Myalgia [3 (30%)]<br>Rhinorrhea [2 (20%)]<br>Nasal congestion [2 (20%)]<br>Dizziness [2 (20%)] |
| Yu et al.[21] | China | Single-centre | 7 | 32 | 0 | 7 (100%) | NA | 1 (14.3%) | NA | NA | NA | Fever [6 (85.7%)]<br>Cough [1 (14.3%)]<br>Shortness of breath [1 (14.3%)] |
| Guan et al.[22] | China | Multicentre | 1099 | 46.7[a] | 640 (58.1%) | 459 (41.9%) | NA | 42 (3.8%) | NA | 55 (5.0%) | NA | Fever [975 (88.7%)]<br>Conjunctival congestion [9 (0.8%)]]<br>Nasal congestion [53 (4.8%)]<br>Headache [150 (13.6%)]<br>Cough [745 (67.8%)]<br>Sore throat [153 (13.9%)]<br>Sputum production [370 (33.7%)]<br>Fatigue [419 (38.1%)]<br>Hemoptysis [10 (0.9%)] Shortness of breath [205 (18.7%)]<br>Myalgia or arthralgia [164 (14.9%)]<br>Chills [126 (11.5%)] |
| Shen et al.[23] | China | Single-centre | 9 | 7.6 | 3 (33.3%) | 6 (66.7%) | NA | 2 (22.2%) | NA | NA | NA | Fever [4 (44.4%)]<br>Cough [1 (11.1%)]<br>Sore throat [1 (11.1%)] |
| Zhang et al.[24] | China | Multicentre | 645 | 45.3[b] | 328 (50.9%) | 317 (49.1%) | NA | 53 (8.2%) | NA | 22 (3.4%) | NA | Fever [540 (83.7%)]<br>Cough [425 (65.9%)]<br>Expectoration [225 (34.9%)]<br>Hemoptysis [11 (1.7%)] |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhao et al.[25] | China | Single-centre | 91 | 46 (Median) | 49 (53.8%) | 42 (46.2%) | 2 (2.2%) | 14 (15.4%) | 11 (12.1%) | Nausea [11 (12.1%)] | NA |
| Pan et al.[11] | China | Multicentre | 204 | 52.9 | 107 (52.5%) | 97 (47.5%) | 2 (1%) | 35 (17.2%) | 81 (39.7%) | Vomiting [4 (2%)] | |
| Liu et al.[26] | Taiwan | Multicentre | 321 | 4–88 (Range) | 151 (47%) | 170 (53%) | 3 (0.9%) | 23 (7.2%) | NA | 3 (0.9%) | NA |
| Mi et al.[27] | China | Multicentre | 10 | 68.4 | 2 (20%) | 8 (80%) | 1 (10%) | NA | NA | Vomiting [1 (10%)] | NA |

Sore throat [97 (15%)]
Nasal obstruction [36 (5.6%)]
Muscle ache [71 (11%)]
Fatigue [118 (18.3%)]
Shortness of breath [26 (4%)]
Headache [67 (10.4%)]
Fever [75 (82.4%)]
Cough [59 (64.8%)]
Fatigue [35 (38.5%)]
Chest distress [21 (23.1%)]
Pharyngalgia [19 (20.9%)]
Myalgia [15 (16.5%)]
Arthodynia [8.8%)]
Chill [21 (23.1%)]
Dizziness [3.3%)] polypnea [19 (12.1%)]
Disturbance of consciousness [3 (3.3%)]
Fever [95 (46.6%)]
Weakness [54 (26.5%)]
Muscle pain [15 (7.4%)]
Fever [144 (44.9%)]
Chills [9 (2.8%)]
Malaise [52 (16.2%)] Myalgia or arthralgia [40 (12.5%)]
Cough [146 (45.5%)]
Sore throat [100 (31.2%)]
Rhinorrhoea, sneezing, nasal stuffiness [96 (29.9%)]
Chest tightness or pain [18 (5.6%)]
Dyspnea [11 (3.4%)] Loss of smell or taste
[42 (13.1%)]
Headache [34 (10.6%)]
Dizziness [6 (1.9%)]
Itching, congestion, or pain in the eyes [6 (1.9%)]
Fever [7 (70%)]
Cough [7 (70%)]
Fatigue [7 (70%)]
Sore throat [4 (40%)]
Dyspnea [5 (50%)]
Chest pain [1 (10%)]
Nasal congestion [1 (10%)]
Headache [1 (10%)]
Dizziness [3 (30%)]

(*continued on next page*)

