

**GASTROINTESTINAL MANIFESTATIONS OF COVID-19: A SYSTEMATIC REVIEW
AND META-ANALYSIS**

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ABSTRACT

Objective: At present, the novel coronavirus disease (COVID-19) is causing a major pandemic. COVID-19 is caused by Severe Acute Respiratory Syndrome-2 (SARS-CoV-2). In COVID-19, the patient generally presents with fever, dry cough, and respiratory and signs and symptoms. Other system involvement has also been reported. Abdominal pain, diarrhea, vomiting, and nausea are the predominant gastrointestinal symptoms, underlined in the literature. In this article, we summarized the important GIT characteristics of the disease. **Methods:** We conducted a literature search using four databases (PubMed, Google Scholar, Web of Science, and Clinicaltrials.gov). Our search strategy included MeSH terms and keywords for COVID-19, SARS-CoV-2, and gastrointestinal system from inception to December 2020. After excluding review articles, duplicates, and non-relevant, we included 60 studies out of 558 articles reporting gastrointestinal (GI) manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Using the 'meta' package (Schwarzer et al.) in the R programming language, version 4.0.2, a compute pooled analysis using the random effect model was performed. **Results:** The overall prevalence any GI signs and symptoms in affected patients with COVID-19, was 27% (95% CI: 21-35) (p<0.05) (I² =94%). GI as an initial presentation was reported in five studies with prevalence of 34% (95% CI: 05-83) (p<0.01) (I² =88%), diarrhea 16% (95% CI: 12-19) (p=0.01) (I² =94), anorexia 29% (95% CI: 22-38) (p<0.01) (I² =96%), abdominal pain 16% (95% CI: 11-20) (p<0.01) (I² =95%), and nausea/vomiting 17% (95% CI: 13-22) (p<0.01) (I² =88%). Severe COVID-19 with GI symptoms were reported with prevalence of 25% (95%CI: 19-31) (p<0.01) (I² =90%). Haptic abnormality was reported with prevalence of 22% (95% CI: 14-33) (p<0.01) (I² =97%). **Conclusion:** We perceive that COVID-19 may have several gastrointestinal manifestations, and in many cases, GI involvement may precede typical upper respiratory tract symptoms. Holistic knowledge of the spectrum of the COVID-19 GI consequences is crucial to get a hold of the virus spread.

KEYWORDS: COVID-19, SARS-COV-2, Gastrointestinal, Hepatic manifestation.

INTRODUCTION

The novel SARS-CoV-2, also known as coronavirus 2019 (COVID-19), first originated in Wuhan, China, during late December of 2019 before rapidly disseminating throughout the world being declared and being declared a pandemic by WHO in March 2020.^[1] SARS-CoV-2 was initially considered a primary respiratory illness with symptoms of shortness of breath (SOB), cough, and fever. However, there is a broad appreciation of the SARS-CoV-2 to produce a wide

range of symptoms like diarrhea, anorexia, vomiting, and abdominal pain.^[2]

Current Center for Disease Control (CDC) testing guidelines for covid-19 recognize the diversity of symptoms possible testing for patients presenting with fever, cough, shortness of breath, chills, myalgia, the new loss of taste or smell, abdominal pain, vomiting, diarrhea, or sore throat.^[1] In clinical practice, respiratory symptoms are prioritized by both patients and healthcare workers for testing and pre-emptive isolation

precautions, following the worldwide effort to halt the virus spread and mitigate its effects on the global population.^[3] This review and meta-analysis's objective is to determine whether isolated GI symptoms warrant testing for COVID-19 and whether GI symptoms, alone or in combination with respiratory symptoms, are associated with severe disease or mortality.

MATERIAL AND METHODS

Search strategy and study design

We conducted a literature search using four databases (PubMed, Embase, Web of Science, and Clinicaltrials.gov). Our search strategy included MeSH terms and keywords for COVID-19, SARS-CoV-2, and gastrointestinal system from inception to December 2020. After excluding review articles, duplicates, and

non-relevant, we included 60 studies out of 234 articles reporting gastrointestinal (GI) manifestations such as nausea, vomiting, abdominal pain, and diarrhea as per PRISMA guidelines (Figure 1). We included any literature that reported the presence or absence of GI manifestations in a sample of more than five COVID-19 positive patients, including diarrhea, nausea, vomiting, anorexia, abdominal pain, or hepatic injury, with or without the presence of respiratory viral manifestations. Three authors independently reviewed each article for inclusion and extracted data.

Study characteristics and Quantitative analysis:

Our search identified 558 unique articles, of which 60 met the inclusion criteria (Figure 1).

