Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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ORIGINAL ARTICLE

The liver injury and gastrointestinal symptoms in patients with Coronavirus Disease 19: A systematic review and meta-analysis

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Summary
Backgrounds: Since December 2019, novel coronavirus (SARS-CoV-2)-infected pneumonia (COVID-19) occurred in Wuhan, and rapidly spread throughout China. Our study aimed to evaluate the association of liver injury and gastrointestinal symptoms (GIS) with the progression of COVID-19.
Methods: A comprehensive search was performed on the PubMed to identify eligible studies that summarized the liver injury and GIS in COVID-19.
Results: A total of 21 studies with 3024 patients were included. Up to 53% patients had liver dysfunctions and the degree of liver damage was associated the severity of the disease. The prevalence of diarrhoea, nausea/vomiting or abdominal pain in patients with COVID-19 were 9.1%, 5.2% and 3.5%, respectively. No significant was found in the prevalence of diarrhoea (OR, 1.24; 95%CI, 0.90 to 1.72; $I^2 = 0\%$, $P = 0.19$) and nausea/vomiting (OR, 1.24; 95%CI, 0.57 to 2.69; $I^2 = 61\%$, $P = 0.58$) between severe and non-severe patients. In addition, diarrhoea (OR, 1.22; 95%CI, 0.50 to 2.98; $I^2 = 0\%$, $P = 0.66$) and nausea/vomiting (OR, 1.09; 95%CI, 0.46 to 2.62; $I^2 = 0\%$, $P = 0.84$) were not associated with the prognosis of COVID-19 patients.
Conclusions: The incidences of GIS in patients with COVID-19 is relatively low and are not associated with the COVID-19 progression. Gastroenterologists should pay more attention to the liver injury induced by SARS-CoV-2 during the course of infection.

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Introduction

Since December 2019, novel coronavirus (SARS-CoV-2)-infected pneumonia (COVID-19) occurred in Wuhan and spread rapidly across the world [1,2]. The pathogen was confirmed to be a distinct clade from the β-coronaviruses, which was officially named SARS-CoV-2 with the disease termed COVID-19. Liver injury has been reported in several recent COVID-19 studies, but its incidence varies [3,4]. In addition, Gu et al. and Xiao et al. concluded that gastrointestinal symptoms (GIS) (diarrhoea, vomiting or abdominal pain) should not be ignored during the outbreak of COVID-19 [5,6]. Song et al. also reported a case with diarrhoea as the onset symptom, and emphasized that gastrointestinal system might be a potential route for SARS-CoV-2 infection [7]. However, the latest epidemiological study showed a relatively low prevalence of gastrointestinal symptoms induced by SARS-CoV-2 [3]. Therefore, we performed a systematic review and meta-analysis to determine the liver injury and the prevalence of GIS in COVID-19 patients.

Methods

Search strategy

This meta-analysis was performed and reported according to the PRISMA statement [8]. The study was approved by the Ethics Committee of the Zhongnan Hospital of Wuhan University (No. 2020011). A literature search was performed on the PubMed library from inception to 31 March 2020. The search strategy was a combination of (''COVID-19'' OR ''2019-ncov'' OR ''SARS-CoV-2'') AND (''clinical features'' OR ''clinical characteristics''). The relevant papers were also searched manually to identify additional studies that might have been missed in the above literature search.

Inclusion and exclusion criteria

A PICOS criteria was applied to strict the inclusion and exclusion criteria. Inclusion criteria were as follows:

- studies about clinical characteristics of COVID-19;
- number of samples > 10;
- study contains indicators of liver dysfunction, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB)/globulin (GLB) and total bilirubin (TB);
- specific gastrointestinal symptoms such as diarrhoea, nausea, vomiting, and abdominal pain are described.

Exclusion criteria were as follows:

- case reports, letters or reviews;
- non-English studies;
- technical guideline;
- unrelated research.

Data extraction

The data were extracted independently by two authors (Haizhou Wang and Fan Wang) from the included studies based on the following terms:

- study ID;
- date;
- group size;
- patient demographics;
- group design;
- liver dysfunction, including ALT/AST/ALB/GLB/TB;
- GIS, including abdominal pain, diarrhoea and nausea or vomiting.