*Table 1. (continued)*

| Study/author | Country | Multicentre / Single- centre | No. of patients | Age (mean) | Gender | | Gastrointestinal (GI) Symptoms | | | | Non – GI Symptoms |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Male | Female | Abdominal Pain | Diarrhea | Anorexia | Nausea/ Vomiting | Other GI Symptoms | |
| Cao et al.[28] | China | Single-centre | 199 | 58.3 | 120 (60.3%) | 79 (39.7%) | 5 (2.5%) | 4 (2%) | 2 (1%) | Nausea [9 (4.5%)] Vomiting [6 (3%)] | Abdominal discomfort [6 (3%)] | Limited activity [10 (100%)] Fever [182 (91.5%)] Rash [2 (1%)] Sleep disorders and disturbances [1 (0.5%)] Unconsciousness [1 (0.5%)] Facial flushing [1 (0.5%)] |

Data are presented as N (%).
[a] Mean calculated using Xiang Wan method.
[b] Mean calculated using Cochrane method.

score of 6.6 of the 16 studies, with all studies being ranked of good quality by the said scale.

### 3.2. Clinical findings

The main clinical findings and lab values are discussed in Tables 1 and 2 respectively. The study included a total of 3646 patients, most of which were males (53.5%) and the rest comprised of females (46.5%). Patients included in the study encompassed all age groups, but most of them lied in the 46.56 ± 13.54-year range. Fever (32.3%) was the most common non-GI presenting symptom along with cough (22.9%), sputum production (9.7%) and fatigue (8.7%), dyspnea (1.3%) (Table 1). Zhang et al. reported greater abnormal imaging findings in patients with fever, cough, and expectorations ($p = <0.001$, $p = 0.016$, $p = 0.033$ respectively).[24] The same study also provided evidence that patients with pre-existing comorbid conditions, especially Hypertension (16.8%), were more likely to have abnormal chest imaging findings ($p = 0.013$).[24] A total of 2703 patients had chest CT performed to look for abnormalities, and 2374 patients (87.82%) to have abnormal findings on their chest imaging. The most common chest abnormality reported on imaging was bilateral ground glass opacities. We meta analyzed the effect size and the heterogeneity of the most commonly reported GI symptoms, and eggers tests and funnel plots were used to determine publication bias, as shown in Figs. 3 and 4. The most commonly presenting gastrointestinal symptom in patients who tested positive for COVID 19 was diarrhea (47%, $I_2 = 0.00$, $z = 4.62$, effect size = 0.02 CI = 95%) (Figs. 2–4), second most common being anorexia (19%, $I_2 = 66.63\%$, $z = 1.52$) (Figs. 3 and 4). Other commonly reported gastrointestinal symptoms include nausea (29%, $I_2 = 0.00$, $z = 2.87$) (Figs. 3 and 4), abdominal pain (3%, $I_2 = 0.02$, $z = 0.27$) (Figs. 3 and 4), emesis and transaminitis. Other commonly reported GI symptoms include nausea, vomiting, abdominal pain. One study reported 28.38% of the patients lacking common respiratory symptoms and having only GI symptoms as the presenting complaint.[17] Interestingly, one study by Lin et al., reported esophageal ulcers in 1 patient revealing SARS-CoV 2. The same study reported that in 2 patients with severe COVID-19 disease, sampling from esophageal, stomach, duodenal and rectal aspirates showed presence of SARS-CoV 2, indicating widespread disease in severe patients.

[18] A study by Jin et al. reported several significant facts about COVID-19 with GI disease.[17] The study discussed an increased transition to ICU care among COVID-19 patients with GI disease vs without GI

*Table 2. Studies that distinguished COVID-19 patients with GI symptoms from patients without GI symptoms, the following additional variables were extracted: first author, number of patients with GI symptoms, population type, comorbidities, presence of COVID-19 RNA in stool sample, laboratory findings, treatment, disease severity and outcome. The extracted data is represented in Table 2.*

