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DOI:
10.1016/S2468-1253(20)30126-6

Document Version
Peer reviewed version

Citation for published version (Harvard):
Mao, R, Qiu, Y, He, J-S, Tan, J-Y, Li, X-H, Liang, J, Shen, J, Zhu, L-R, Chen, Y, Iacucci, M, Ng, SC, Ghosh, S & Chen, M-H 2020, 'Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis', *The Lancet Gastroenterology & Hepatology*, vol. 5, no. 7, pp. 667-678. https://doi.org/10.1016/S2468-1253(20)30126-6

Manifestations and Prognosis of Gastrointestinal and Liver Involvement in Patients with COVID-19: a Rapid Systematic Review and Meta-analysis

Short Title: Gastrointestinal and Liver Involvement in COVID-19

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Conflict of interest :

All authors declared no conflict of interest

Grant support: None

Author contributions:

R Mao and MH Chen conceived the study. S Ghosh, MH Chen, S Ng supervised the overall study. R Mao and Y Qiu wrote the manuscript. R Mao, Y Qiu, JS He, JY Tan and XH Li analyzed the data. J Shen, J Liang, LR Zhu, Y Chen and M Iacucci critically revised the manuscript.

Research in context

Evidence before this study

The emergence and spread of COVID-19 has brought great challenges to global public health. There are increasing number of studies reporting the gastrointestinal (GI) symptom and liver injury in patients with COVID-19, and severe patients tend to have a higher risk of developing GI symptoms and abnormal liver function. However, results were inconsistent with remarkable heterogeneity among studies and the exact magnitude of GI and liver involvement remains uncertain. Study providing detailed pooled estimates of incidence of gastrointestinal and liver involvement in COVID-19 is needed. Whether this unique group of patients has a poor disease course remains unclarified.

Added value of this study

We searched the PubMed, Embase, Web of Science，WHO database of publications, the Lancet COVID-19 Resource Centre, NEJM, JAMA, BMJ, Gastroenterology, GUT, American Journal of Gastroenterology, and Centers for Disease Control and Prevention (CDC) COVID-19 publications. We present pooled estimate rate of GI symptom and liver injury in COVID-19. Furthermore, we present the subgroup analysis of severe vs non-severe cases, patients in Hubei province vs outside Hubei, and paediatric vs adult patients. Features of patients with pre-existing digestive diseases and initially presenting with GI symptoms were summarized. The disease course of patients with digestive system involvement was further analysed.

Implications of all the available evidence

Digestive symptom and liver injury are not uncommon in patients with COVID-19. Compared with non-severe cases, severe cases with COVID-19 had a higher risk of developing GI symptoms and liver injury. Paediatric patients have equivalent prevalence of presenting with GI symptoms compared to adult patients. Patients in Hubei had higher rate of abnormal liver functions compared to those outside Hubei. One tenth of patients with COVID-19 may present only with GI symptoms without respiratory symptoms. Patients with digestive system involvement have delayed diagnosis with a tendency to progress to severe/critical type and a poor disease course.

Summary

BACKGROUND: The prevalence and prognosis of digestive system involvement including gastrointestinal symptoms and liver injury in patients with COVID-19 remains largely underappreciated. Here we performed a meta-analysis to quantify the effects of COVID-19 on digestive system.

METHODS: We systematically searched databases for studies reporting digestive system symptoms in COVID-19 patients up to April 4, 2020. Raw data from studies were pooled to determine effect estimates.

FINDINGS: We analyzed findings from 35 studies including 6,686 COVID-19 patients that met inclusion criteria. The pooled estimate of digestive system comorbidities rate was 4% (95% CI: 2%- 5%; range: 0%–15%; I^2=74%). The pooled rate of digestive symptoms was 15% (95% CI: 10%- 21%; range: 2%–57%; I^2= 96%) with nausea and/or vomiting, diarrhoea and loss of appetite being the three most common ones. The pooled estimate of abnormal liver functions was 19% (95% CI: 9%-32%; range: 1%-53%; I^2= 96%). Subgroup analysis showed patients with severe cases had higher rate of GI symptoms (OR1.61, 95% CI: 1.26-2.06, p=0.0040, I^2=35%) and liver injury (OR 2.2, 95% CI: 1.60-3.02, p<0.001, I^2=36%,) compared to non-severe cases. Patients in Hubei province where the COVID-19 initial outbreak happened in China are more likely to present with abnormal liver functions (all < 0.01) compared with those outside Hubei. Paediatric patients have similar prevalence of GI symptoms compared to adult patients. About 10% (95% CI: 4%- 19%; range: 3%–23%; I^2= 97%)

patients presented with GI symptoms alone without respiratory features. Patients with GI system involvement tend to have delayed diagnosis (SMD 2.85, 95% CI: 0.22-5.48, p=0.030, I^2=73%) and poor disease course.