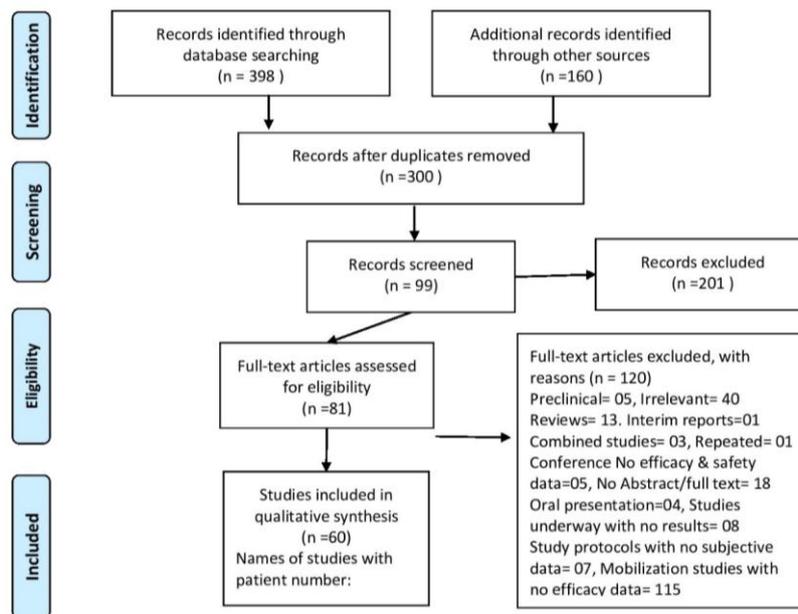


Figure 1: PRISMA flow sheet.

These comprised 10796 COVID-19 positive patients from different countries. Most studies focused on adult patients and the hospital setting. Many studies centered on specific hospitalized subpopulations, such as medical staff, healthcare workers, family clusters, orthopedic, pregnant, or critically ill patients. All defined COVID-19 cases exclusively by positivity on an upper respiratory swab polymerase chain reaction (PCR). There were only three prospective studies.

More than three studies reported data sufficiently similar to calculating a pooled prevalence; we performed a random-effects meta-analysis. Our study's primary outcome was the proportion of COVID-19 infected patients who experienced a period of isolated gastrointestinal symptoms. We also calculated pooled ratios of patients with any experience of GI manifestations, such as anorexia (loss of appetite). We performed a pooled analysis of proportions of

COVID-19 positive patients with elevated alanine transaminase (ALT) or aspartate transaminase (AST) and weighted according to the number of patients in each study with enzyme level measurements. In a secondary analysis, we measured the odds ratio (OR) of severe COVID-19 versus non-severe COVID-19 based on the presence of any GI symptom. Using the 'meta' package (Schwarzer et al.) in the R programming language, version 4.0.2, a compute pooled analysis using the random effect model was performed.

RESULTS

The most frequent symptom recorded in the studies was diarrhea (55 studies), abdominal pain (40 studies), nausea/vomiting (30 studies), anorexia (15 studies) (Table 1).

Table 1: Studies included in our study.^[1-60]