| Study/author | No. of patients | Population type | Comorbidities | Presence of covid-19 RNA In stool sample | Laboratory findings | Treatment | Disease severity | | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Non-severe | Severe | |
| Jin et al.[17] | 74 | NA | Hypertension [12 (16.22%)] Diabetes [7 (9.46%)] Chronic liver disease [8 (10.81%)] Heart disease [1 (1.35%)] | Negative [74 (100%)] | Elevated ALT [17 (23%)] Elevated CRP [17 (23%)] | Antiviral therapy [66 (89.19%)] Antibiotic therapy [31 (41.89%)] Corticosteroid [11 (14.86%)] Mechanical ventilation [5 (6.76%)] | 57 (77%) | 17 (23%) | NA |
| Lin et al.[18] | 58 | Adult [57 (98.2%)] Paediatric [1 (1.7%)] | Hypertension [10 (17.2%)] Diabetes mellitus [3 (5.2%)] Cardio-cerebrovascular disease [3 (5.2%)] Malignant tumour [4 (6.9%)] Chronic lung disease [1 (1.7%)] Chronic kidney disease [1 (1.7%)] | Positive [22 (52.4%)] | Elevated ALT [5 (8.6%)] Elevated AST [4 (6.9%)] | NA | 44 (75.9%) | 14 (24.1%) | Discharged [23 (39.7%)] Remained in hospital [35 (60.3%)] |
| Yu et al.[21] | 1 | Pregnant [1 (100%)] | NA | No stool culture conducted | Normal Leucocytes [1 (100%)] Decreased Lymphocytes [1 (100%)] Decreased Platelets [1 (100%)] Normal ALT [1 (100%)] Normal AST [1 (100%)] Elevated CRP [1 (100%)] Elevated D-Dimer [1 (100%)] Elevated Serum Ferritin [1 (100%)] | Antiviral therapy [1 (100%)] Antibiotic therapy [1 (100%)] Corticosteroid [1 (100%)] Non-invasive ventilation [1 (100%)] | 1 (100%) | NA | Discharged [1 (100%)] |

(*continued on next page*)

*Table 2. (continued)*

| Study/author | No. of patients | Population type | Comorbidities | Presence of covid-19 RNA In stool sample | Laboratory findings | Treatment | Disease severity | | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Non-severe | Severe | |
| Shen et al.[23] | 2 | Paediatric [2 (100%)] | NA | No stool culture conducted | Normal Leucocytes [2 (100%)] Normal Lymphocytes [2 (100%)] Normal CRP [2 (23%)] Normal ALT [2 (100%)] Normal AST [2 (100%)] | Antiviral therapy [2 (100%)] Oxygen support [2 (100%)] | 2 (100%) | NA | Discharged [1 (50%)] Remained in hospital [1 (50%)] |
| Pan et al.[11] | 103 | Adult [100 (100%)] | Respiratory system disease [7 (6.80%)] Fatty liver [1 (0.97%)] Hepatic insufficiency [1 (0.97%)] Gastritis [1 (0.97%)] GERD [1 (0.97%)] Cardiovascular system disease [23 (22.3%)] Nervous system disease [1 (0.97%)] Endocrine system disease [10 (9.71%)] Malignant tumour [8 (7.77%)] | No stool culture conducted | Elevated ALT [21 (20.4%)] Elevated AST[17 (16.5%)] | Antiviral therapy [94 (91.26%)] Antibiotic therapy [79 (76.70%)] Corticosteroid [44 (42.72%)] Intravenous immunoglobulin [39 (37.86%)] Nebulized a-interferon [57 (55.34%)] | 66 (64.1%) | 37 (36%) | Discharged [84 (81.55%)] Died [19 (18.45%)] |
| Mi et al.[27] | 1 | Adult [1 (100%)] | COPD [1 (100%)] Osteoporosis [1 (100%)] | No stool culture conducted | Elevated Leucocytes [1 (100%)] Decreased Lymphocytes [1 (100%)] Normal Platelets [1 (100%)] Normal ALT [1 (100%)] Normal AST [1 (100%)] Elevated CRP [1 (100%)] | Antiviral therapy [1 (100%)] Antibiotic therapy [1 (100%)] Non-invasive ventilation [1 (100%)] | NA | 1 (100%) | Died [1 (100%)] |