INTERPRETATIONS: Our study showed that digestive symptom and liver injury are not uncommon in patients with COVID-19. Compared with non-severe cases, severe cases with COVID-19 had a higher risk of developing GI symptoms and liver injury. Paediatric patients with COVID-19 have equivalent risk of GI symptoms compared with adult patients. One tenth of patients with COVID-19 may present only with GI symptoms without respiratory symptoms. Patients with digestive system involvement have delayed diagnosis with a tendency to have a poor disease course.

FUNDINGS: None

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has been tremendously impacting the entire world since December 2019. As of April 3rd, 2020, more than 900 000 laboratory-confirmed cases and more than 50 000 deaths in over 100 countries had been reported. [1]

Respiratory tract manifestations such as fever and cough are the most common reported symptoms in patients with COVID-19.[2] The evidence of digestive system involvement in COVID-19 was first reported by a group in China.[3] Emerging data showed that the gastrointestinal (GI) tract and liver might also represent target organs of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), based on the findings that cell receptor angiotensin converting enzyme II (ACE2), the major receptor of SARS-CoV-2, is expressed in GI tract as well as liver cells.[4] More importantly, the evidence of SARS-CoV-2 detection in patients' stool and the potential faecal-oral route transmission have raised great concern and posed a challenge for control and prevention of COVID-19.[5-7]

There are increasing number of studies reporting the GI symptom and liver injury in patients with COVID-19, and severe patients tend to have a higher risk of developing GI symptoms and abnormal liver function.[2] However, results were inconsistent with remarkable heterogeneity among studies and the exact magnitude of GI and liver involvement remains uncertain. Compared to adult patients, paediatric patients seem to

have clinically milder symptoms and showed less alterations in radiological and laboratory testing parameters.[8] Whether paediatric patients had lower risk of GI and liver involvement remains unclear. Moreover, several studies have provided information on the epidemiology and clinical manifestation of the disease outside Hubei province. Whether the GI manifestation and liver injury in disease in Hubei differs from that outside Hubei has seldom been evaluated.[9, 10]

More importantly, the prognosis of COVID-19 patients with GI symptoms is still largely unknown. Recent studies[11, 12] implied that COVID-19 patients with digestive symptoms may have a worse clinical outcome compared to those without digestive symptoms, emphasizing the importance of including symptoms such as diarrhoea to diagnose COVID-19 early. As demonstrated by a recent study, the rate of the severe/critical type was also markedly increased in COVID-19 patients with GI symptoms than in those without GI symptoms. Moreover, COVID-19 patients with GI symptoms had significantly higher complications of acute respiratory distress syndrome (ARDS) and liver injury than those without these symptoms.[11] Pan et al[12] also showed that as the severity of the disease increased, digestive symptoms became more pronounced.

We performed a systematic review and meta-analysis of current emerging studies reporting GI symptoms and liver injury in patients with COVID-19 based on different disease severity, age groups and geographical regions. We also explored the disease course of this subgroup of patients with GI symptoms. We aimed to update the information with high evidence level and provide insights into the epidemiology of

digestive system involvement in COVID-19 as an urgent issue in presentation of COVID-19.

Materials and Methods

The study was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (The PRISMA Statement) (**Supplementary material**).

