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META-ANALYSIS

Hepatic and Gastrointestinal Complications during COVID-19: A Meta-Analysis of Meta-Analyses

Jaseela Majeed, Sapna Yadav, Rekha Garg, Danish Kamal, Ramsha Iqbal, Palka Mittal, Abhishek Dadhich, Puneeta Ajmera

Delhi Pharmaceutical Sciences and Research University, New Delhi, India.

Correspondence to: Dr. Puneeta Ajmera, Email: puneeta_22@yahoo.com, ORCiD: 0000-0002-6237-2235

ABSTRACT

Objective: This meta-analysis is aimed to quantify the findings of different meta-analyses performed on the association of hepatic and gastrointestinal complications and corona virus diesease (COVID-19) severity.

Methods: Four databases i.e., PubMed, Google Scholar, Cochrane, and Web of science were used for the systematic search of the literature from January 2020 till July 2021. "Quality of Reporting of Meta-analyses (QUOROM) checklist was used to examine the comprehensiveness of reporting in the meta-analysis. Sixteen systematic review and meta-analysis studies met inclusion criteria.

Results: Pooled results indicated that diarrhea was a significant symptom in COVID-19 patients (OR=2.70, 95% CI 1.16 to 6.29, p-value 0.020) along with abdominal pain (OR=3.87, 95% CI 2.86 to 5.23, p-value <0.001), nausea (OR=2.81, 95% CI 1.13 to 6.97, p-value 0.030), and vomiting (OR= 2.91, 95% CI 1.31 to 6.49, p-value 0.009). Pooled results also indicated a rise in alanine transaminase (ALT) level (OR= 3.81, 95% CI 1.71 to 8.45 p-value <0.001) and bilirubin level (OR=2.89, 95% CI 1.38 to 6.04, p-value <0.001) in COVID-19 patients. A significant association of aminotransferase (AST) with COVID-19 (OR=5.81, 95% CI 2.82 to 12, p-value <0.001) was also present.

Conclusion: Severe acute respiratory syndrome coronavirus-2 can cause damage to the liver cells which may lead to an elevated level of inflammatory markers and liver enzymes (ALT/AST).

Keywords: Coronavirus, COVID-19, Cirrhosis, Liver Disease, SARS-CoV-2.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an infectious, communicable, and contagious virus that first showed up in December 2019 and has since produced a pandemic of the acute respiratory disease known as "coronavirus disease 2019," (COVID-19) that is endangering human health and public safety.[1,2] Primarily COVID-19 symptoms comprise dry cough, dyspnea, high body temperature, and weakness. Most infected individuals had mild to moderate respiratory illnesses and healed without the need for medical care. People with COVID-19 who also had underlying illnesses such as cancer, diabetes, chronic respiratory diseases, or cardiovascular disease were more likely to experience life-threatening consequences.[2] It is also reported that COVID-19 not just affects the respiratory system but is also found liable for gastrointestinal (GI), cardiovascular, and hepatobiliary complications.[3]

At present several studies have reported the association between COVID-19 and GI and liver dysfunction.[4-8] Studies have reported that patients suffering from COVID-19 have GI symptoms such as nausea, vomiting, abdominal pain, diarrhea, loss of appetite, GI bleeding, and increased levels of liver enzymes.[4,5] SARS-COV-2 virus enters the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is abundantly present in the lungs, kidneys, stomach, liver, bile duct, small intestine, and colon.[6] In a recent study, it was found that the occurrence of GI symptoms was 17%, the incidence of diarrhea was 12.4%, nausea and vomiting was 9.0%, 22.3% had a loss of appetite, and abdominal pain was 6.2%.[7] It is demonstrated that liver dysfunction in individuals infected with COVID-19 may be due to injury to bile duct cells.[2,8] The accurate cause of liver injury is ambiguous, but it can be due to direct damage to hepatocytes or biliary epithelium, and liver impairment due to the increased immune response of the body.[9]

Systematic reviews and meta-analyses are the maximum levels of evidence that can be assigned to a

structured search approach, with critical assessments reducing bias and allowing for a summative conclusion. Such analyses make it easier for busy clinicians to keep updated by aggregating data from different studies and facilitating evidence-based practice. These studies are frequently used in the development of clinical guidelines. Several systematic reviews and meta-analysis on hepatic and GI complications have been undertaken throughout the pandemic, but no comprehensive study has been conducted to extract the results of published systematic reviews and meta-analyses to determine the prevalence of hepatic and GI complications among COVID-19 patients. Therefore, this meta-analysis aims to compile all systematic reviews and meta-analyses published on the association between hepatic and GI symptoms and COVID-19 to better identify available data, highlight knowledge gaps, and emphasize the necessity for additional meta-analyses.

To the best of our knowledge, the present work is the first meta-analysis of meta-analyses to assess the association between serum levels of aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, and GI symptoms with the severity of COVID-19 infection.

The findings of this study could be useful for healthcare professionals and policymakers in an in-depth understanding of the disease severity and comorbidities like GI and liver complications.

METHODS

This meta-analysis was performed using "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)" guidelines (Figure 1).[10]

Search Methods

PubMed, Google Scholar, Cochrane and Web of science databases were used for systematic search of literature using search terms: "("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy" [Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31 [Date - Publication]) OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields])) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields] OR ("hepatic"[All Fields] OR "hepatophyta"[MeSH Terms] OR "hepatophyta"[All Fields] OR "hepatics"[All Fields]) OR ("liver cirrhosis"[MeSH Terms] OR ("liver"[All Fields] AND "cirrhosis"[All Fields]) OR "liver cirrhosis"[All Fields] OR "cirrhosis"[All Fields] OR "fibrosis"[MeSH Terms] OR "fibrosis"[All Fields]) OR ("digestive system"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields]) OR "digestive system"[All Fields] OR "gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields] OR "gastrointestine"[All Fields]) OR "GI"[All Fields]) AND "Meta-analysis"[All Fields]" from January 2020 till July 2021.

Eligibility Criteria

Meta-analysis of studies done on COVID-19-associated liver dysfunction and GI symptoms and written in English were included.