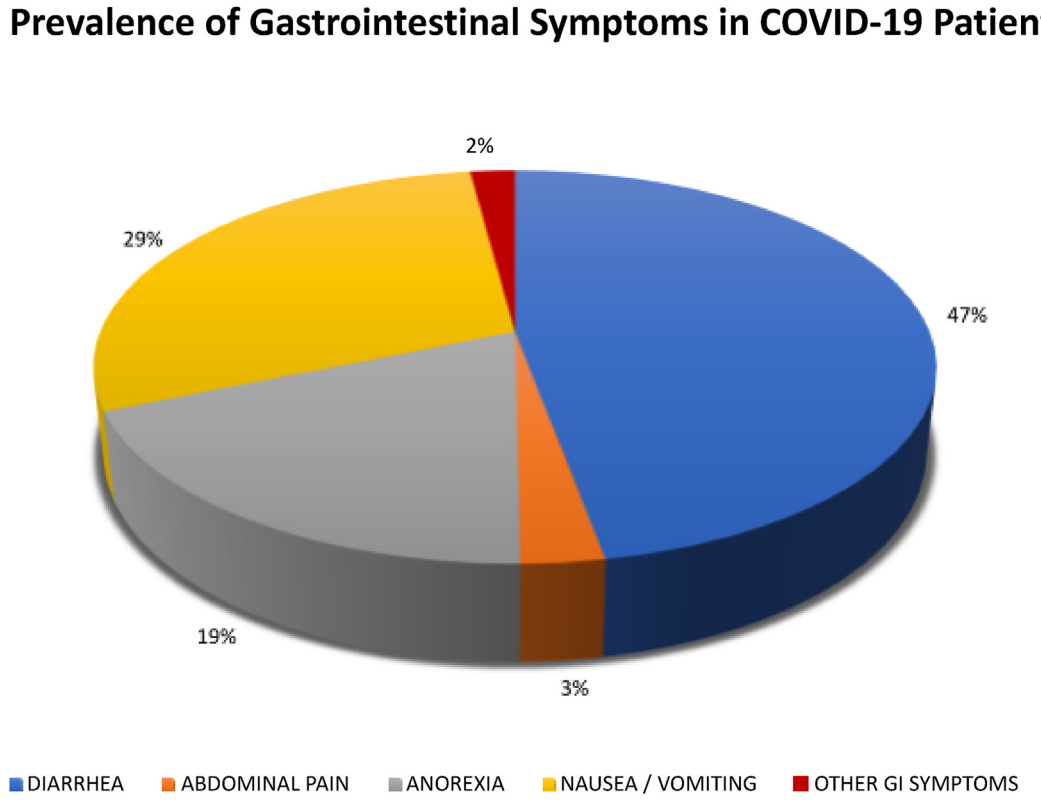



*Fig. 2. Pie chart.*

disease (6.76% vs 2.08%; p = 0.034). Intriguingly, the study showed a significant increase in adverse effects in COVID-19 patients with GI symptoms, namely ARDS and liver injury (p = 0.034; p = 0.035). The study also discussed the phenomenon of family clustering, i.e. patients with GI symptoms had family clustering vs patients without GI disease (31.08% vs 20.45%; p = 0.037), suggesting fecal-oral transmission. To test the hypothesis, fecal samples were collected for viral RNA detection, but 100% of them came back negative (Table 2). This is a strikingly different finding than Lin et al.,[18] which reported positive fecal samples for viral RNA in 52.4% of the patients (Table 2). Jin's study had 41.89% of the patients taking antibiotics, which could suggest that the GI symptoms being caused in the patients could, in part, be due to the adverse effects of the medication. Overall, out of the pooled patients who had GI symptoms, 132 patients had their stool samples taken for detection of viral RNA, and 16.7% came back positive, 9 of which had no GI symptoms at the time of sample collection.

[18] The duration of viral shedding in fecal samples remains largely unknown. These numbers might partly be due to lower frequency of fecal RNA testing in patients with COVID-19 because current literature does not provide guidelines as to when the fecal samples should be taken for patients with COVID-19. Significant increase in AST and ALT in patients who had GI symptoms has been identified by Pan et al. and Jin et al. independently,[11,17] with Pan et al. reporting increases in AST and ALT in 16.5% and 20.4% of the people with GI symptoms versus 5% and 5.9% in patients without GI symptoms (PAST = 0.008; PALT = 0.002). However, no association was reported with increases in ALT and AST with disease severity.[14,22,24,25] Seven patients out of the pooled population were pregnant women, and they were followed through the course of their pregnancies. No one developed severe disease, however, on delivery, one of the neonates tested positive for SARS-CoV 2 RNA, suggesting vertical transmission of the virus as well.[21] We took data from 6 studies that specifically talked about GI symptoms in COVID-19 patients and calculated the number of people who had severe disease. We found out that the patients who had COVID-19 with GI symptoms had a statistically significant correlation with disease severity (p = 0.002) and had a strong linear correlation with disease severity (r = 0.965). We calculated the correlations of disease outcomes with certain patient characteristics in COVID-19 patients with GI symptoms. We found out that patients with comorbidities had a higher chance of mortality in the disease (p < 0.001). We also concluded