Search strategy and selection criteria

Literature Search

A systematic literature search of PubMed, Embase (Elsevier) and Web of Science databases was performed on April 4th, 2020 (updated April 10th, 2020), using the keywords “coronavirus,” “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2”, “novel coronavirus”, “nCoV,” “2019-nCoV,” and “COVID-19.” Considering the urgency of the topic and the need to increase the sensitivity of the search, a gray literature search was performed using the same keywords on Google Scholar to capture the most recently published articles. Furthermore, the World Health Organization(WHO) database of publications, the Lancet COVID-19 Resource Centre, NEJM, JAMA, BMJ, Gastroenterology, GUT, American Journal of Gastroenterology and Centers for Disease Control and Prevention (CDC) COVID-19 publications were screened for potentially relevant publications. Additional articles were retrieved by

screening the reference lists of included studies and from the archives of the reviewers. Literature search was restricted to English language. One of the reviewers (YQ) with experience in database searches designed the search strategy, which was subsequently revised by other reviewers. In consideration of the date of the earliest confirmed reports of COVID-19, the search was limited to 2020 with the start date of January 1st 2020. Because of the large number of records identified from the gray literature, the Google Scholar search was limited to titles. However, no additional limits were applied in the PubMed, Embase or Web of Science search. Records were managed by EndNote X 9.0 software to exclude duplicates.

Eligibility Criteria and Study Selection

Eligible studies reported the epidemiological, clinical features of COVID-19, and the prevalence of GI findings in infected patients. Literature were included with restriction to English language. Given that pre-print papers in database such as bioRvix and medRvix were not peer-reviewed, we did not include the publications in our present analysis to avoid any potential misinformation being disseminated at present. The following studies were excluded: (a) duplicate publications, (b) reviews, editorials, (c) single case report and (d) studies pertaining to other coronavirus-related illnesses, such as Middle East respiratory syndrome (MERS), and (d) small case series (<10 cases). Two reviewers (YQ, JSH) independently screened the titles and abstracts according to

these eligibility criteria. Disagreement was discussed with other reviewers and subsequently resolved via consensus.

Risk of Bias

Two reviewers (JSH, JYT) independently rated the quality of included studies using the National Institutes of Health Quality Assessment Tool for Case Series Studies[13]. Any disagreement was resolved by the third senior reviewer (RM).

Data extraction and definitions

The two investigators (QY and JSH) who performed the literature search also independently extracted the data from included studies. Disagreements were resolved by a third investigator (RM) or by consensus. We extracted the following variables: author, date, study design, country, patient demographics, number of participates in severe and non-severe disease group, the prevalence of clinical GI symptoms such as vomiting, nausea, diarrhoea, loss of appetite, abdominal pain, and belching, together with digestive system comorbidities including liver disease, and gastrointestinal diseases. Liver injury was defined according to the studies. Any kind of abnormal of liver damage indices such as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and total bilirubin (TB) was also classified as liver injury. The disease severity was defined according to the studies, mainly based on the symptoms present at diagnosis, in some cases, patients with pulse oxygen saturation

(SpO2)<90%[14] or need of intensive care unit (ICU) care[15] or with ARDS[16] were also classified as severe cases. COVID-19 was diagnosed on the basis of the WHO interim guidance.[17]

Data Synthesis and Statistical Analysis

For estimate of standardised mean difference (SMD) or weighted mean differences, we used 2 simple formulas proposed by Hozo et al[18] to estimate the mean using the values of the median, the low and high ends of the range, and the sample size. The odds ratio (OR, 95% confidence intervals (CI)) was used to describe the ratio of the probability of events occurring in severe vs. non-severe patients with COVID-19. Owing to heterogeneity within and between studies, a random effect model was used to estimate the average effect and its precision, which would give a more conservative estimate of the 95% CI. We used the I^2 statistic and Cochran's Q test to assess statistical heterogeneity. A meta-analysis was planned to assess the association of GI symptoms and liver injury with demographic data, outcomes, and disease characteristics. The meta-analysis was performed using the metaprop command of the meta package in R (version 3.2.0) for pooling single-armed rates, Stata (version 12.1) with the commands metareg (for meta-regression) for assessment of publication bias, and Review Manager (RevMan version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for all the other analyses.

Publication Bias

Funnel-plot asymmetry as proposed by Begg and Egger et al[19] was used to investigate the possibility of publication bias.