Articles including only systematic reviews without meta-analysis, narrative review, or a mini-review that just explained the management of symptoms or described the symptoms, retrospective or a cross-sectional study to evaluate the outcomes of coronavirus patients were excluded (Figure 1).

Study Selection

Articles and abstracts of all the studies were examined autonomously by two researchers (SY and DK) to see if they met the inclusion and exclusion criteria. A thorough search of the references of selected articles that met inclusion criteria was manually conducted to ensure that no relevant studies were missed out. All the included meta-analyses were rechecked by a senior researcher (PA). When the abstract data was not enough, the entire text was examined. The decision to include them was taken after a cautious assessment of the meta-analyses and the resolution of a disagreement between the three researchers.

Data extraction

Variables such as title of the study, year of publication, author's name and country, sample size, duration of the study, study design, inclusion and exclusion criteria of the study, journal's name, and results of the meta-analyses including effect sizes along with their

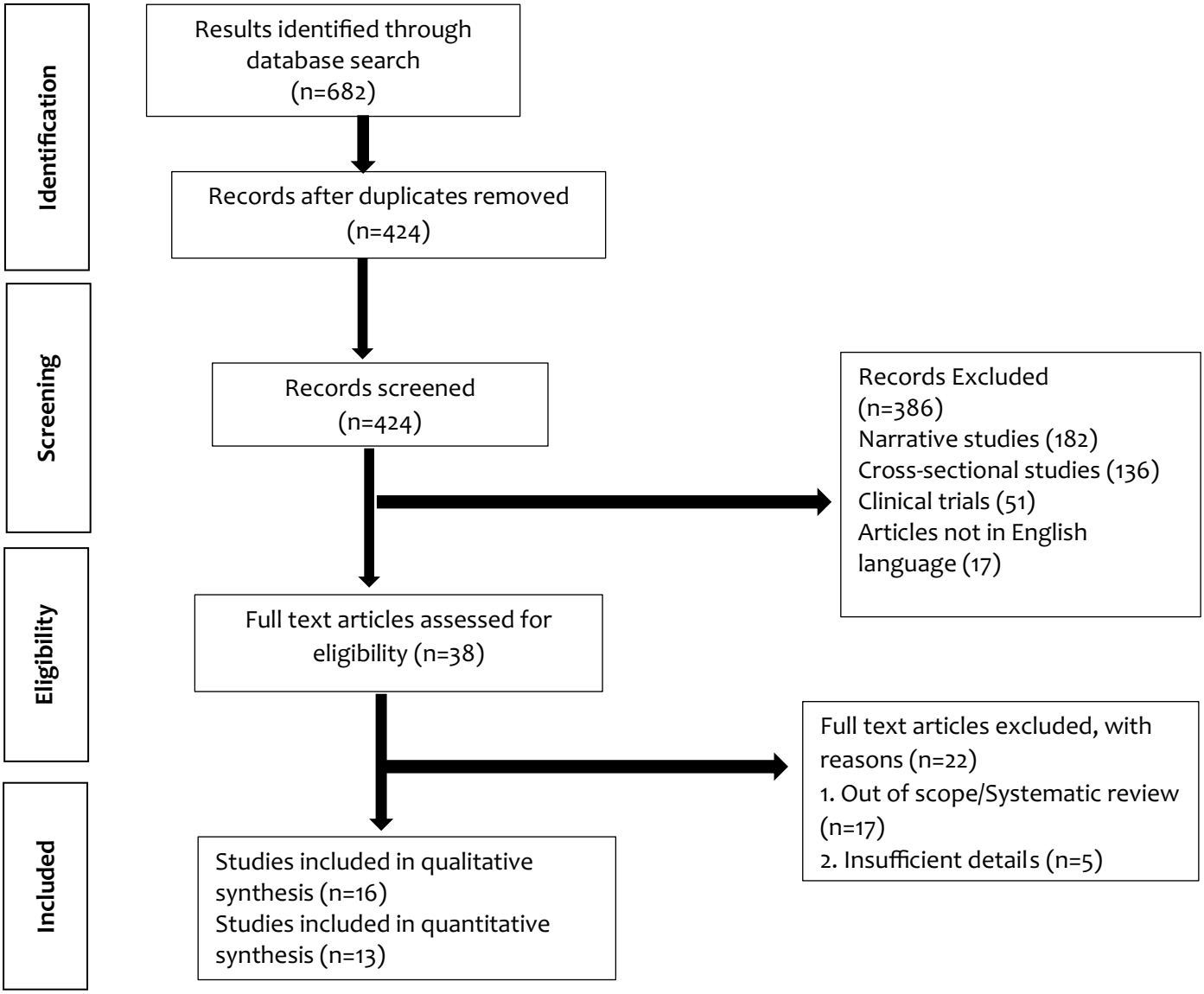

Figure 1: PRISMA flow diagram of study selection[10]

associated p-values and confidence intervals (CI) were extracted from the included studies.

Comprehensiveness & Internal Validity

The "Quality of Reporting of Meta-analyses (QUOROM)" checklist was used to examine the comprehensiveness of reporting in the meta-analysis of study who met the inclusion criteria.[11] This checklist comprises eighteen items, and each of those eighteen items received an additional point when more than half of the conditions were met. The internal validity of included meta-analyses was assessed using Assessment of Multiple Systematic Reviews (AMSTAR).[12] In a systematic review, AMSTAR-2 assesses the quality of both reporting and methodology. With a kappa score of 0.7 for agreement on individual questions and an interclass correlation coefficient of 0.84, it demonstarted strong reliability and validity.[13-15] Two reviewers (PA and JM) completed the QUOROM and AMSTAR checklists for all studies included and discussed the differences to achieve a consensus.

Data Pooling

A summary meta-analysis model for Odd Ratio (OR) with a 95 percent confidence interval (CI) was used to combine the results of the included meta-analyses. When a review reported an relative risk (RR), the data was transformed into an OR using the review's primary data. RevMan 5.4 software was used to conduct the meta-analysis.