Discrepancies would be solved through discussion.

Statistical analysis

The Cochrane Review Manager (RevMan) program (RevMan 5.3, Denmark) and OpenMeta Analyst were used to pool and analyze the aforementioned outcomes extracted from the included studies. For the AEs (dichotomous data), odds ratios (OR) with 95% confidence intervals (CI) were selected to report the risk estimates following the Mantel-Haenszel method [9]. In addition, the heterogeneity among the studies we included was assessed by the Q and I^2 statistic [10]. When $I^2 < 50\%$, the fixed effects model was applied to estimate risk using the DerSimonian and Laird method because of lower heterogeneity. In contrast, the random effects model was used when I^2 was > 50% [9]. A P value < 0.05 was considered to be statistically significant.

Results

Search results and liver injury in COVID-19

Fig. 1 showed the search flowchart and twenty-one studies were included with a total of 3024 COVID-19 patients [3,5,11—20,2,21—27]. The baseline characteristics of the included studies was presented in Table 1. First, we evaluated how the liver is affected based on the included study. A total of 16 studies reported liver comorbidities or ALT/AST/ALB/GLB/TB abnormalities (Table 2). The data showed that 0.8-11% of COVID-19 patients had chronic liver comorbidities and 2.6-53% patients had abnormal levels of ALT, AST and TB, and 6-98% had abnormal levels of ALB during the COVID-19 progression. Moreover, patients with severe conditions or non-survival patients had higher rates of liver dysfunction. Thus, liver injury was more common in severe cases than mild cases in COVID-19.

The prevalence of GIS

Diarrhoea was the most common gastrointestinal symptom (19 studies included symptoms of diarrhoea) and selected as the primary outcome, while its prevalence was only 9.1% (95%CI, 6.3% to 11.9%, Fig. 2a). Fourteen studies reported symptoms of nausea or vomiting, with the prevalence of 5.2% (95%CI, 3.5% to 7.0%, Fig. 2b). In addition, only four