Role of the funding source

There is no funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

1.Study selection

Among the 8,948 records that were identified through electronic and hand-search strategies after removal of duplication, two reviewers (YQ and JSH) independently evaluated the titles and abstracts, removed 8,896 irrelevant studies, and selected 52 potentially relevant reports that were identified and retrieved for detailed evaluation. Two studies[20, 21] were excluded due to lack of absolute numbers for outcomes, 8 studies[22-29] were excluded due to case series with patients <10, and 7 studies were further excluded due to being pre-print papers in database medRvix, thus 35 studies[2, 8, 9, 12, 14-16, 30-57], comprising 6,686 patients with COVID-19 met the inclusion criteria and were included in the quantitative synthesis (**Figure 1).**

2. Characteristics and assessment of quality of the included studies

The main characteristics of patients and studies included in the meta-analysis are shown in (**Appendix, Supplementary Table 1**). The majority of studies were from China, except one from Singapore[31] and one from United States.[30] The studies included mainly adult patients except four paediatric studies[8, 37, 43, 54] and 6 studies[2, 9, 38, 45, 46, 53] with small group of paediatric patients (36 patients in total). All the included studies were rated low by National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies (**Appendix, Supplementary Table 2**).

3. Gastrointestinal features

3.1 Digestive system comorbidities

By combining 21 studies reporting GI data of patients with COIVD-19 at diagnosis, the pooled estimate of digestive system comorbidities (i.e underlying gastrointestinal disease and liver disease) rate was 4% (95% CI: 2%- 5%; range: 0–15%; I^2=74%; **supplementary. Figure 1**). Specifically, the pooled estimate rate of liver disease comorbidities was 3% (95% CI: 2%–4%; range: 0– 25%; I^2=57%). The most reported digestive system comorbidities included chronic hepatitis or liver cirrhosis, and peptic ulcer.

3.2 Gastrointestinal symptoms as the initial presenting symptoms

Gastrointestinal symptoms as the initial symptoms have been reported in several case series. [40] COVID-19 induced diarrhoea at onset was first reported in a patient with COVID-19, [58] and subsequently confirmed by cases in Singapore [31] and Japan[59].

The pooled estimate of GI symptoms as presenting symptoms was 10% (95% CI: 4%-19%; range: 3%–23%; I^2= 97%; 5 studies, **supplementary Figure 2**). Patients presenting with GI symptoms had longer duration from illness onset to admission (SMD 2.85, 95% CI: 0.22-5.48, p=0.030, I^2=73%).

The result regarding detection of COVID-19 virus Ribonucleic Acid (RNA) in stool or rectal swab is summarized in **Appendix, Supplementary Table 3**.[5, 8, 31, 37, 59-64] The

positivity rate of COVID-19 viral RNA in faecal samples was 54% (95%CI 44%-64%, I^2= 28%).

3.3 Rate of gastrointestinal symptoms

GI symptoms and abnormal liver function in patients with COVID-19 from the included studies are summarized in **Appendix, Supplementary Table 4.** Combining all 29 studies (n=6,064) reporting GI symptoms in patients with COVID-19 at diagnosis, the pooled rate of digestive symptoms was 15% (95% CI: 10%- 21%; range: 2%–57%; I^2= 96%; **supplementary Figure 3**). Specifically, nausea and/or vomiting, diarrhoea and anorexia were the main GI symptoms. The pooled estimate rate of diarrhoea was 9% (95% CI: 6%- 12%; range: 1%– 34%; I^2=89%; 26 studies(n=), **Figure 2a**).The pooled estimate of nausea and/or vomiting rates were 7% (95% CI: 5%- 9%; range: 1%–22%; I^2=88%; 18 studies(n=)), loss of appetite was 21% (95% CI: 9%–44%; range: 1%– 79%; I^2=98%; 8 studies (n=), and abdominal pain was 3% (95% CI: 2%–5%; range: 1%– 4%; I^2=31%; 6 studies(n=)), respectively **(Figure 2b-d**).

3.4 Liver injury

Regarding presence of liver injury, the pooled estimate of 12 studies (n=1,267) was 19% (95% CI: 9%-32%; range: 1%-53%; I^2= 96%; **supplementary Figure 4**). More specifically, the pooled estimate of the rate of elevated ALT was 18% (95% CI: 13%–25%; range: 4%–40%; I^2= 90%), elevated AST was 21% (95% CI: 14%–29%; range:

4%–53%; I^2= 92%), and elevated TB was 8% (95% CI: 3%–18%; range: 1%–31%; I^2= 94%; **Figure 3a-c**). The pooled estimate of the rate of decreased ALB (albumin) was 32% (95% CI: 3%–89%; range: 6%–78%; I^2=98%; **Figure 3d**).