Author	Location	Number of COVID Patients	Any GI symptom	GI First Symptom	Diarrhea	Anorexia	Elevated LFTs	Severe COVID
Cai X	China	5	4	4	2	2	3	2
Chang	China	13	1	N/A	1	N/A	N/A	0
Chen G	China	21	4	N/A	4	N/A	6	11
Chen J	China	12	4	0	4	N/A	0	0
Chen J	China	249	N/A	N/A	8	8	N/A	N/A
Chen M	China	11	5	N/A	2	N/A	N/A	N/A
Chen N	China	99	N/A	N/A	2	N/A		N/A
Chen Q	China	9	2	N/A	2	N/A	N/A	4
Chen Q	China	145	N/A	N/A	39	62	N/A	43
Chen T	China	274	N/A	N/A	77	66	84	274
Chen Y	China	42	8	N/A	7	N/A	N/A	11
Cholankeril	USA	116	37	0	12	22	26	N/A
Dai	China	234	N/A	N/A	9	N/A	N/A	15
Diao	China	6	1	N/A	1	N/A	N/A	0
Effenbergger	Austria	40	N/A	N/A	22	N/A	N/A	N/A
Garazzino	Italy	168	N/A	N/A	22	N/A	N/A	N/A
Guan	China	1099	N/A	N/A	42	N/A	158	173
Hajifathalian	USA	1059	350	N/A	234	240	657	N/A
Han C	China	206	117	13	67	102	N/A	0
Han R	China	108	15	N/A	15	N/A	N/A	N/A
Han YN	China	32	6	N/A	N/A	N/A	10	4
He	China	204	N/A	N/A	19	12	N/A	69
Hossain	USA	119	60	N/A	N/A	N/A	N/A	29
Huang C	China	38	1	N/A	1	N/A	15	13
Huang L	China	7	1	1	1	N/A	N/A	N/A
Huang LE	China	8	7	0	6	3	0	0
Huang Y	China	34	5	N/A	5	N/A	15	N/A
Jin	China	651	74	N/A	56	N/A	N/A	64
Kim	Korea	28	N/A	N/A	14	N/A	6	6
Klopfenstein	France	114	55	N/A	55	N/A	N/A	4
Lechien	Europe	1420	N/A	N/A	473	649	N/A	0
Lei P	China	14	3	N/A	3	N/A	4	N/A
Lei Z	China	20	N/A	N/A	5	N/A	N/A	N/A
Li	China	658	N/A	N/A	18	N/A	39	N/A
Li	China	83	7	N/A	N/A	N/A	N/A	25
Lian	China	465	N/A	N/A	36	N/A	99	49
Lin	China	95	11	N/A	5	5	1	20
Liu F	China	10	3	N/A	0	N/A	N/A	5
Liu J	China	40	N/A	N/A	3	N/A	N/A	13
Liu J-Y	Taiwan	321	26	N/A	23	N/A	N/A	N/A
Liu K	China	137	11	N/A	11	N/A	N/A	N/A
Liu W	China	6	4	N/A	N/A	N/A	4	1
Liu Y	China	12	3	N/A	2	N/A	3	5
Liu Z	China	72	N/A	N/A	2	N/A	15	8
Lo	Macau	10	N/A	N/A	8	N/A	1	4
Luo	China	183	N/A	N/A	68	180	N/A	N/A
Mao	China	214	N/A	N/A	41	N/A	N/A	88
Mi	China	10	1	N/A	0	N/A	4	7
Mo	China	155	N/A	N/A	7	N/A	N/A	37
Nicoletti	Italy	42	13	N/A	2	N/A	8	N/A
Nobel	USA	278	97	N/A	56	N/A	N/A	N/A
Palaiodimos	New York	200	N/A	N/A	66	N/A	N/A	N/A
Pan	China	204	103	6	35	81	N/A	N/A

Pung	Singapore	17	N/A	N/A	4	N/A	N/A	2
Qian GQ	China	91	N/A	N/A	21	23	N/A	9
Redd	USA	318	195	N/A	107	110	N/A	N/A
Saeed	Norway	9	9	9	1	N/A	N/A	0
Shao	China	136	N/A	N/A	27	N/A	N/A	136
Shen	China	9	2	2	2	N/A	2	0
Shi S	China	416	16	N/A	16	N/A	N/A	N/A

The overall prevalence of any GI signs and symptoms in affected patients with COVID-19 was 27% (95% CI: 21-

35) ($p < 0.05$) and consequent heterogeneity ($I^2 = 94%$) (Figure 2).

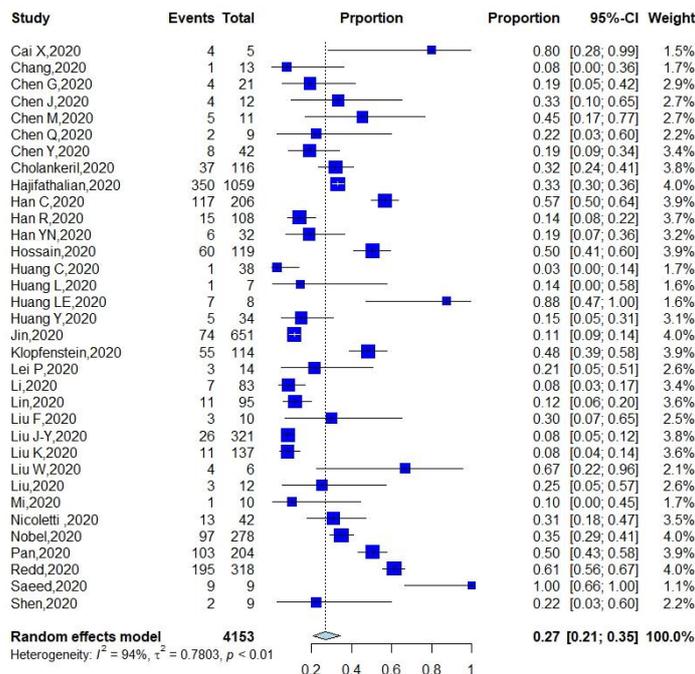


Figure 2: Overall prevalence of GI symptoms in patients with COVID-19 was 27% (95%CI 21-35%) ($p < 0.01$).