Statistical analysis plan

On the natural logarithm scale, a meta-analysis of the OR was done and then reverted to its original scale.

Random-effects (RE) models were used to pool studies and integrate OR and prevalence, as well as their 95 percent CI. I^2 greater than 0.50 was used to determine effect magnitude heterogeneity across studies. Results of the meta-analysis and subsequent forest plots were also computed.

RESULTS

Study Selection Search Results

During the literature search, 682 articles were found as relevant studies. After the removal of duplicates and studies not fulfilling eligibility criteria, 424 records were identified and screened thoroughly. A total of 38 full-text articles were assessed and re-screened. Finally, after further exclusions, sixteen articles for qualitative and thirteen articles for quantitative analysis were included (Figure 1).

Characteristics of Included Studies

Eligibility criteria and outcomes are described in table 1 and characteris-tics of included studies are presented in table-2.[3,5,7,9,16-26] Sixteen systematic review and meta-analysis studies met our inclusion criteria. The recent study meeting eligibility criteria were published in the year 2021. Most of the studies were conducted in China, two in the USA, two in Iran, and one each from India, Greece, Italy, Oman, Saudi Arabia, Spain, and Japan.[5] The sample size ranged from 3722 in the study of Wu *et al.*[18] to 24299 in the study of Kovalic *et al.*[7] The studies were conducted in different hospitals, universities, medical centers, and residential societies. The age of participants varied from children to old age up to 80 years.

Assessment of Comprehensiveness of Reporting

The "QUOROM" was referred to assess the quality of each article included in the study. For each of the eighteen items in QUOROM where more than 50% of the criteria have been met, one point is added to the evaluation. In the present meta-analysis, most of the studies were of good quality as per the assessment on AMSTER. The patient intervention control outcome (PICO) components are covered in all the included studies' research questions and inclusion criteria for the review. Only two studies had established review methodologies before conducting the reviews. Four studies did not disclose how the study designs were chosen to be included in the review.[6,21,23,25]

A comprehensive literature search strategy was clear /partially clear in all the studies. In eight studies the review authors performed study selection in duplicate while in two studies review authors did not perform data extraction in duplicate.[5-7,16-18,23-26] In all the selected reviews, a list of excluded studies and justification of the exclusions along with adequate details of the included studies were given. The risk of bias description and a satisfactory explanation for heterogeneity was presented in all the studies.

Findings of Hepatic and GI Symptoms

The results for diarrhea were reported by 268 studies with 61,269 participants. RE model was employed due to significant heterogeneity across these studies (I^2=98%, Tau^2=1.08). Pooled results indicated that diarrhea was a significant symptom in COVID-19 patients (OR=2.70, 95% CI 1.16 to 6.29, p-value 0.020) [Figure 2(a)].

The results for abdominal pain were reported by 268 studies with 61,269 participants. RE model was employed due to significant heterogeneity across these studies (I^2=75%, Tau^2=0.25). Pooled results indicated that abdominal pain was a significant symptom in COVID-19 patients (OR=4.37, 95% CI 2.70 to 7.10, p-value <0.001) [Figure 2(b)].

The results for nausea were reported by 268 studies with 61,269 participants. RE model was employed due to significant heterogeneity across the trials (I^2 =96%, Tau^2=1.22). Pooled results indicated that nausea was one of the symptoms in COVID-19 patients (OR=2.81, 95% CI 1.13 to 6.97, p-value 0.030) [Figure 2 (c)].

The results for vomiting were reported by 268 studies with 61,269 participants. RE model was employed due to significant heterogeneity across the trials (I^2 =95%, Tau^2=0.93). Pooled results indicated that vomiting was one of the symptoms in COVID-19 patients (OR= 2.91, 95% CI 1.31 to 6.49, p-value 0.009) [Figure 2 (d)].

The outcomes of AST were reported by 499 studies with 105,896 participants. RE model was employed due to significant heterogeneity across these Studies (I^2=99%, Tau^2=1.47). Pooled results indicate a significant association of AST with COVID-19 (OR=5.81, 95% CI 2.82 to 12, p-value <0.001) [Figure 2 (e)].

The outcomes of ALT were reported by 497 studies with 106,065 participants. RE model was employed due to significant heterogeneity across the trials (I^2 =99%, Tau^2=1.78). Pooled results indicated that increased ALT level was associated with COVID-19 (OR= 3.81, 95% CI 1.72 to 8.45, p-value <0.001) [Figure 2 (f)].

The outcomes of bilirubin were reported by 232 studies with 51,640 participants. RE model was employed due to significant heterogeneity across these studies (I^2=98%, Tau^2=0.95). Pooled results indicate a rise in bilirubin levels in COVID-19 patients (OR= 2.89, 95% CI 1.38 to 6.04, p-value 0.005) [Figure 2 (g)].