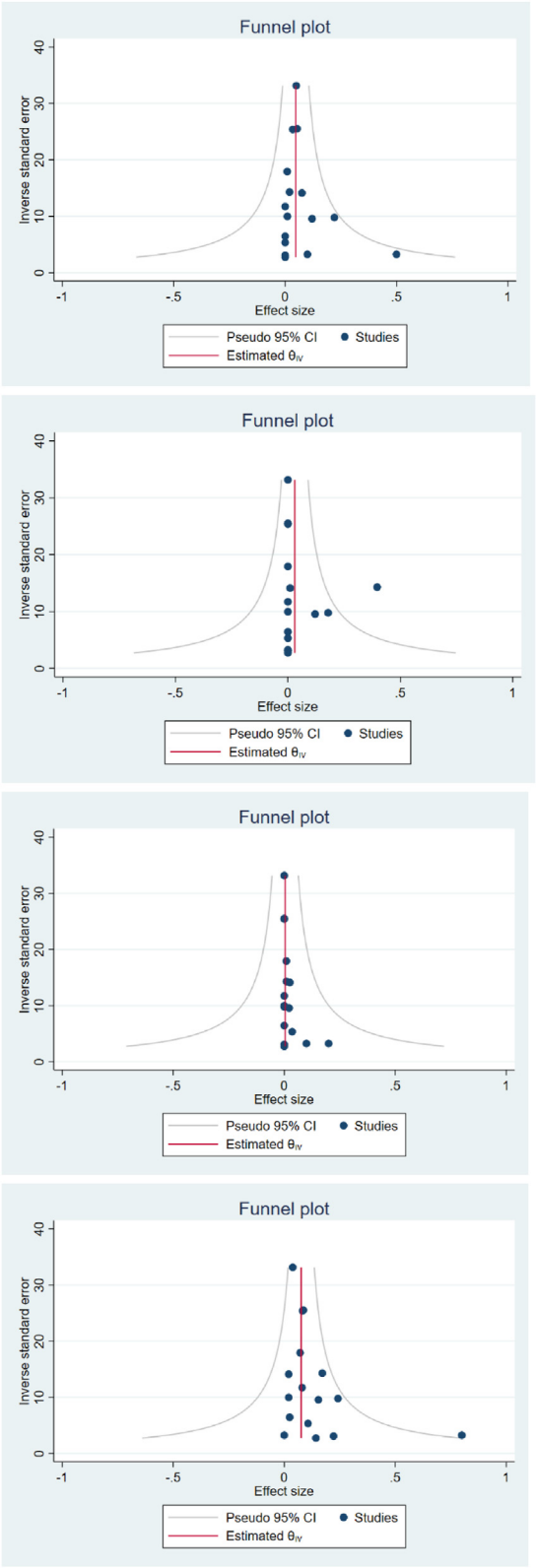
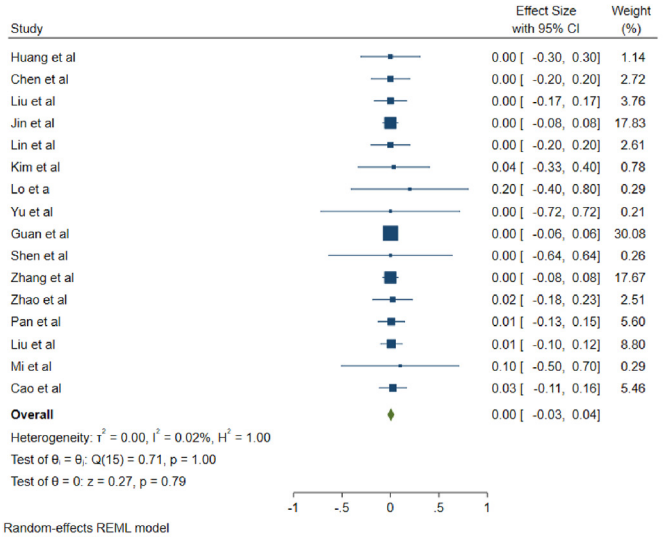


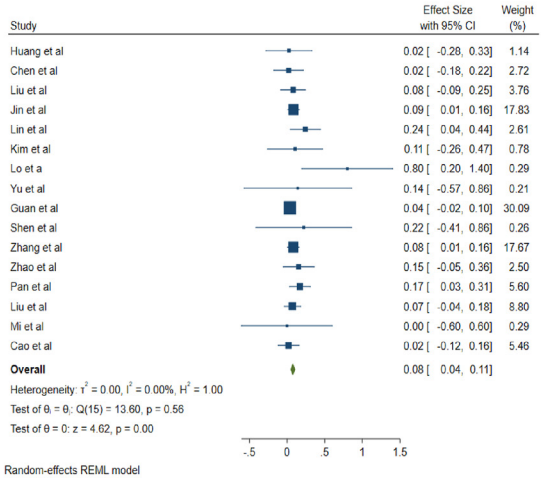

*Fig. 3. Funnel plot: The effect size and the heterogeneity of the most commonly reported GI symptoms. The most commonly presenting gastrointestinal symptom in patients who tested positive for COVID 19 was diarrhea (47%, I 2 = 0.00, z = 4.62, effect size = 0.02 CI = 95%, second most common being anorexia (19%, I 2 = 66.63%, z = 1.52).*