Diarrhea, nausea, abdominal pain, and vomiting were included in the definition of GI symptoms. Anorexia was not included in the description of GI symptoms. GI as an initial presentation was reported in five studies with the

prevalence of 34% (95% CI: 05-83) ($p < 0.01$) with consequent heterogeneity ($I^2 = 88%$) (Figure 3). Out of 234 patients, 80 patients reported GI symptoms as an initial presentation of COVID-19.

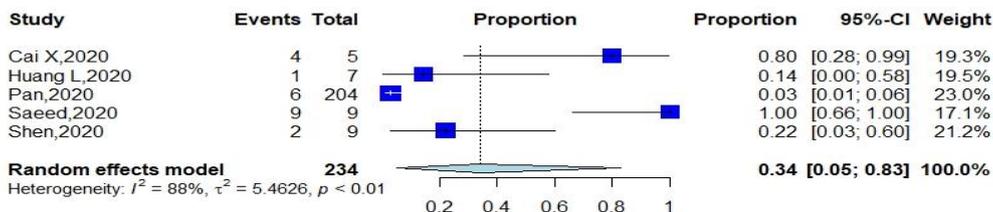


Figure 3: Overall prevalence of GI symptoms at presentation in patients with COVID-19 was 34% (95%CI 05-83%).

The prevalence of GI symptoms in 60 studies that reported GI symptoms as the only symptom at first illness presentation was also similar (34%, 95% CI 05–83, $I^2 = 94%$) (Figure 3). GI symptoms lasted for a median duration of 4.5 (± 1.9) days, based on three studies, but patients presented later in their natural disease course (median duration of 13.2 [± 5.4] days after onset of first symptoms).

Regarding specific symptoms, diarrhea was reported in 1656 patients out of 10352 patients with a prevalence of 16% (95% CI: 12-19) ($p = 0.01$) with consequent heterogeneity ($I^2 = 94$) (Figure 4). Diarrhea was defined as usually more than three loose stools per day, but few studies quantified the severity of any GI symptoms.

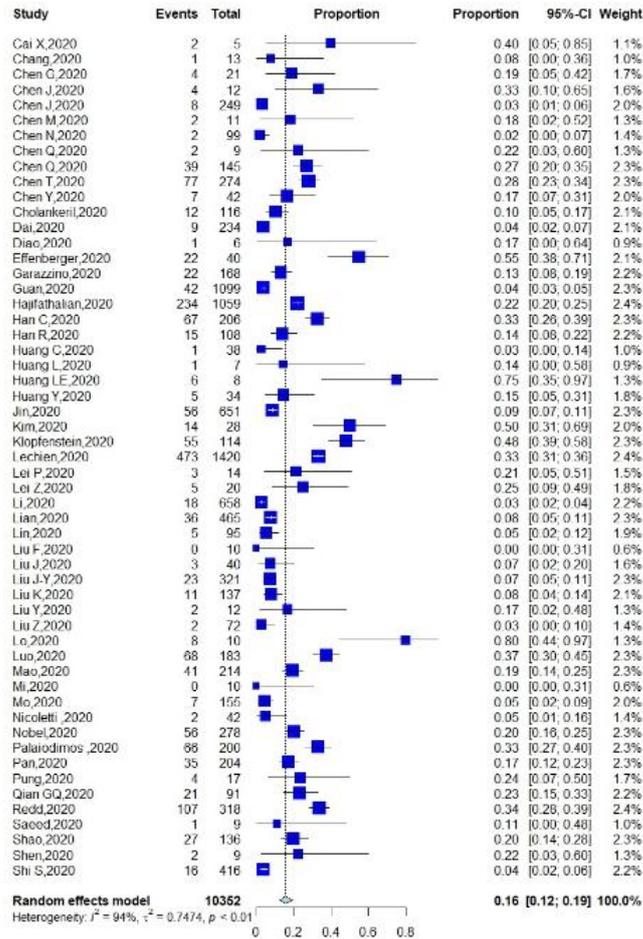


Figure 4: Overall prevalence of diarrhea in COVID-19 infection was 16% (95%CI 12-19%).

Anorexia was reported in 1339 patients out of 4619 (p<0.01), with consequent heterogeneity (I2 =96%) patients with prevalence of 29% (95% CI: 22-38) (Figure 5).