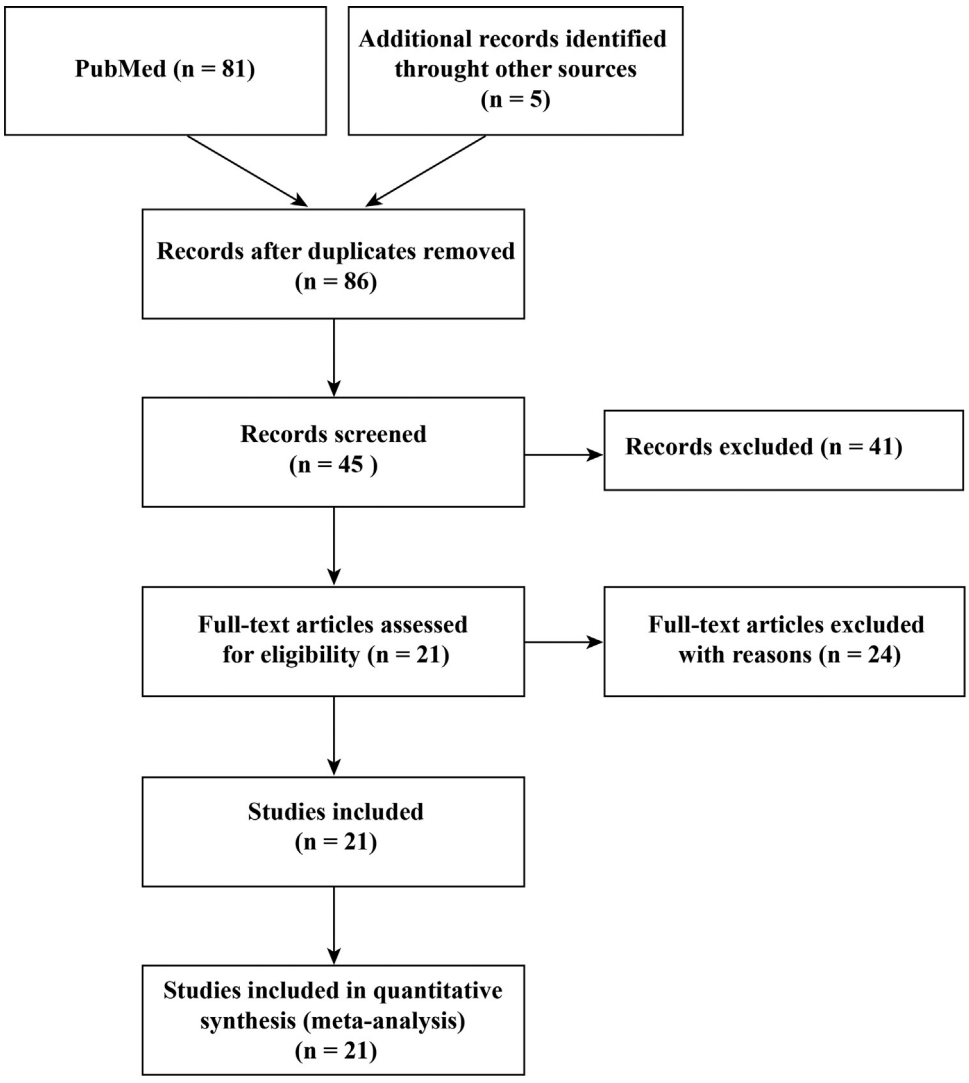

Figure 1 Flow chart of the whole procedures in this meta-analysis.

studies reported abdominal pain, with the prevalence of 3.5% (95%CI, 1.7% to 5.4%, Fig. 2c).

Severe vs. non-severe

We then compared the prevalence of GIS between severe and non-severe patients. The definition of severe and non-severe also includes intensive care unit (ICU) vs. non-ICU and generally vs. refractory. Seven studies were included, and the results showed that no significant was found in the prevalence of diarrhoea between severe and non-severe patients (OR, 1.24; 95%CI, 0.90 to 1.72; $I^2 = 0\%$, $P = 0.19$) (Fig. 3a). In addition, the severe patients also had similar prevalence of nausea or vomiting with non-severe patients (OR, 1.24; 95%CI, 0.57 to 2.69; $I^2 = 61\%$, $P = 0.58$) (Fig. 3b).

Survival *vs*. non-survival

The relationship between GIS and prognosis of COVID-19 was also analyzed. Three studies were included, and the results also indicated that diarrhoea was not associated with the prognosis of COVID-19 patients (OR, 1.22; 95%CI, 0.50 to 2.98; $I^2 = 0\%$, $P = 0.66$) (Fig. 4a). The results also showed no significant difference in the prevalence of nausea/vomiting between non-survival and survival patients (OR, 1.09; 95%CI, 0.46 to 2.62; $I^2 = 0\%$, $P = 0.84$) (Fig. 4b).

Discussion

In this study, we found that the prevalence of diarrhoea, nausea/vomiting, and abdominal pain in COVID-19 patients was 9.1%, 5.2%, and 3.5%, respectively. Meanwhile, they were not associated with the disease progression and patient prognosis. However, liver damage caused by SARS-CoV-2 infection was associated with disease progression.

Diarrhoea is the most common GIS in coronavirus infections, while nausea and vomiting are not specific. Moreover, nausea and vomiting are not necessarily caused by SARS-COV-2 infection and may be the result of various system dysfunctions. Therefore, diarrhea is the focus symptom of gastroenterologists on patients with coronavirus infection. It was reported that the prevalence of diarrhoea in