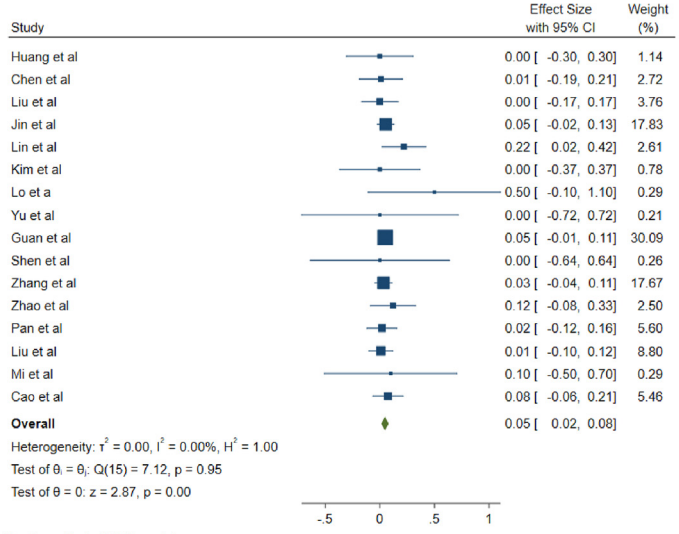
that patients who had GI symptoms had prolonged hospital stays ($p < 0.001$), which was also mentioned by Pan et al., who reported the same finding.[11] However, a direct correlation of the presence of diarrhea, which is the most reported GI symptom in COVID-19 patients, with patient mortality, could not be established ($p = 0.684$). We also tested the possibility that diarrhea could be an adverse effect of the treatment being given, namely antibiotics, antivirals, and corticosteroids, but no significant association was established between the two either, indicating that diarrhea is in fact one of the prominent symptoms of COVID-19. Raises in AST and ALT were not associated with worse disease outcome ($p = 0.184$). In our study, 8.8% and 10.9%of the population with GI symptoms had elevated AST and ALT respectively. More research needs to be done in this area, with more studies being carried out on the hepatobiliary aspect of the disease. These results indicate towards the need to test more potential hypothesis for more conclusive evaluations.

## 4. Discussion

COVID-19, caused by SARS-CoV-2, is a global pandemic, manifested by an infectious pneumonia. Although primary presentation is respiratory in nature, with fever, cough and dyspnea, being most common features.[22] However, increasing number of studies have reported GI and hepatic manifestations. Gastrointestinal involvement has also been reported in 20–25% of patients with MERS-CoV and SARS-CoV infection. [29,30] Our review of 16 studies involving 3646 patients aims to provide a comprehensive overview of prevalence of GI symptoms and liver injury in COVID-19 patients. Accumulated data of gastrointestinal complaints in COVID-19 patients showed that the GI tract and liver might also be the target organs of SARS-CoV-2. While the etiology is not established yet, its ability to infect GI tract is correlated with ACE 2 expression in epithelial cells of stomach, ileum and colon, and liver cholangiocyte.[4] This hypothesis is supported by Xiao et al., who detected high viral staining in these areas.[6] Another route of SARS-CoV-2 damaging the digestive system might be through provoking an inflammatory response. This response, secondary to viremia, may alter the gut flora, which, in turn, affect the respiratory flora and cause acute respiratory distress syndrome (ARDS). This "gut–lung axis" effect may help explain the gastrointestinal symptoms in COVID-19 patients with respiratory involvement.[6,11,17] However, further studies exploring these underlining mechanisms are needed. Although the most frequently reported symptoms in COVID-19 patients were