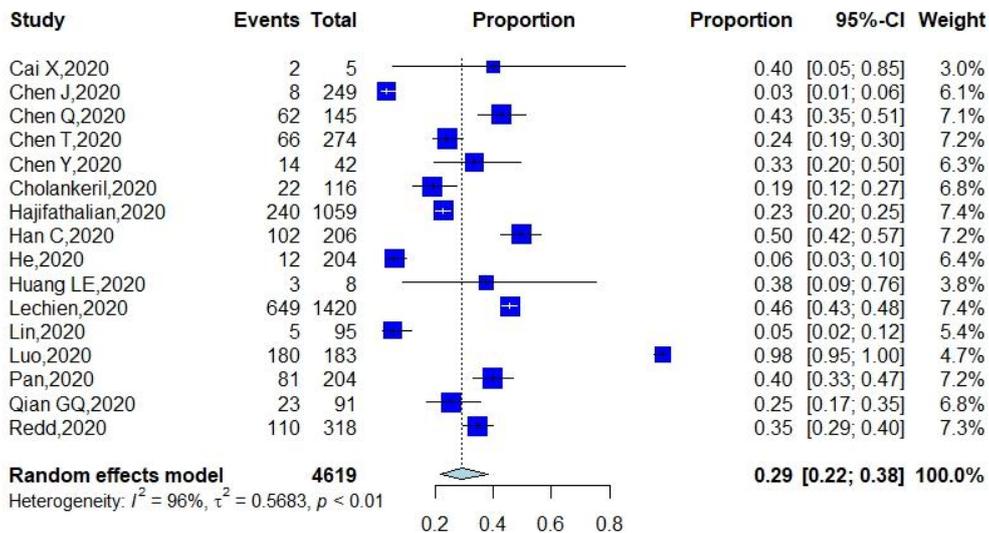


Figure 5: Overall prevalence of anorexia in COVID-19 infection was 29% (95%CI 22-38%).

Abdominal pain was reported in 1291 patients out of 8070 patients with prevalence of 16% (95% CI: 11-20) (p<0.01) with consequent heterogeneity (I2 =95%) (Figure 6).

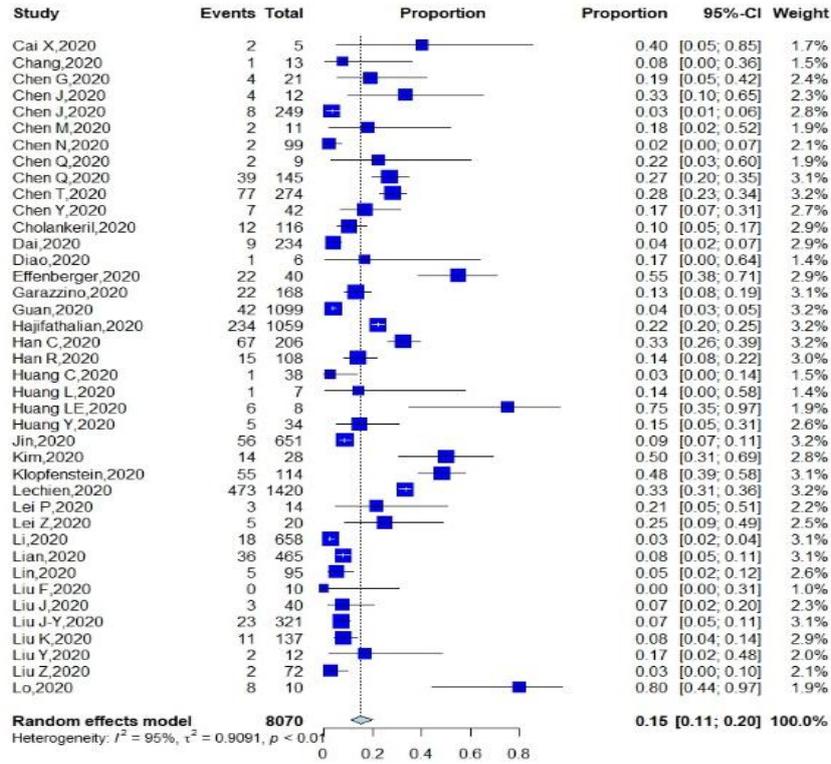


Figure 6: Overall prevalence of abdominal pain in COVID-19 infection was 16% (95%CI 11-20%).

Nausea or vomiting was reported in 573 patients out of 3372 patients with prevalence of 17% (95% CI: 13-22) (p<0.01) with consequent heterogeneity (I2 =88%) (Figure 7).