Table 1: Eligibility criteria and outcomes of included studies

Sr. No.	Author	Country	Eligibility	Outcome
SR1	Kovalic *et al* (7)	USA	Studies reporting CLD in coronavirus-infected patients.	CLD prevalence was linked to a more severe coronavirus infection as well as overall mortality.
SR2	Mao *et al* (5)	China	Clinical as well as epidemiological features of coronavirus infection. Prevalence of GIT findings in COVID-19 patients.	Abnormal liver functions were seen in 19% of people. When compared to patients with non-severe COVID-19, patients with severe COVID-19 exhibited greater rates of abnormal liver function, including elevated ALT and AST.
SR3	Sharma *et al* (16)	USA	Liver disease/acute liver injury. Elevated levels of liver enzymes.	Overall, 2.6 percent of people had CM-CLD, 26.5 percent had COVID-19-ALI, 41.1 percent had high AST, and 29.1 percent had elevated ALT. COVID-19-ALI and high ALT had no significant relationship with poor outcomes, whereas CMCLD did.
SR4	Wan *et al* (17)	China	Studies reporting digestive symptoms in Coronavirus infected patients.	Digestive symptoms was prevalent in 30%. Tiredness, myalgia, and ARDS were higher. Moreover, diarrhoea and liver dysfunction are more comm-on in severe/ critical patients.
SR5	Abdulla *et* al (3)	Omen	Studies reporting RT-PCR positive confirmed cases. investigations of liver biomarkers (AST, ALT, albumin, bilirubin, and their mean serum values in COVID-19 patients with severe and non-severe cases).	Infection with COVID 19 causes liver function abnormalities such as hypoalbuminēmia, hyperbilirubinemia, and increased aminotransferase levels. To avoid adverse results, liver indicators should be evaluated and monitored regularly.
SR6	Kumar *et al* (9)	India	Studies reporting liver function investigations like serum bilirubin, AST, ALT, and ALP in COVID patients. Median/mean levels are reported for disease severity.	liver function abnormalities, GGT, hypoalbuminemi, and aminotransferas increases, are common. Patient with severe illness are more likely to have these abnorm-alities.
SR7	*Wu et al* (18)	China	Studies performed on COVID-19 human survivors/ non-survivors, severe/ non-severe, and laboratory-confirmed COVID-19 cases. Studies published in English with the availability of raw data.	COVID-19 patients' mortality and severity are significantly linked to liver impairment. The serum AST levels of non-survivors and severe COVID-19 patients are higher than those of survivors and non-severe patients. The findings provide a foundation for better clinical liver care in COVID-19 patients.
SR8	Zhao *et al* (19)	China	COVID-19 patients with nucleic acid confirmation and clinical confirmation in chinese population.	In Chinese patients with COVID-19, there is more risk of liver injury, and the risk and severity of liver injury are linked with the severity of infection.
SR9	Samiodust *et al* (20)	Iran	Data regarding complication findings and liver abnormalities were included. Patients were confirmed and diagnosed using WHO-recommended criteria.	The prevalence of liver injury in severe cases can be greater than in milder cases.

Table 1: Eligibility criteria and outcomes of included studies (Cont..)

SR10	Zarifian*et al* (21)	Iran	Any study that provided information on biomarkers of liver function in patients with a COVID-19 diagnosis confi-rmed by RT- PCR was included.	Preexisting comorbidities may influence the prevalence of GI symptoms in COVID -19 patients. In the absence of previous disorders, diarrhea and moderate elevations in liver enzymes are allegedly the most common gastrointetinal and hepatic symptoms of COVID-19.
SR11	*Bziezi et* al (22)	Saudi Arabia	In all trial designs, patients of any age or gender with a confirmed COVID-19 diagnosis.	Tran-saminases and total bilirubin levels in COVID-19 patients have not altered significantly.
SR12	Paliogiannis *et al* (23)	Italy	Studies that provide continuous data on serum albumin levels in COVID-19 patients. Studies of COVID-19 patients with varying degrees of illness severity or clinical outcomes.	When comparing COVID-19 patients with severe disease or poor outcomes to those with milder disease, serum albumin values are considerably lower. Age, location, and inflammatory status all have a role in the variation between studies.
SR13	Ampuero *et al* (24)	Spain	COVID-19 related non-fatal severe sequelae, intensive care unit (ICU) hospitalization, or mortality in adults. Studies reporting a dichotomized upper limit of normal ALT, AST, or Total bilirubin.	The examination of AST, ALT, and total bilirubin routinely in all patients affected by SARS-CoV-2 to predict those at risk of having COVID-19 issues had a considerably higher chance of developing severe COVID-19 compared to those with normal liver function tests upon admission.
SR14	Rokkas *et al* (25)	Greece	Published full articles or letters to the Editor written in English. Cohort studies with extractable data on the digestive system's participation in SARS-Cov-2.	8.9% of patients will experience symptoms such as diarrhoea, vomiting, and abdominal pain. The GI systemcould be a target organ for SARS-CoV-2, and a fecal transmission route should be considered.
SR15	Hayashi *et al* (6)	Japan	Existence of raised liver enzymes or/and GI symptoms in patients who have been diagnosed with COVID-19 by RT-PCR.	Severe COVID-19 is likely to be accompanied by abdominal pain. Individuals with COVID-19 may have a slightly lower frequency of diarrheal symptoms with abdominal pain than patients with other viral infectious illnesses that primarily attack the respiratory system.
SR16	Zeng *et al* (26)	China	Investigations on the clinical characteristics of COVID-19. Samples > 10. Indications of liver dysfunction, such as ALT, AST, ALP, and total bilirubin are included in the study. Diarrhoea, nausea, vomiting, and abdominal pain	The severity of the disease was linked to liver impairment induced by SARS-CoV-2 viral infection. GI was found t o be moderately common but not linked with illness progression, with diarrhoea accounting for 9.1%, nausea/vomiting for 5.2 percent, and abdominal pain accounting for 3.5 percent.

-ALT: Alanine transaminase, ALP: Alkaline phosphates, AST: Aspartate aminotransferase, ALI: Acute liver injury, GGT: Gama-glutamy transferase, CM-CLD: Comorbid chronic liver disease, COVID-19: Choronavirus disease 2019, RT-PCR: Reverse transcription polymerase chain reaction, SARS-COV-2: Sever acute respiratory syndrome choronavirus-2