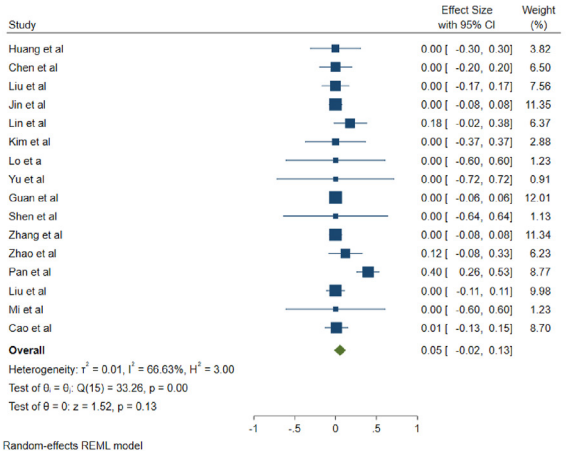




*Fig. 4. Funnel plot: The effect size and the heterogeneity of the most commonly reported GI symptoms. Other commonly reported gastrointestinal symptoms include nausea (29%, I 2 = 0.00, z = 2.87).*

fever (32.3%) and cough (22.9%),[14,15,16,17,22,24,25,27] evidence of the involvement of the digestive system in patients with COVID-19 has now been reported by an increasing number of studies. In our review, overall, the pooled estimate of gastrointestinal symptoms was reported in up to 16.5% of patients. A large multicenter study conducted by Pan and colleagues reported that 50% of 204 patients presented with GI symptom as their chief complaint. 3% showed only GI symptoms and reported no respiratory complaints in their disease course. Significant longer time from onset to admission in patients with abdominal symptoms as compared to those without GI complaints was observed (9·0 days vs 7·3 days).[11] It is possible that nationwide data on gastrointestinal symptoms might have been under reported as primary focus initially was given to fever, cough and SOB; increasing the ratio of omitted patients who were afebrile and did not exhibit typical respiratory symptoms. COVID-19 patients with digestive symptoms have diverse presentations, such as diarrhea, loss of appetite, vomiting, and abdominal pain. Diarrhea appeared to be the most common GI complaint in our review, with incidence of 47%. Nausea/vomiting was the second most reported symptom (29%) in our review, followed by anorexia (19%) and abdominal pain (3%). Studies hint towards the aggravation of GI symptoms in patients receiving antibiotics and antivirals during hospitalization. [18,19,28] Kim et al. reported higher incidence of diarrhea in patients on lopinavir-ritonavir in comparison to those who did not receive such treatment (53% vs 11%) respectively.[19] 14% of lopinavir–ritonavir recipients experienced gastrointestinal adverse events.[28] Lin and colleagues recorded significant association of diarrhea and antibiotic treatment ($p = 0.034$).[18] SARS-CoV-2 infection also jeopardizes liver function. Elevation of liver enzymes such as aspartate transferase (AST), alanine transferase (ALT), and total bilirubin, has been reported by few observational studies. [11,14,15,17,18,22] Pan et al. reported that up to 35% of the patients with GI symptoms established impaired hepatic function during hospitalization [Table 2]. Rate of increased AST and ALT was higher in such patients than in those without GI symptoms. [11,17] Deranged liver enzymes have shown to be more prevalent in severe patients. [14,15] Careful monitoring of liver enzymes is necessary as it may serve as an indicator of severe disease progression. Although the exact mechanism of hepatic injury is not known, it may be associated with viral invasion of liver cholangiocytes expressing ACE2.[32] Other hypothesis proposed the possibility of drug hepatotoxicity. In addition, immune mediated systemic inflammation, such as cytokine storm and pneumonia-associated hypoxia, might also play role in development of liver injury, particularly in critically ill COVID-19 patients.[34] Gastrointestinal manifestations were observed to be significantly associated with disease severity (p-value = 0.002). Pan et al. studied the consequences of 103 COVID-19 patients with digestive symptoms. Digestive symptoms became more pronounced as the sickness advanced to severity.[11] Patients categorized as "Severe" demonstrated different laboratory features. Huang and colleagues showed that AST was raised in 62% of ICU patients.[14] Chen et al. reported increased serum ALT up to 7590 U/L and AST up to 1445 U/L in a severe patient. Severe cases had decreased Albumin (26·3–30·9 g/L).[15] Increased LDH and CRP levels were significantly higher in severe patients compared to patients in mild or moderate group. [17,20] We found significant association between GI manifestations and patient outcome (p-value = 0.000). Jin et al. observed that patients with digestive symptoms were more likely to be admitted in ICU than patients without digestive symptoms. Moreover, COVID- 19 patients with gastrointestinal symptoms had significantly higher rates of complications such as ARDS and liver injury than those without GI symptoms.[17] The concern of COVID-19 transmission through fecal-oral route, in addition to respiratory droplets, was raised when RNA of SARS-CoV-2 was first detected in the stool sample of the COVD- 19 patient in the United States.[5] Isolation of viral RNA from GI epithelial cells provide the evidence of viral invasion and infection[6] and shedding of these infected enterocytes might be the source of detected viral components in stool sample. Lin et al. reported SARS-CoV-2 RNA detection in stool specimens in over 50% of patients with GI symptoms. 39% had positive stool sample but reported no GI symptoms, hence, there wasn't significant difference regarding proportion of positive stool samples in patients with and without GI symptoms.