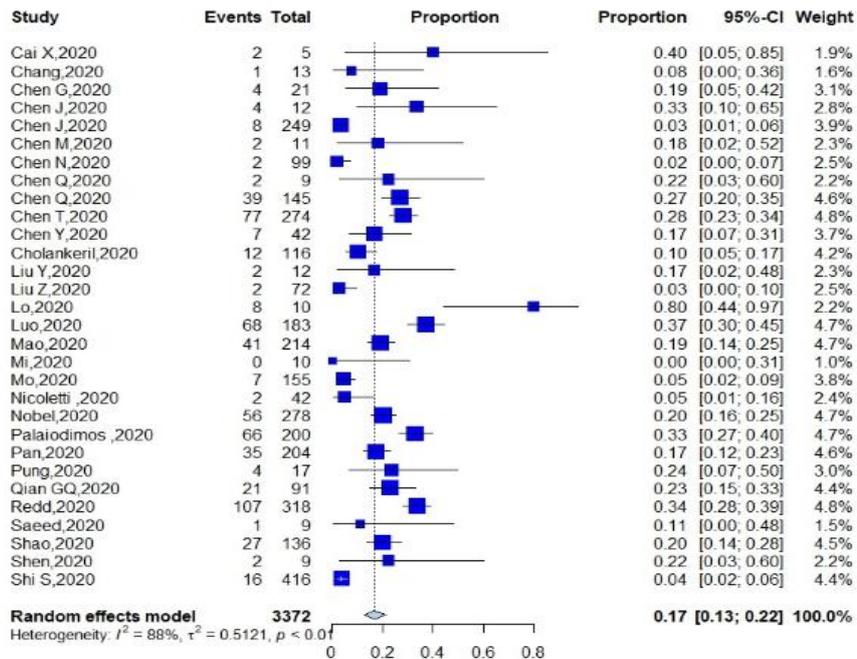


Figure 7: Overall prevalence of nausea/vomiting in COVID-19 infection was 17% (95%CI 13-22%).

Out of 60 studies, 31 studies reported severe cases of COVID-19. A severe case of COVID-19 includes those patients that require hospitalization, fever more than 101, and symptomatic for the last ten days. Severe case were reported in 1115 patients out of 4462 patients with prevalence of 25% (95% CI: 19-31) (p<0.01), with consequent heterogeneity (I2 =90%) (Figure 8).

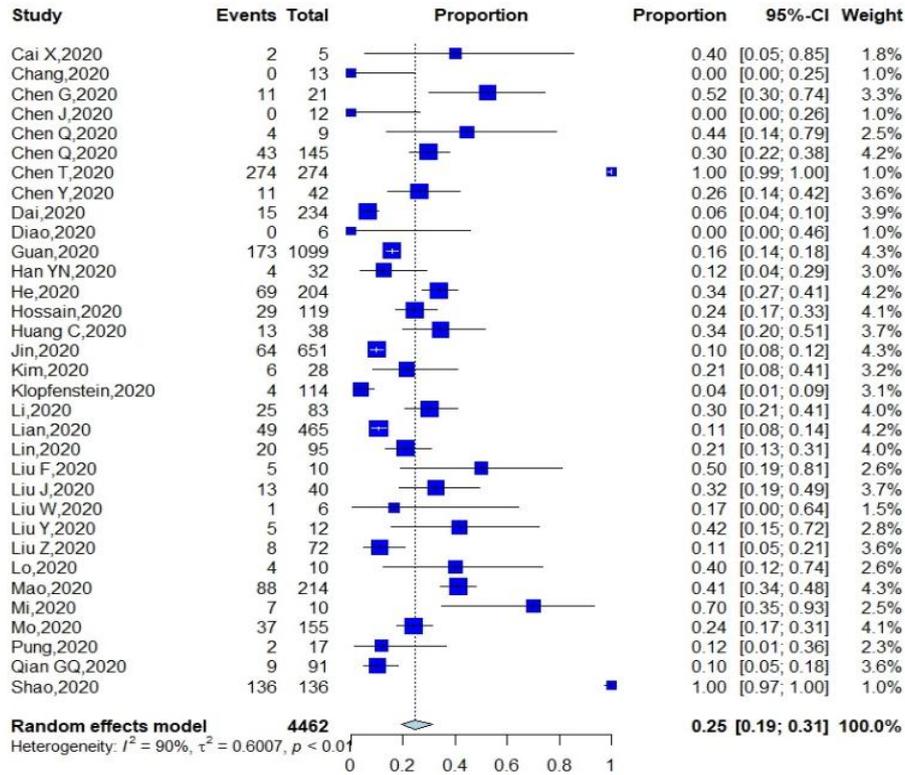


Figure 8: Overall prevalence of severe COVID-19 infection with GI symptoms was 26% (95%CI 19-31%).