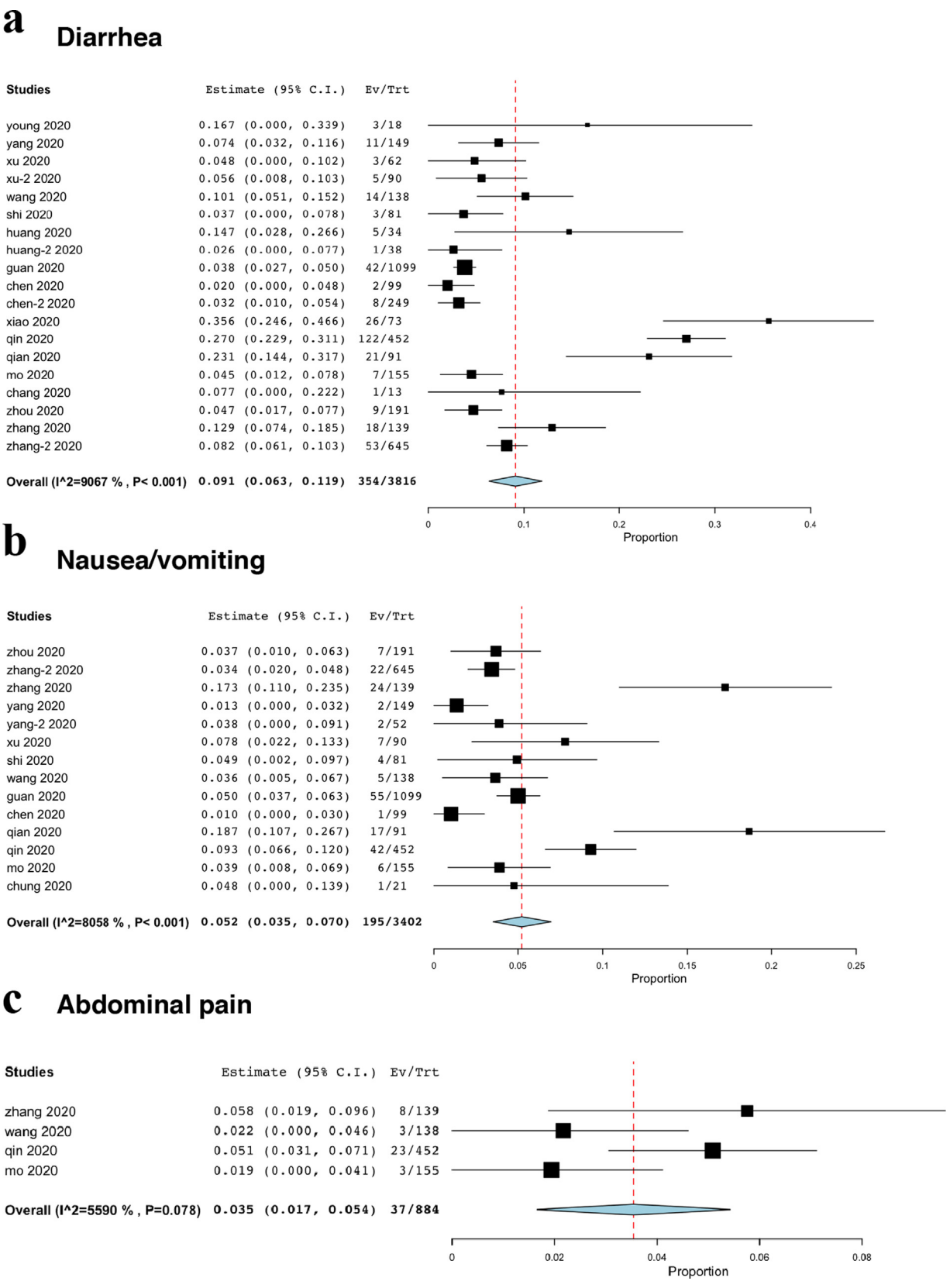

Figure 2 The prevalence of gastrointestinal symptoms. (a) diarrhoea; (b) nausea/vomiting; (c) abdominal pain.

Table 1 Baseline characteristics of the included studies.