3.5The clinical course of patients with GI symptoms

The proportion of severe/critical cases was markedly increased in COVID-19 patients with GI symptoms compared with those without GI symptoms (31.6% vs.13.4%, OR 3.97, 95% CI: 1.49-10.62, p=0.0060, I^2=79%, **Figure 4**). However, the risk of severe disease was not increased among patients with digestive/liver-related comorbidities (OR 0.57, 95% CI:0.15, 2.18, p=0.41, I^2=44%) when compared with patients without these comorbidities (supp. **Figure** 5).

Patients with GI symptoms had a higher risk of ARDS (OR 2.96, 95% CI: 1.17- 7.48, p=0.020) and liver injury (OR 2.71, 95% CI: 1.52-4.83, p<0.01) (**supp. Figure 6**). However, the pooled rate of discharge (OR 0.72, 95% CI: 0.37-1.41, p=0.34, n=458, **Figure 4**) , the length of hospital stay (SMD 1.70, 95% CI: -0.81, 4.21, P=0.18, n=341) and the rates of death (OR 1.21, 95% CI: 0.68-2.16, p =0.52, I^2=8%, **Figure 4**) were comparable between patients with and without GI symptoms.

4. Subgroup analysis

4.1 Severe Vs non-severe COVID-19

We analysed the difference in GI symptoms between severe and non-severe patients with COVID-19 (Figure 5). Patients with severe cases were more likely to present with GI symptoms compared to non-severe ones (OR 1.61, 95% CI: 1.09, 2.36, p=0.020, I^2=44%). More specifically, a higher risk of patients presenting with abdominal pain (OR 7.15, 95% CI: 1.95, 26.27; p=0.0030, I^2=0) was observed in the severe group compared to those in non-severe patients. However, there were no statistically significant difference between severe and non-severe patients in loss of appetite (OR 2.83, 95% CI: 0.92, 8.69, p=0.070, I^2=64%), diarrhoea (OR 1.22, 95% CI: 0.81-1.84; p=0.35, I^2=0) , or nausea and/or vomiting (OR 1.23, 95% CI: 0.69-2.19; p=0.49, I^2=32%).

A higher risk of liver injury was observed in the severe group compared to those in non-severe group with an OR of 2.2 (95% CI: 1.60-3.02, p<0.001, I^2=36%, **Figure 6**). The value of liver damage indices such as ALT (standardized mean difference(SMD), 0.46; 95% CI, 0.27 to 0.65; P < 0.001) and AST (SMD, 0.36; 95% CI, 0.12 to 0.60; P = 0.0030) and TB (SMD, 0.28; 95% CI, 0.02 to 0.54; P = 0.030**)** levels were significantly elevated in patients with severe group compared with non-severe group (**Supplementary. Figure 7**). However, the pooled analysis failed to demonstrate a significant difference in albumin (ALB) levels between two groups (SMD,- 0.23; 95% CI, -0.51 to 0.06; P =0 .11; **Supplementary. Figure 7**).

4.2 Patients in Hubei vs. outside Hubei

We further analysed the differences between patients in Hubei (the place of COVID-19 initial outbreak in China, n=4,009) vs. outside Hubei province (n=2,677). The incidence of overall GI symptoms at diagnosis (17%[95%CI 10-28%] vs. 9%[95%CI 6-14%]; p= 0.078) were comparable between the two groups. There was a higher proportion of patients in Hubei presenting with nausea and/or vomiting(8%[95%CI 5-11%] vs. 4%[95%CI 3-7%]; P=0.045) compared to those outside Hubei (**Appendix, Supplementary Table 5**). Other symptoms including diarrhoea and loss of appetite were comparable between patients in Hubei and outside Hubei.

However, there is a higher risk of liver injury in patients of Hubei compared to those outside Hubei (21% [95%CI 4-59%] vs. 10% [95%CI 4-25%]; P<0.01).This trend is further confirmed by the data that a larger proportion of patients in Hubei had elevated ALT (25% [95%CI 17-35%] vs. 15% [95%CI 9-23%]; P=0.069) , AST (30% [95%CI 18-46%] vs. 16% [95%CI 11-24%]; P=0.053) and TB (24% [95%CI 16-33%] vs. 4% [95%CI 2-9%]; P<0.001) compared to cases outside Hubei (**Appendix, Supplementary Table 5**).