Table 2: Characteristics of included studies

Study Type	Authors	Range of years of included studies	Primary studies (n)	Qualitative (n)	Quantitative (n)	Meta-analyses cited (n)
SR1	Kovalic *et al* (7)	01/01/ 2019 to 16/05/2020	74 (24299)	78	74	93
SR2	Mao *et al* (5)	01/01/2020 to 04/04/ 2020	35 (6686)	29	35	964
SR3	Sharma *et al* (16)	01/12/2019 to 30/06/2020	24 (12,882)	50	24	74
SR4	Wan *et al* (17)	Upto 24/04/2020	64 (15141)	64	44	8
SR5	Abdulla *et al* (3)	Upto 20/06/2020	12 (6,976)	0	12	12
SR6	Kumar *et al* (9)	01/12/2019 till 05/04/ 2020	128 (6081)	0	128	153
SR7	Wu *et al* (18)	Upto 17/04/2020	13 (3722)	0	13	47
SR8	Zhao *et al* (19)	01/01/2020 to 10/04/2020.	57(9889)	57	57	23
SR9	Samiodust *et al* (20)	01/01/2019 to 03/04/2020	21 (4191)	21	21	17
SR10	Zarifian *et al* (21)	01/01/2020 to 10/04/2020	67 (13251)	67	67	54
SR11	Bzeiz *et al* (22)	Inception to 31/08/2020.	35 (10,692)	-	23	26
SR12	Paliogiannis *et al* (23)	10/2020	67 (6141)	-	67	42
SR13	Ampuero *et al* (24)	Upto 16/04/2020	26 (14253)	26	-	20
SR 14	Rokkas (25)	Upto 10/04/2020	37 (5601)	-	-	100
SR15	Hayashi *et al* (6)	01/12/2019 to 30/06/ 2020	44 (15305)	44	44	24
SR16	Zeng *et al* (26)	01/12/2019 and 16/10/2020	21(5285)	21	21	27

Meta-analysis for Diarrhea

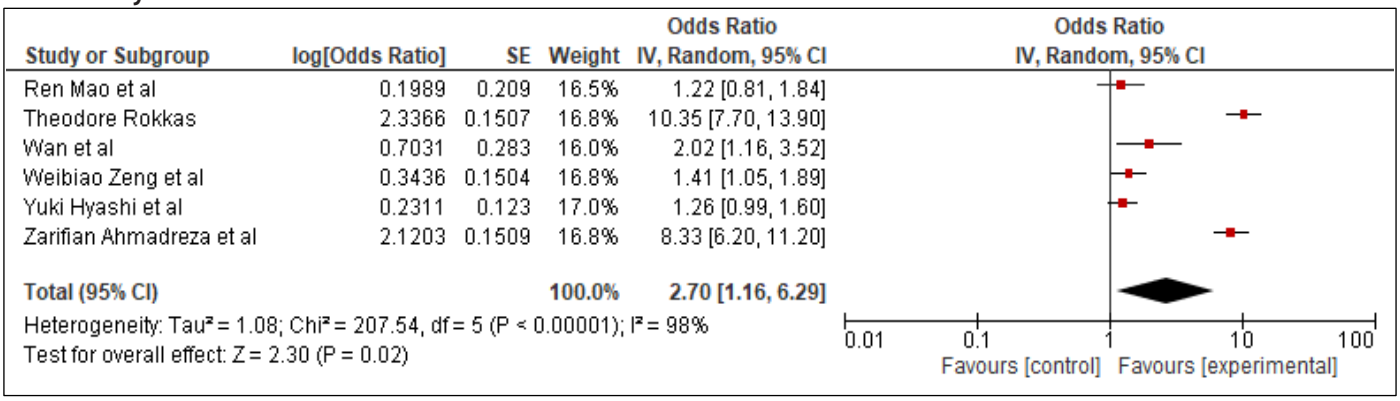

Figure 2(a): Forest plot for the prevalence of diarrhea in COVID-19 patients

Meta-analysis for Abdominal Pain

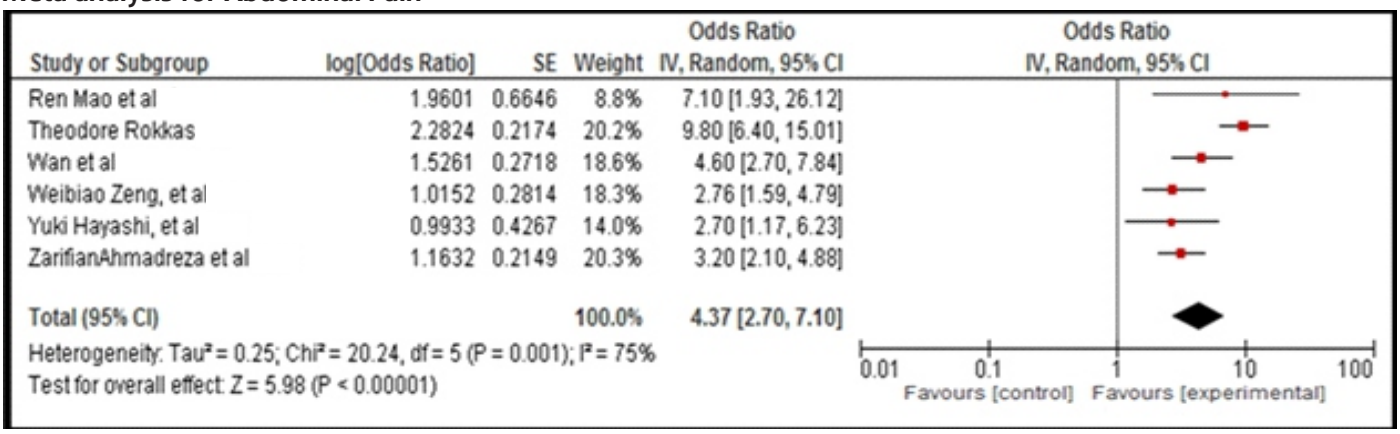

Figure 2(b): Forest plot for the prevalence of abdominal pain in COVID-19 patients