Study ID	Date	Group size	Gender (M/F)	Age (mean)	Gastrointestinal symptoms
Zhou 2020	12/29/2019-1/31/2020	Non-survival (54) Survival (137)	16/38 56/81	69 52	Nausea or vomiting and diarrhoea
Zhang 2020	16/1/2020-3/2/2020	Non-severe (82) Severe (58)	38/44 33/25	51.5 64	Nausea, abdominal pain and diarrhoea
Young 2020	23/1/2020-3/2/2020	Non-severe (12) Severe (6)	7/5 2/4	37 56	Diarrhoea
Yang 2020	12/24/2019-1/26/2020	Non-survival (32) Survival (20)	21/11 14/6	64.6 51.9	Vomiting
Yang 2020	17/1/2020-10/2/2020	Overall (149)	81/68	45.11	Diarrhoea and nausea or vomiting
Xu 2020	10/1/2020-26/1/2020	Overall (62)	35/27	41	Diarrhoea
Xu 2020	17/1/2020-10/2/2020	Overall (90)	39/51	50	Diarrhoea, nausea and vomiting
Wang 2020	1/1/2020-28//2020	Non-ICU (102) ICU (36)	53/51 22/14	51 66	Diarrhoea, vomiting and abdominal pain
Shi 2020	12/20/2019-1/23/2020	Overall (81)	42/39	49.5	Diarrhoea and vomiting
Huang 2020	12/2019-1/2020	Overall (34)	14/20	56	Diarrhoea
Huang 2020	12/16/2019-1/2/2020	Non-ICU (28) ICU (13)	19/9 11/2	49 49	Diarrhoea
Guan 2020	12/11/2019-1/29/2020	Non-survival (67) Survival (1032) Non-severe (926) Severe (173)	45/22 592/437 537/386 100/73	63 46 45 52	Diarrhoea and nausea or vomiting
Chen 2020	1/1/2020-1/20/2020	Overall (99)	67/32	55.5	Diarrhoea, nausea and vomiting
Chen 2020	1/20/2020-2/6/2020	Overall (249)	126/123	51	Diarrhoea
Xiao 2020	2/1/2020-2/14/2020	Overall (73)	41/32	43	Diarrhoea
Qin 2020	1/10/2020-2/12/2020	Non-severe (166) Severe (286)	80/86 155/131	53 61	Diarrhoea, nausea and vomiting, abdominal pain
Qian 2020	1/20/2020-2/11/2020	Mild (82) Severe (9)	NA	49 66	Diarrhoea, nausea and vomiting
Mo 2020	1/1/2020-2/5/2020	General (70) Refractory (85)	33/37 55/30	46 61	Diarrhoea, nausea, vomiting and abdominal pain
Chang 2020	1/16/2020-1/29/2020	Overall (13)	NA	34	Diarrhoea
Zhang 2020	1/17/2020-2/8/2020	Normal CT (72) Abnormal CT (573)	33/39 295/278	34 46	Diarrhoea, nausea and vomiting
Chung 2020	1/1/2020-2/5/2020	Overall (21)	13/8	51	Nausea

Abbreviation: ICU: intensive care unit; M: male; F: female; CT: computed tomography.

patients with Middle East Respiratory Syndrome (MERS) and SARS was 30% and 10.6%, respectively [28]. One study indicated that MERS coronavirus could survive in simulated gastrointestinal fluids and has the ability to infect intestinal organoid models [28]. Hui et al. also proposed that SARS-CoV can be transmitted through the fecal-oral route [29]. Furthermore, Zhang et al. found that in the later stage of SARS-CoV-2 infection, the proportion of positive anal swabs was much higher than that of throat swabs [30]. The prolonged existence of SARS-CoV-2 viral RNA

Table 2 Comorbidity with liver injury in patients with SARS-CoV-2 infection.