Twenty four studies reported abnormalities in liver function in COVID-19 patients. Reported patients had an abnormality in aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatases, or any

one of these. A total of 927 patients reported hepatic enzymes abnormality of 4218 patients with prevalence of 22% (95% CI: 14-33) ($p < 0.01$) with consequent heterogeneity ($I^2 = 97\%$) (Figure 9).

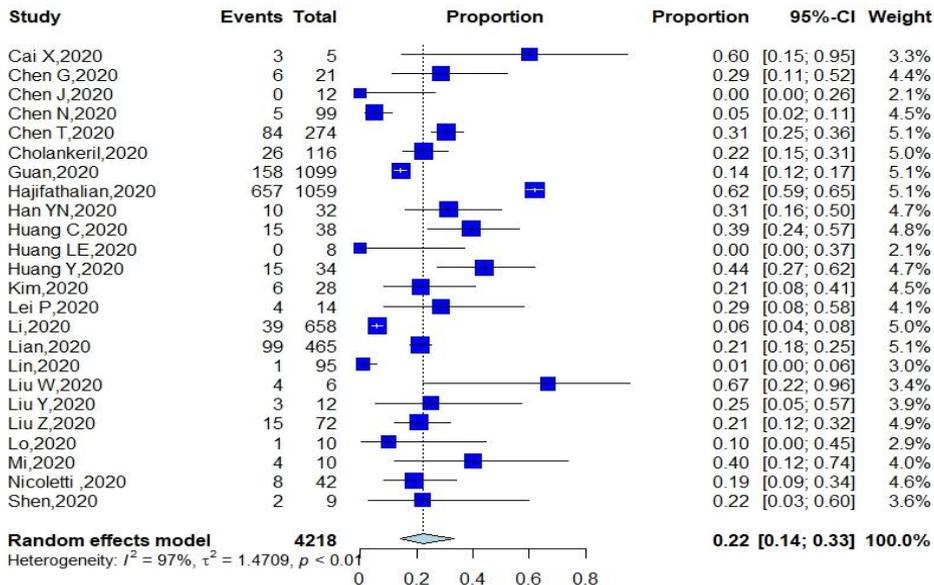


Figure 9: Overall prevalence of hepatic manifestations in COVID-19 infection was 22% (95%CI 14-33%).

DISCUSSION

This meta-analysis represents the most extensive study of gastrointestinal manifestations of COVID-19 to date, with more than 10,000 patients from 60 articles. Overall,

GI symptoms are common in COVID-19, including 16% with diarrhea, 29% with anorexia, 17% with nausea or vomiting, and 16% with abdominal pain in most recent studies. One-quarter of patients also demonstrated hepatic abnormality. Presentation with GI symptoms

without any typical respiratory symptoms or fever is uncommon but remains clinically pertinent for a pandemic of this extent, occurring in 1.5% of patients.

Our primary analysis demonstrated that 1% (95% CI 0–6%) of COVID-19 patients present with isolated GI symptoms is lower than reported up to 2% in previous studies. For example, an earlier study by Mao *et al.* reported that 10% of the patients infected with COVID-19 presented with only GI signs and symptoms, and a corresponding cohort study from a single hospital in China by Han *et al.* described isolated GI symptoms in 23% of SARS-CoV-2 patients.^[3,42] However, Han *et al.* study was not able to evaluate a true prevalence of gut symptoms among all COVID-19 patients. Furthermore, our data-analysis identifies and comprises several studies with zero prevalence of isolated GI symptoms that were not involved in the Mao review. Even if the inclusive prevalence of isolated GI symptoms is comparatively low, 1% represents hundreds of COVID-19 cases daily in the US alone, with both clinical and public health implications, and requires urgent evaluation.^[43,44]

Anorexia in COVID-19 may be the result of systemic inflammation rather than a real digestive sign.^[45] The increased prevalence of GI symptoms have been reported in some studies due to the inclusion of this non-specific infectious symptom, a discrepancy the clinician should keep in mind, when interpreting this literature.^[2,46]