Meta-analysis for Nausea

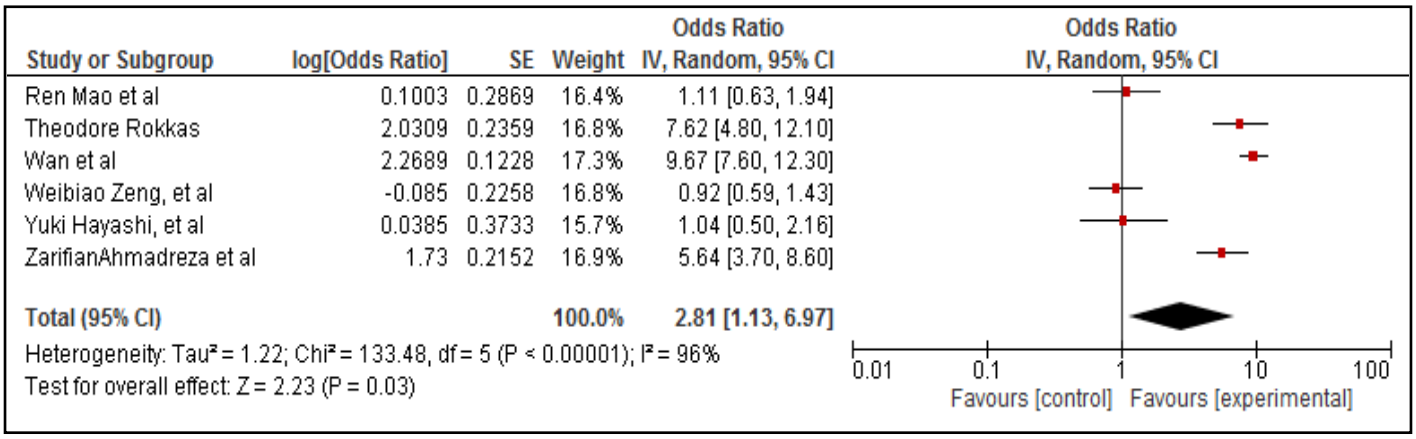

Figure 2(c): Forest plot for the prevalence of nausea in COVID-19 patients

Meta-analysis for Vomiting

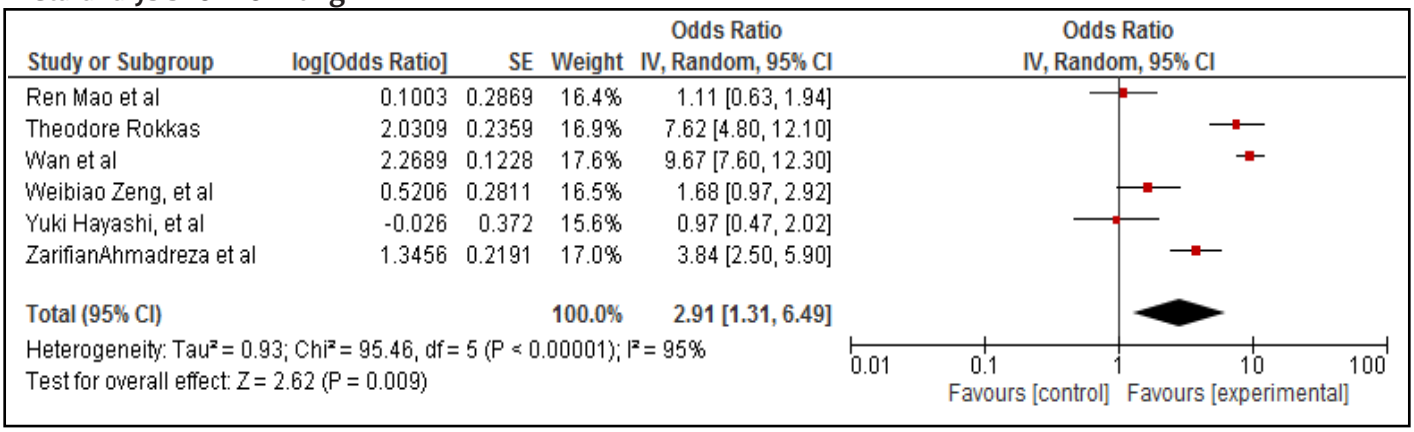

Figure 2(d): Forest plot for the prevalence of vomiting in COVID-19 patients

Meta-analysis for AST

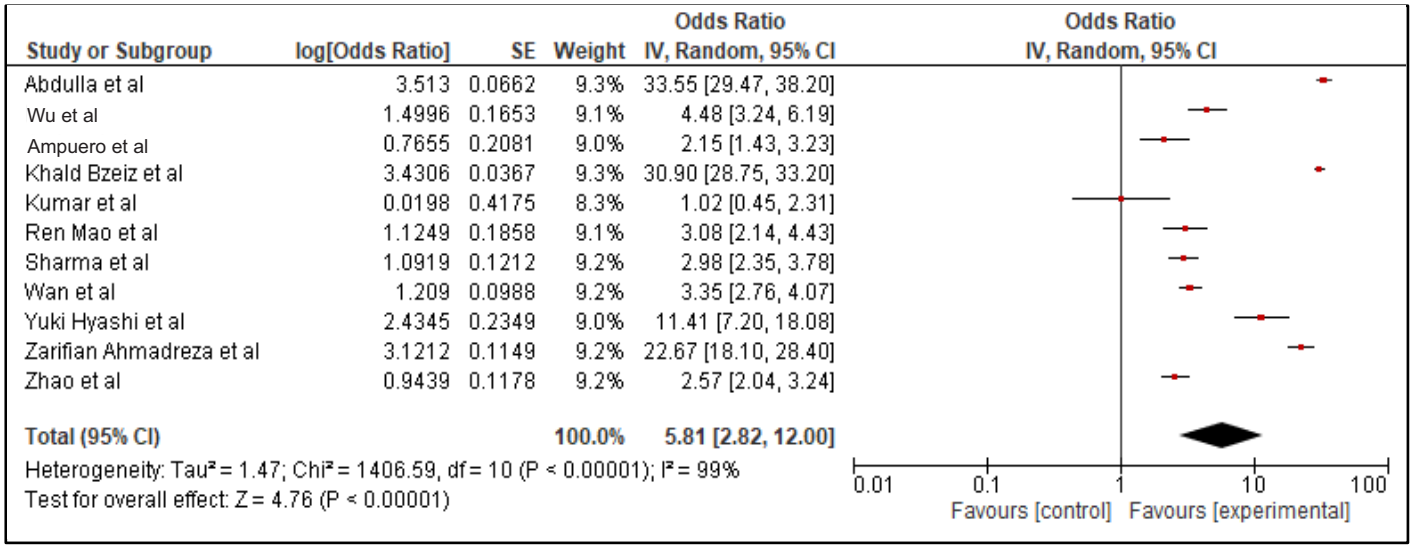

Figure 2 (e): Forest plot for Odds Ratio for the association between AST and COVID-19