Study ID	Patients number	Patients with pre-existing liver conditions	Total patients with abnormal liver function	Notes
Chen et al.	249	2 (0.8%) patients had chronic hepatitis B virus infection	NA	AST/ALT/ALB levels were within normal range.
Chen et al.	99	NA	ALT abnormal (28%) AST abnormal (35%) ALB abnormal (98%) TB abnormal (18%)	43 (43.4%) patients had liver function abnormality, with ALT or AST above the normal range
Guan et al.	1099	23 (2.1%) patients had chronic hepatitis B virus infection	ALT abnormal (21.3%) AST abnormal (22.2%) TB abnormal (10.5%)	ALT abnormal: severe (19.8%) vs. non-severe (28.1%) survival (19.9%) vs. non-survival (40.8%) AST abnormal: severe (39.4%) vs. non-severe (18.2%) survival (20.1%) vs. non-survival (50.0%) TB abnormal: severe (13.3%) vs. non-severe (9.9%) survival (9.8%) vs. non-survival (20.8%)
Huang et al.	41	1 (2%) patients had chronic liver disease	AST abnormal (37%)	AST abnormal: ICU (62%) vs. non-ICU (25%)
Huang et al.	34	1 (2.9%) patients had chronic liver disease	ALT abnormal (23.5%) AST abnormal (20.6%) ALB abnormal (73.5%) TB abnormal (8.8%)	NA
Mo et al.	155	7 (4.5%) patients had chronic liver disease	NA	The levels of ALT/AST all increased slightly, but all were within the normal range. The levels of ALB/GLB all decreased slightly, but all were within the normal range.
Qian et al.	91	NA	ALT abnormal (7.7%) AST abnormal (9.9%) ALB abnormal (47.3%)	NA
Qin et al.	452	6 (1.3%) patients had chronic liver disease	NA	NA
Shi et al.	81	7 (9%) patients had chronic liver disease	AST abnormal (53%)	The average level of ALT was 46.2U/L.
Wang et al.	138	4 (2.9%) patients had chronic liver disease	NA	The levels of ALT/AST/TB all increased slightly in the ICU group, but all were within the normal range.
Xu et al.	62	7 (11%) patients had chronic liver disease	AST abnormal (16.1%)	The average level of ALT was within the normal range.
Yang et al.	149	NA	ALT abnormal (12.1%) AST abnormal (18.1%) ALB abnormal (6.0%) TB abnormal (2.68%)	NA

Table 2 (*Continued*)

Study ID	Patients number	Patients with pre-existing liver conditions	Total patients with abnormal liver function	Notes
Yang et al.	52	NA	Liver dysfunction (29%)	NA
Zhang et al.	645	24 (3.7%) patients had chronic liver disease	NA	The levels of ALT/AST/TB all increased in the abnormal CT imaging group, but all were within the normal range. The levels of ALB decreased in the abnormal CT imaging group, but all were within the normal range.
Zhang et al.	140	8 (5.7%) patients had fatty liver and abnormal liver function	NA	NA
Zhou et al.	191	NA	ALT abnormal (31%)	The levels of ALB decreased below the normal range in the non-survival group.

Abbreviation: AST: aspartate aminotransferase; ALB: albumin; GLB: globulin; ALT: alanine aminotransferase; TB: total bilirubin; ICU: intensive care unit; NA: not applicable.