4.3 Adult vs Paediatric patients

We further analysed whether digestive symptoms varied between adult (n=6420) and paediatric patients (n=266). GI symptoms including diarrhoea (9%[95%CI 6-13%] vs. 10%[95%CI 6-15%], p=0.78), and nausea and/or vomiting(7% [95%CI 5-9%] vs. 6% [95%CI 4-11%]; P=0.95) were comparable between the two groups (**Appendix,**

Supplementary Table 5). Similarly, paediatric patients with COVID-19 had an equivalent risk of liver injury (10% [95%CI 4-22%] vs. 18% [95%CI 8-35%]; P= 0.32), as compared with adult cases. However, paediatric patients were less likely to present with elevated ALT compared with adult patients (7% [95%CI 3-18%]; P=0.034 vs. 20% [95%CI 14-28%]) (**Appendix, Supplementary Table 5**).

5. Publication bias

Significant publication bias was found either by funnel plot or by the Egger test (p <0.01) for GI symptoms (**supplementary. Figure 8**) but not for liver injury (p= 0.18).

Discussion

An increasing number of studies reported the involvement of the digestive system in patients with COVID-19. The present study aimed to investigate the pooled rate of GI symptoms and liver injury in COVID-19. Overall, the pooled rates of GI symptom and liver injury were 15% and 19% in patients with COVID-19, respectively. As the severity of the disease increases, digestive symptoms and liver injury become more pronounced. About 10% patients presented with GI symptoms alone without respiratory features. Patients with GI system involvement tend to have delayed diagnosis, higher risk of severe/critical disease and development of ARDS.

Over the course of the current pandemic, some patients can initially present with abdominal symptoms even without fever or respiratory manifestations[58]. In a large multicentre study,[12] of 204 patients with COVID-19 in three heavily affected hospitals during the initial outbreak in China, 99 patients (48.5%) presented with digestive symptoms as their chief complaint. There were 7 cases presenting with digestive symptoms but no respiratory symptoms. Luo[40] reported a large case series (n=1,141) of hospitalised patients with SARS-CoV-2 infection, 183 (16%) presented with gastrointestinal symptoms only. Wang et al [33] also found around one in ten (10.1%) patients initially presented with diarrhoea and nausea 1 to 2 days prior to development of fever and dyspnoea. In the present study, about 10% (95% CI: 4%- 19%; range: 3%–23%; I^2= 97%) patients presented with GI symptoms alone without respiratory features.

Patients with digestive symptoms had a variety of manifestations, such as loss of appetite (83 (83.8%) cases), diarrhoea (29 (29.3%) cases), vomiting (8 (0.8%) cases), and abdominal pain (4 (0.4%) cases). [12]According to the present study, 15% (95% CI: 10%- 21%) patients with COVID-19 presented with digestive symptoms, including nausea and/or vomiting with a pooled rate of 7% (95% CI: 5%- 9%), diarrhoea 9% (95% CI: 6–12%), loss of appetite 21% (95% CI: 9–44%), and abdominal pain 4% (95% CI: 3–4%). Autopsy studies are important to help investigate the histopathological change of GI tract in COVID-19. Currently there is only one published autopsy report in an 85-year-old man with COVID-19, which showed segmental dilatation and stenosis in the small intestine.[64] Further studies are needed to clarify whether this finding is secondary to COVID-19 or a pre-existing GI comorbidity.

In addition to digestive symptoms, patients with COVID-19 are also at risk of developing liver injury. Recent studies have shown that patients had varying degrees of liver function abnormalities, the incidence ranged from 14.8% to 53%, mainly indicated by abnormal ALT and AST levels, accompanied by slightly elevated bilirubin levels. The albumin was decreased in severe cases and the level of albumin was around 26.3-30.9 g/L.[32] In our study, the pooled estimate of liver injury was 19% (95% CI: 9%-32%). Our findings indicate that one in five patients will develop liver function abnormalities, especially in severe cases (may be as high as 53%), thus special notice

of liver dysfunction should be taken in treating COVID-19 patients over the hospitalisation period.

The characteristics of the liver injury was slight elevation in hepatocyte related enzymes including ALT and AST. Cholangiocyte related enzymes such as alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT) were also reported to be slightly elevated in a few patients (3.1% and 3.0%).[65] Studies on the exact mechanism of COVID-19 related liver injury are scarce. Liver abnormalities of COVID-19 patients may be due to viral infection in liver cells or other causes such as drug toxicity and systemic inflammation [66]. A recent postmortem biopsy study in a COVID-19 patient showed moderate microvascular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either COVID-19 infection or drug-induced liver injury.[67] [68] Similar to the situation in SARS, drugs such as antivirals might potentially cause liver injury in COVID-19. [69] However, one study reported that there was no statistical difference between patients on medication or not when stratified by the prehospital medications including antibacterial drugs, antiviral drugs (abidol, oseltamivir, acyclovir), and antipyretic drugs with paracetamol (acetaminophen).[68] Further studies are warranted in this setting.