[18] Lo et al. detected positive viral RNA in stool samples in up to 90% of patients, independent of GI symptoms presence. Lag in viral detection in nasopharyngeal specimens and delay of viral RNA conversion in stool samples was recorded.[20] Xiao et al. also found that more than 20% patients with of SARS-CoV-2 infection have positive viral RNA in stool even after negative conversion of viral RNA in the respiratory tract.[6] These evidences of viral persistence in stool after resolution of respiratory colonization hypothesize a fecal–oral route of transmission and raise the concerns regarding

current discharge policy.[13] For patients undergoing recovery, their infectivity potential remains unknown, thus extended isolation and viral stool testing is recommended. Fecal oral being a potential mode for virus transmission has made it increasingly important for the health authorities to ensure a secure waste disposal mechanism from the transmission sites such as hospital toilets along with aggressive hygiene measures adopted by the general public including regular hand washing, disinfecting toilets along with improving sanitation to limit transmission. Our review has its own limitations. First, the included studies are geographically limited to Asian region, mainly China. Diversity is required which might help better understand relationship between digestive symptoms, disease severity and prognosis. Second, due to lack of universal protocol, assessment of disease status has become difficult. A standardized model should be set forth. Third, Chinese databases were not included in the view of language restriction. Fourth, studies included were mostly retrospective in nature, creating the possibility of biasness. Fifth, the extracted data is based on hospitalized patients, GI involvement due to COVID-19 cannot be generalized. Sixth, during data extraction, it was indistinct which patient reported which GI symptom hence, due to overlapping, assessment of independent GI symptom affecting disease prognosis and patient outcome could not be efficiently documented. Lastly, due to lack of sufficient data on stool PCR detection, it is difficult to weigh the consequences of fecal-oral transmission hence, future studies are needed on this subject. In conclusion, COVID-19 is a novel coronavirus infection that can lead to acute respiratory infection. Our review highlights that in addition to the respiratory manifestations, patients with COVID-19 often presents with GI symptoms. Patients with GI involvement have a longer time from onset to admission and more laboratory abnormalities, such as raised liver enzymes. Compared with COVID-19 patients without digestive symptoms, those with digestive symptoms might develop severe disease and have a poor disease progression developing complications such as ARDS. Data regarding fecal viral shedding in the current pandemic imply that SARS-CoV-2 could be transmitted by the fecal-oral route. This calls for additional studies for better understanding of the origin, viral evolution, infectivity, transmissibility, pathogenicity and future hostadaption. As more research emerges, we will have a better understanding of Covid-19 related gastrointestinal symptoms.

## Conflict of interest

There is no conflict of interest.

## Appendix

ANNEXURE 1:

| QUERY NO. | SEARCH QUERY | NOTES |
|---|---|---|
| #1 | 2019 novel coronavirus OR COVID-19 OR SARS-CoV-2 OR Novel coronavirus OR Coronavirus disease 2019 virus OR 2019-nCoV OR COVID19 OR SARS2 OR Wuhan coronavirus OR Severe acute respiratory syndrome coronavirus 2 | COVID-19 search terms |
| #2 | Gastrointestinal OR Diarrhea OR Digestive OR Vomiting OR Abdominal Pain OR Abdominal discomfort OR Anorexia OR Nausea | Gastrointestinal symptoms search terms |
| #3 | #1 AND #2 | Identification of articles concerning COVID-19 patients with Gastrointestinal symptoms published from 01 December |
| #4 | “2019/12/01"[Date - Publication]: “2020/05/10" [Date - Publication | 2019 to 10 May 2020 |
| #5 | #3 AND #4 | Exclusion of Review, Meta- analysis, Systematic Review, Editorial, Comment articles from results |
| #6 | review[Publication Type] OR meta-analysis [Publication Type] OR Systematic Review[Publication Type] OR editorial [Publication Type] OR comment[Publication Type] | |
| #7 | #5 NOT #6 | |
| #8 | “systematic review"[Title] OR “editorial” [Title] OR “review"[Title] OR “meta-analysis"[Title] OR “Comment"[Title] | |
| #9 | #7 NOT #8 | |

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