In exploring the remarkable heterogeneity inherent in analyzing large numbers of studies, geography, and data publication date developed significantly associated with the reported prevalence of GI manifestations. The prevalence of diarrhea, abdominal pain, and nausea/vomiting in publications written after 1st April were almost twice that of publications before 1st April and in Europe or North American publications compared to Asia. This is because earlier cases and publications began in Asia, the effect of country versus publication date is challenging to unscramble. As COVID-19 was first demonstrated as a respiratory illness, a comprehensive collection of signs and symptoms literature occurred to a lesser extent earlier in the COVID-19 pandemic. The results of the most extensive studies are illustrative. Guan *et al.* underlined 3.8% of infected patients had diarrhea and 5% nausea or vomiting. However, study investigators and reviewers said incomplete disease course records due to overwhelmed medical infrastructure and clinically rather than research-driven data collection.^[47] Cholankeril *et al.* reported a higher prevalence of diarrhea (12%) and nausea or vomiting (12%). However, the authors and investigators acknowledged testing criteria had not included extra-pulmonary symptoms at the time of review.^[48] In contrast, Hajifathalian *et al.* clearly defined GI symptoms and systematically evaluated the infected patients for extra-pulmonary manifestations. They reported an even higher incidence of diarrhea among infected patients (22%).^[29] We suggest that the pooled

analysis from the most recent studies (diarrhea with prevalence of 16% (95% CI: 12-19) (p=0.01) (I2 =94), anorexia with prevalence of 29% (95% CI: 22-38) (p<0.01) (I2 =96%), abdominal pain with prevalence of 16% (95% CI: 11-20) (p<0.01) (I2 =95%), and nausea/vomiting with prevalence of 17% (95% CI: 13-22) (p<0.01) (I2 =88%).

We found hepatic abnormality to be even more prevalent than GI symptoms, with 25% of patients having elevated transaminases. The mechanism of hepatic injury in COVID-19 patients is not yet well understood. Angiotensin-converting enzyme 2 (ACE 2) receptors are located on bile duct epithelium and hepatocytes, and liver injury is more likely due to immune activation.^[49,50] than direct viral cytopathic effect.^[51,52] Many cases of liver dysfunction in severe COVID-19 is possible multifactorial, including insults from hypoxia, hypoperfusion, thrombosis, and hepatotoxic medications. Even in patients with abnormal levels, the average transaminase level was not severely elevated (<50 U/L), suggesting that liver inflammation is mild and not a significant part of COVID-19 related inflammation. Finally, synthetic liver dysfunction linked to COVID-19 infection has yet to be described.^[53]

Our meta-analysis has notable limitations. As a review of many observational studies, there is a great degree of heterogeneity, which is only partially described by subgroup analyses. The prevalence approximates of less variably defined outcomes such as isolated GI symptoms, diarrhea, nausea, and vomiting are more consistent than the consequences of "any" GI symptoms or anorexia. The majority of included studies in our study are Chinese and from hospitalized settings, and generalizability to other regions and less critically ill patients is one limitation. Lastly, no reviews had a low bias risk. This rating was usually due to the absence of COVID-19 hostile comparison groups, suboptimal depth of GI symptoms, and lack of proper follow-up of COVID-19 patients. Recent articles have drawn attention to the flawed methodology and systematic approach of many early COVID-19 studies, driven by overwhelmed healthcare organizations needing rapid information dissemination with abbreviated quality peer review.^[55,56] These limitations are notwithstanding, our review is the largest to-date of the peer-reviewed data and literature, including separate subgroup analysis of literature published since early 2020, to provide the most updated estimates of GI's prevalence hepatic manifestations of COVID-19 infection.

We advocate comprehensive testing for COVID-19, including patients presenting with isolated GI symptoms or unexplained LFTs elevations—when possible, testing resources are abundant. While COVID-19 with isolated GI symptoms may be uncommon enough (1–2%) to warrant testing on this basis alone when COVID-19 testing resources are scarce, these patients should contemplate self-quarantine to monitor for the appearance of other symptoms, including fever, myalgia,

cough, and SOB. The significant role of digestive manifestations in COVID-19 is precise, but many knowledge gaps regarding their pathophysiology and prognostic value persist. Further research should continue through well-designed prospective studies for more detailed data.

CONCLUSION

We perceive that COVID-19 may have several gastrointestinal manifestations, and in many cases, GI involvement may precede typical upper respiratory tract symptoms. Our study highlights the need for high-quality data from the recent studies, including patients from the community setting, and further exploration of the underlying mortality causes. The most prevalent clinical information which we meet is that diarrhea and abdominal pain. Therefore, an extraordinary catalog of suspicion for such patients will be fundamental to prevent or, at least, minimum contact to health care providers and other high-risk patients. The above analysis of the gastrointestinal manifestations of COVID-19 will help the gastroenterologist to have a crucial preparation, which is of supreme importance to prevent infections.

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