The link between GI involvement and disease severity of COVID-19 has been proposed recently. In a multicentre study, Lei et al. [12]investigated the prevalence and outcomes of COVID-19 patients with digestive symptoms. In 99 patients who presented with digestive symptoms as chief complaint, a longer time from onset to admission was

observed compared to patients without digestive symptoms (9.0 days vs. 7.3 days). As the severity of the disease increased, digestive symptoms became more pronounced. Patients without digestive symptoms were more likely to be cured and discharged than patients with digestive symptoms (60% vs. 34.3%).[12] This was consistent with the study from Wang et al who found that patients admitted to the ICU were more likely to have abdominal pain and loss of appetite compared with the non-ICU patients.[33] In the present study, we performed subgroup analysis to investigate the difference in GI symptoms between severe and non-severe patients with COVID-19. Indeed, there was a higher prevalence of GI symptoms (OR 1.61, 95% CI: 1.09-2.36, p=0.020), including anorexia (OR 2.83, 95% CI: 0.92-8.691, p=0.070), and abdominal pain (OR 7.15, 95% CI: 1.95-26.27; p=0.0030) in the severe group compared to the non-severe cases. Cai et al [65] showed liver injury occurred more frequently in severe patients (36.2% vs. 9.6%, p<0.001) than non-severe patients. We also found a significantly higher risk of liver function abnormalities in the severe group compared to those in non-severe group(OR 2.2, 95% CI: 1.60-3.02, p<0.001). In COVID-19 cases who died, the incidence of liver injury might reach as high as 58.06% [70] and 78% [71]. One study reported that serum ALT and AST levels increased up to 7590 U/L and 1445 U/L respectively in a severe COVID-19 patient.[32]

In the present study, we further investigated the disease course and outcomes in subgroups of patients with digestive system involvement. We found patients presenting with initial GI symptoms had longer duration from illness onset to admission (SMD

2.85, 95% CI: 0.22-5.48, p=0.030), and the rate of the severe/critical type was markedly increased when compared to those without GI symptoms (31.6% vs.13.4%, OR 3.97, 95% CI: 1.49-10.62, p=0.0060). Patients with GI symptoms also had a higher risk of ARDS (OR 2.96, 95% CI: 1.17- 7.48, p=0.020). No significant difference was seen when considering pooled rates of discharge (OR 0.72, 95% CI: 0.37-1.41, p=0.34), length of hospital stay (SMD 1.70, 95% CI: -0.81, 4.21, P=0.18) and rates of death (OR 1.21, 95% CI: 0.68-2.16, p =0.52) between patients with and without GI symptoms. This may be due to the relatively low incidence of each event. Moreover, the risk of severe case was not increased among COVID-19 patients with existing digestive/liver-related comorbidity when compared with patients without such comorbidity (OR 0.57, 95% CI:0.15, 2.18, p=0.41). Thus, the newly presenting GI symptoms rather the existing digestive/liver-related comorbidity were predictive of severe disease course. Altogether, our findings supported the importance of including symptoms like diarrhoea to diagnose COVID-19 early.

The characteristics of patients with imported COVID-19 outside Hubei may vary from patients in Hubei. An early study including 80 imported cases of COVID-19 in Jiangsu Province showed that imported cases exhibited mild or moderate symptoms and lower proportion of liver dysfunction compared with the cases in Wuhan.[38] Our subgroup analysis suggested that there was no difference in rate of overall GI symptoms. Patients in Hubei had a higher risk of presenting with abnormal liver function. It might be argued

that there were more severe cases in Hubei compared with those outside Hubei, which may result in the higher percentage of patients with abnormal liver function in Hubei. However, our present analysis included studies that did not show significant difference in percentage of severe cases between Hubei and outside Hubei (data not shown). This needs to be further investigated in future studies.