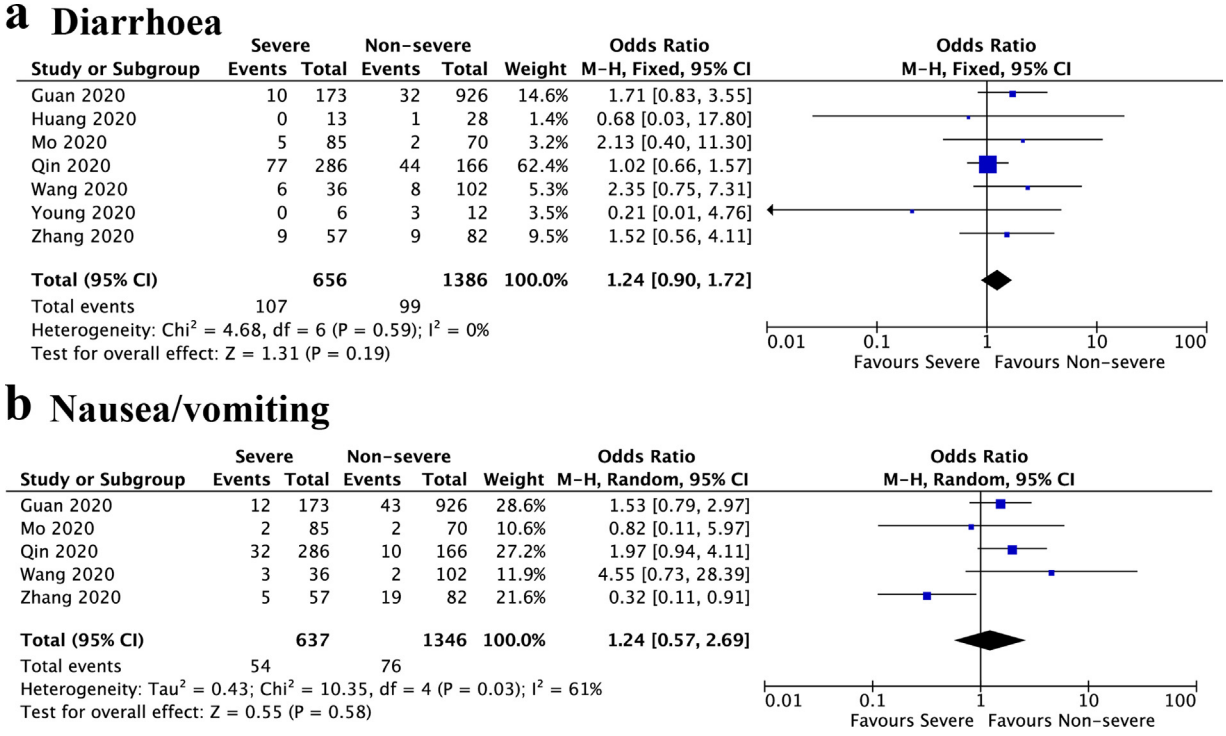

Figure 3 Forest plot showed the odds ratio of diarrhoea (a) and nausea/vomiting (b) between severe and non-severe patients. M-H, Mantel—Haenszel; CI, confidence interval.

in faecal samples was also observed by Wu et al. [31]. They found that 55% of COVID-19 patients had anal swab positive results, and the average positive time of throat swab was 16.7 days, while the average positive time for anal swabs was 27.9 days. Importantly, positive staining of viral nucleocapsid protein (NP) and angiotensin-converting enzyme 2 (ACE2) could be visualized in the cytoplasm of stomach, duodenum and rectal gland epithelial cells through immunofluorescence [5]. These might provide the basis for virus mutation to obtain fecal-oral transmission capability. However, it is necessary to further identify whether diarrhoea is induced by antiviral drugs or antibiotics. For example, oseltamivir can cause drug-related diarrhoea [32]. Although there are some supportive findings, it is