Meta-analysis for ALT level

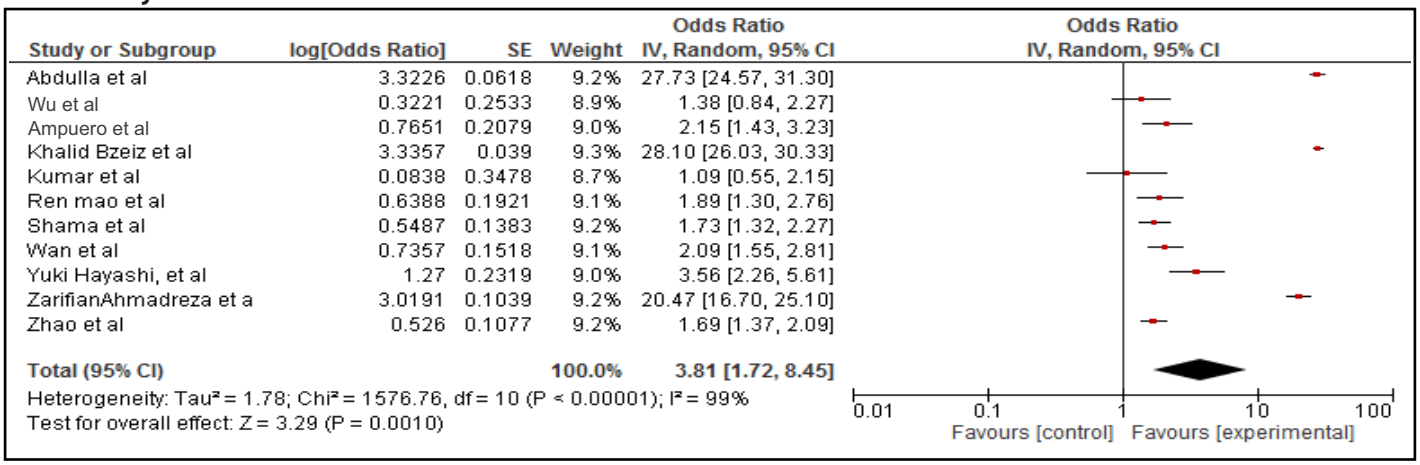

Figure 2 (f): Forest plot for Odds Ratio for the association between ALT and COVID-19

Meta-analysis for Bilirubin level

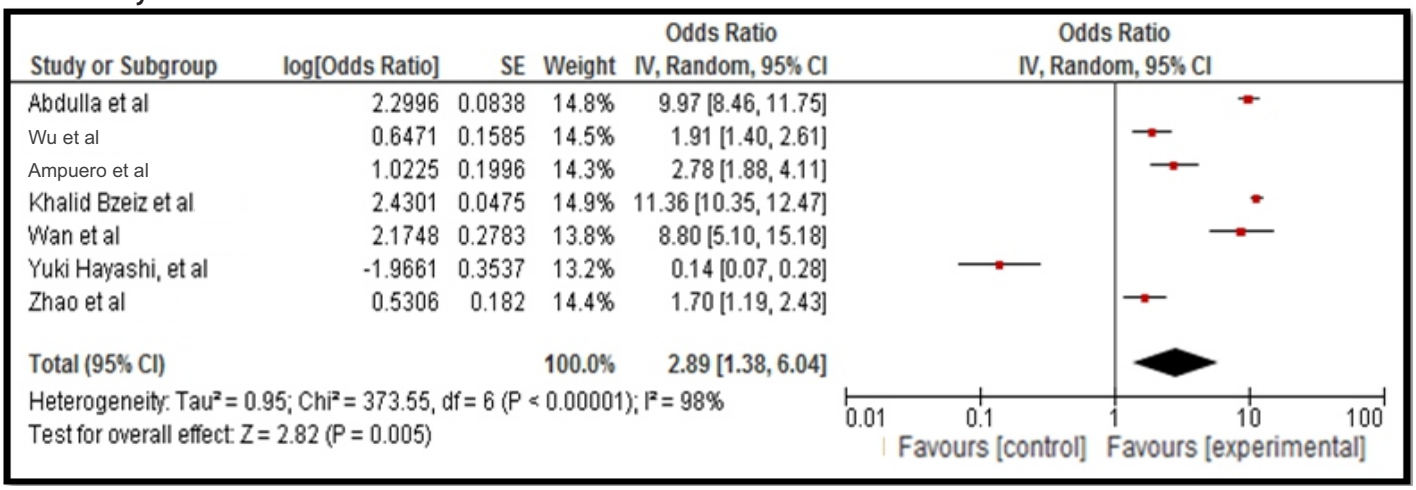

Figure 2 (g): Forest plot for Odds Ratio for the association between Bilirubin levels and COVID-19

DISCUSSION

The primary symptom of COVID-19 is respiratory illness; however, it can also cause complications such pneumonia, hypoxic respiratory failure, and acute respiratory distress syndrome. However, recent research has shown that GI symptoms can occur simultaneously with respiratory symptoms, most notably diarrhea, anorexia, vomiting, and nausea, or they might begin before respiratory symptoms too. What and how SARS-CoV-2 can cause intestinal symptoms in COVID-19 patients is hence a more crucial concern, particularly for those who already have underlying medical conditions. According to research, SARS-CoV-2 enters host cells by attaching to the ACE2 receptor on the cell's surface. SARS-CoV-2 cellular entrance depends on ACE2, hence ACE2-positive cells should be receptive to infection and serve as targetcells.[4,21] It has been discovered that the small intestine, colon, and duodenum, which include enterocytes, express ACE2 the most. The virus invades epithelial cells, releasing cytokines and chemokines that lead to acute intestinal inflammation marked by neutrophil, macrophage, and T cell infiltration. Indirect evidence for this claim may come from the presence of diarrhea in SARS-CoV-2 virus-infected patients 9270. Because a huge number of coronavirus-infected patients with GI symptoms has grown in tandem with the pandemic's spread, researchers have focused on the link between symptoms in the GI tract and COVID-19 seriousness.