A few paediatric cases are reported and their clinical features have yet to be fully evaluated. In a recent landmark clinical investigation on ten paediatric COVID-19 cases in China, these patients had clinically milder symptoms and showed fewer alterations in radiological and laboratory testing parameters.[8] In the present study, we included 4 paediatric studies with 227 patients in total.[8, 37, 43, 54] According to our subgroup analysis, paediatric patients with COVID-19 had a lower risk of elevated ALT, as compared with adult cases. However, the GI symptoms including diarrhoea, and nausea or vomiting were comparable between paediatric and adult patients.

Emerging data showed the prolonged presence of COVID-19 virus RNA in stool samples or rectal swab even after the patients' respiratory specimens were negative.[8, 61] Much attention has been paid to the possibility of virus shedding by gastrointestinal tract and faecal–oral transmission. In the clinical investigation on ten paediatric COVID-19 cases, eight persistently tested positive on rectal swabs even after nasopharyngeal testing was negative. [8] After reviewing all studies testing virus RNA in stool or rectal swabs,

the positive rate of COVID-19 viral RNA in faecal samples was 54% (95%CI 44%-64%), the duration of virus positivity can persist for as long as 47 days after symptom onset (**Appendix, supplementary Table 3**). Data from Wu et al [61]suggest the possibility of extended duration of viral shedding in faeces, for nearly 5 weeks after the patients' respiratory samples tested negative for COVID-19. However, the clinical implication of prolonged faecal virus excretion including its association with disease course, severity and even recurrence of COVID-19 remains unclarified. It clearly may have major public health and clinical policy significance. More studies are needed to demonstrate its replication-competence, its abundance in stool and stability in environment[72-73].

This meta-analysis is potentially limited in several ways. First, an assessment of the methodological quality determined that there were deficiencies in studies evaluated, as all the 35 studies included were considered low-quality. Second, due to lack of sufficient data reported in the original publications, it was not possible to evaluate the effect of other factors, such as gender, age, and comorbidities, on the rate of gastrointestinal symptoms at diagnosis, and risk of liver injury. Third, the criteria for severe COVID-19 differed among studies, which may contribute to the heterogeneity of the meta-analysis. As defined in the methods section, we took the criteria per study, in other cases we defined the severe cases by their symptoms (SpO2<90% or ARDS) or poor prognosis (need of ICU care). Last but not the least, significant heterogeneity and publication bias were observed in our study for estimating the prevalence of

digestive system symptoms. After reviewing each study, the majority of heterogeneity were from nonspecific symptom of appetite loss, and two studies [40, 49] focusing on patients with GI symptoms. When these studies were excluded from the analysis, the pooled rate of digestive symptoms was 7% (95% CI: 5%- 8%; I^2= 78%), which is of modest heterogeneity. The pooled rate is lower than 15% due to the high incidence of loss of appetite. However, the pooled rates of other three symptoms were similar to original results with only mild or modest heterogeneity.

In conclusion, the present systematic review and meta-analysis suggest that the digestive symptoms and liver injury are not uncommon in patients with COVID-19. Compared with non-severe cases, severe cases with COVID-19 had a higher risk of developing GI symptoms and liver injury. Patients in Hubei had comparable risk of developing GI symptoms but higher risk of liver injury than those outside Hubei. Paediatric patients with COVID-19 have equivalent risk of GI symptoms compared with adult patients. One tenth of patients with COVID-19 may present only with GI symptoms without respiratory symptoms. Patients with GI system involvement have delayed diagnosis with a tendency to severe/critical type and a poor disease course. More attention should be paid to the care of these unique group of patients.

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Figure Legends

Figure 1. Study selection

Figure 2. Pooled estimate of GI symptoms spectrum: (a) nausea and/or vomiting, (b) diarrhoea, (c) loss of appetite and (d) abdominal pain in patients with COVID-19.

Figure 3. Estimated incidence of abnormal liver chemistry including (a) elevated ALT, (b) elevated AST, (c) elevated TB, and (d) decreased ALB in patients with COVID-19.

Figure 4. Prognosis of patients with COVID-19: Estimated incidence of (a) severe case, (b) discharge and (c) mortality, stratified by digestive system involvement

Figure 5. Forrest plot of meta-analysis of GI symptoms according to patients' disease severity (severe vs. non-severe).

Figure 6. Forrest plot of meta-analysis of odds ratio of liver chemistry according to patients' disease severity (severe vs. non-severe).