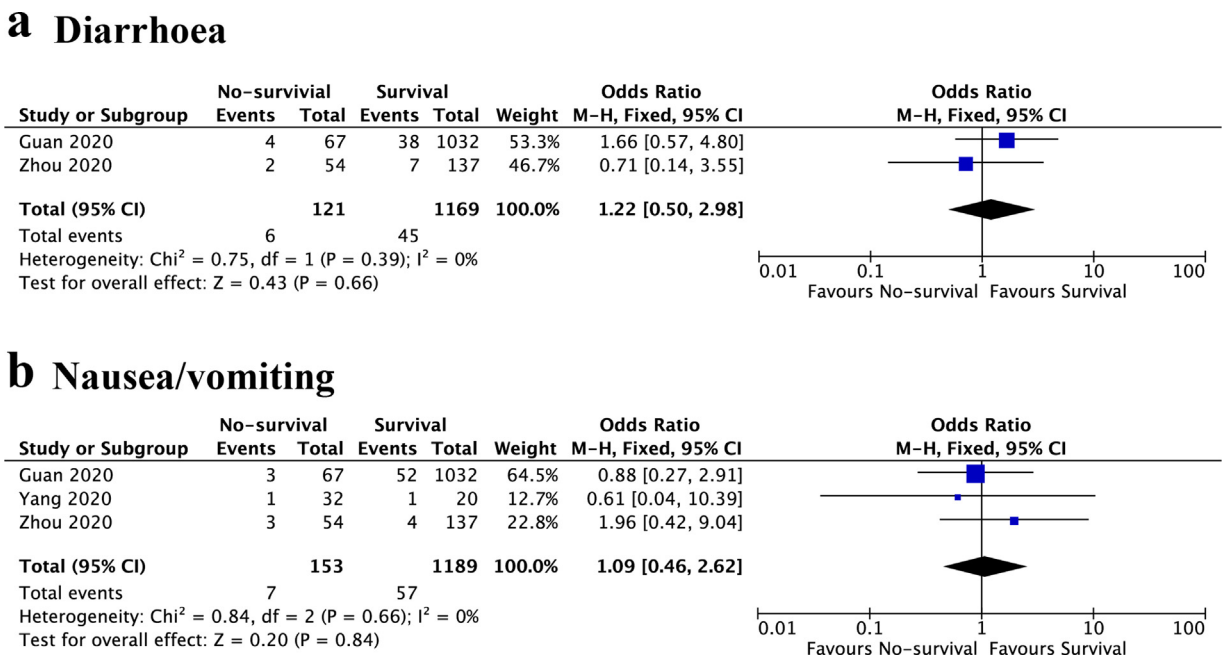

Figure 4 Forest plot showed the odds ratio of diarrhoea (a) and nausea/vomiting (b) between survival and non-survival patients. M-H, Mantel—Haenszel; CI, confidence interval.

premature to determine whether SARS-CoV-2 can be transmitted through the fecal-oral route based on the current studies. Further well-designed studies are needed to identify the role of SARS-CoV-2 on the gastrointestinal tract.

In addition, up to 60% of SARS patients had liver impairment [33]. It was also reported that MERS patients had liver dysfunction [34]. Virus infection of liver cells may be the direct cause of liver damage, and recent study detected SARS-COV-2 RNA in blood samples, which provided a basis for viral exposure in the liver [35]. Several pathological studies further confirmed the presence of SARS-CoV in the liver tissue, although not detectable in the liver of MERS patients [33,36]. Interestingly, Zou et al. found that liver showed lower ACE2 expression levels (< 1% ACE2 positive cells) through re-analyzing single cell RNA sequencing datasets [37], while some studies suggested that cholangiocytes were ACE2-enriched cells in the liver [38]. However, pathological findings found SARS-CoV-2 was not observed in the liver of a patient died from COVID-19 [39]. Therefore, the underlying mechanism of liver dysfunction induced by SARS-CoV-2 need further explore.

Based on the currently published data, it could be determined that liver injury in patients with mild COVID-19 could return to normal without special treatment, whereas liver injury in severe patients was more severe and required liver protection treatment. This may be due to the impaired immune function of patients with COVID-19. Our data showed 6-98% patients had abnormal ALB level and recent studies also demonstrated that lymphopenia, downregulation of CD4+ lymphocytes and cytokine storm were common in the severe or critical cases [14]. For patients with pre-existing chronic liver disease, such as chronic hepatitis B virus (HBV) infection, more evidence is needed to investigate the impact of co-infection (HBV and SARS-CoV-2) on the liver.

There are several limitations in our study. On the one hand, the patients in the results were the relatively focused patient population, mainly in China. During the current evolution into a global pandemic, we are eager to wait for more epidemiological studies in other countries. On the other hand, there are only 3 studies about the prognosis of COVID-19. More studies are needed to determine the relationship between liver dysfunction and disease prognosis.

In conclusion, liver injury caused by SARS-CoV-2 virus infection was associated with the severity of the disease. The prevalence of GIS was relatively low and was not associated with disease progression, with diarrhea of 9.1%, nausea/vomiting of 5.2% and 3.5% abdominal pain.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

HZW and QZ designed the study. HZW, FW and PSQ collected the data. HZW and FW drafted the manuscript. JL, HLW and QZ contributed to revise the manuscript. This study was supported by the Program of Excellent Doctoral (Postdoctoral) of Zhongnan Hospital of Wuhan University (Grant No. ZNYB2019003).

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