The present meta-analysis of 268 studies including 61,269 participants reported the presence of diarrhea as the most common GI issue in COVID-19 infection, in conformity with a previous meta-analysis that assessed 26 studies and 4,676 patients.[7] RE model was employed due to significant heterogeneity across these studies/ trials. Pooled results indicated that there was a significant association in COVID-19 patients. Nausea/vomiting was also found to be the clinical

manifestations of COVID-19 which is often failed to notice by people. ACE 2, an infection gateway, has been reported to be strongly expressed in the GI epithelium, which could lead to nausea and vomiting.[8] We analyzed 268 studies with 61,269 participants, that reported the outcome of nausea and vomiting in meta-analysis. RE model was employed due to significant heterogeneity across the trials for nausea vomiting. Pooled results indicated that nausea and vomiting were associated with COVID-19 patients. Zeng *et al*.[26] performed a systematic review and meta-analysis of 21 studies to rule out an association between GI symptoms and coronavirus infection. There were 98 COVID-19 patients with signs and symptoms of nausea in five investigations, and 41.4 percent of patients with severe disease conditions.[7] There were fifty-nine percent COVID-19 infected patients with vomiting symptoms, and 51.3 percent with severe disease.[4] In our study, we have also investigated liver dysfunction in COVID-19 patients. Because there are ample ACE 2 receptors on the lung cells, SARS-CoV-2 prefers to infect the lungs. Though, bile duct and epithelial cells also have overexpressed ACE 2 receptors, allowing SARS-CoV-2 to bind directly to ACE 2-positive cholangiocytes and disturb liver function, causing changes in ALT and AST.[2] It was found in various studies that up to 11% of COVID-19 patients have liver comorbidities and almost 14% to 53% showed elevated ALT and AST levels during the progression of the illness. A strong substantial association between the severity of the viral infection and the degree of enzyme elevation was found. Patients with mild infection were found to have normal or slightly raised aminotransferase levels while those with severe infection presented with higher elevation.[2]

Saini *et al*. performed a retrospective study on 170 patients admitted with confirmed COVID-19 in a tertiary care center to analyze liver function tests and found 41.5% patients with normal liver enzyme levels, and 58.5% patients with raised liver enzyme levels, out of which (48.31%) had liver injury manifested as an increased liver enzyme.[8] We analyzed sixteen meta-analyses including 497 studies with 106,065 participants and 499 studies with 105896 of participants which reported the outcome of ALT and AST in meta-analysis. RE model was used due to significant heterogeneity across the trials of ALT and AST. Pooled results indicated that increased ALT, and AST level was associated with COVID-19 patients.

A significant association was found between bilirubin level and the severity of COVID-19. According to a study, patients with severe COVID-19 infection exhibited higher serum levels of total bilirubin in comparison to patients with less severe infection.[3] The severe group had a high level of heterogeneity, whereas the non-severe group had a moderate level of heterogeneity. The exact mechanisms of liver injury remain unclear. Zhao *et al* reported in eight studies that the risk of liver injury caused by increased Tuberculosis (TB) was 1.70 times greater in severely COVID-19-infected patients than in non-severe individuals.[19] According to the pooled analysis, the severely COVID-19-infected individuals this had 2.07 times more risk of liver injury than non-severe patients. In this meta-analysis, we analyzed 232 trials with 51640 participants to present the results of bilirubin. RE model was used due to significant heterogeneity across these trials. Pooled results indicated that there was a significant association in COVID-19 patients .

Due to its probable connection to enhanced viral replication in the gut and a high viral load, abdominal discomfort has been proven to be a clinical predictor of more severe disease. Another fundamental mechanism for GI symptoms and pathogenesis is gut dysbiosis, which can be caused by COVID-19 medicines or by the virus itself through the mediation of lung-derived effector CD4+ T cells that enter the small intestine through the gut-lung axis. The authors speculate that the viral load in the GI tract of COVID-19 patients with abdominal pain is higher than that of COVID-19 patients with diarrhoea, nausea, or vomiting given the robust association between viral load and COVID-19 severity.[25] A total of 55 COVID-19 patients with stomach pain were documented throughout eight trials. The results of a meta-analysis showed that there was only a little amount of heterogeneity between studies and that a significant proportion of COVID-19 patients with abdominal pain advanced to severe infection. The fixed-effects model determined that there was a significant correlation between abdominal pain and COVID-19 severity, with the OR of the relationship between stomach pain and severe COVID-19 calculated to be 2.76.[25]

We analyzed 268 studies including 61,269 participants to report the outcomes of abdominal pain in meta-analysis. RE model was employed due to significant heterogeneity across these studies. Pooled results indicated that association is in-significant in COVID-19 patients. When comparing the difference in complications, patients with digestive symptoms were more vulnerable to presenting with ARDS. Mao *et al*, also reported that patients with severe COVID-19 were more likely to present with abdominal pain compared with those with the non-severe disease. As the condition progressed, the prevalence of digestive

problems increased.[5] This conclusion was in line with research by Wan et al.[17] who reported that ICU patients were more likely to experience pain in the abdomen and loss of appetite than non-ICU patients.

Therefore, this meta-analysis of meta-analyses found a strong link between COVID-19 with liver dysfunction as well as GIT symptoms laying the groundwork for the better therapeutic care of COVID-19 and liver disease patients. The only limitation of our study is the variance in sample size of included studies.

CONCLUSION

Patients who were elderly or male and had abnormal liver functions were more likely to acquire severe illness. These results add to a deeper comprehension of the role of liver function tests in COVID-19 diagnosis and may pave the way for better patient management. Identifying nausea and vomiting as key indicators will open up the possibility of learning more about how the SARS Cov-2 virus attacks the GI tract and the brainstem, which will help in the development of preventive measures to treat the symptoms and limit the virus's spread through vomiting. In light of the results of this meta-analysis of meta-analyses, liver damage and GI problems are linked to poor outcomes in COVID-19 patients.

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