



Gastrointestinal and hepatic manifestations of Corona Virus Disease-19 and their relationship to severe clinical course: A systematic review and meta-analysis

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Abstract

Background Many case series on Corona Virus Disease (COVID-19) have reported gastrointestinal (GI) and hepatic manifestations in a proportion of cases; however, the data is conflicting. The relationship of GI and hepatic involvement with severe clinical course of COVID-19 has also not been explored.

Objectives The main objectives were to determine the frequency of GI and hepatic manifestations of COVID-19 and to explore their relationship with severe clinical course.

Methods We searched PubMed for studies published between January 1, 2020, and March 25, 2020, with data on GI and hepatic manifestations in adult patients with COVID-19. These data were compared between patients with severe and good clinical course using the random-effects model and odds ratio (OR) as the effect size. If the heterogeneity among studies was high, sensitivity analysis was performed for each outcome.

Results We included 62 studies (8301 patients) in the systematic review and 26 studies (4676 patients) in the meta-analysis. Diarrhea was the most common GI symptom (9%), followed by nausea/vomiting (5%) and abdominal pain (4%). Transaminases were abnormal in approximately 25%, bilirubin in 9%, prothrombin time (PT) in 7%, and low albumin in 60%. Up to 20% patients developed severe clinical course, and GI and hepatic factors associated with severe clinical course were as follows: diarrhea (OR 2), high aspartate aminotransferase (OR 1.4), high alanine aminotransferase (OR 1.6), high bilirubin (OR 2.4), low albumin (OR 3.4), and high PT (OR 3).

Conclusions GI and hepatic involvement should be sought in patients with COVID-19 since it portends severe clinical course. The pathogenesis of GI and hepatic involvement needs to be explored in future studies.

Keywords 2019-nCoV · Coronavirus · COVID-19 · nCoV-2019 · Novel coronavirus · SARS-CoV-2

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Introduction

Corona Virus Disease (COVID-19) is a new disease, which within 3 months of its origin, has now spread to more than two hundred countries and territories around the world, affecting more than 4,342,000 people and caused more than 292,000 deaths, as of 13 May 2020 [1]. On 11 March 2020, the World Health Organization (WHO) had declared COVID-19 a pandemic because of alarming levels of its spread and severity [2]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is sufficiently genetically divergent from SARS-CoV to be considered a new human-infecting betacoronavirus [3]. It mainly affects the respiratory tract, and the illness ranges in severity from

Bullet points of the study highlights

What is already known?

- Corona Virus Disease (COVID-19) is a global pandemic with a case fatality rate of approximately 3% to 4%.
- It predominantly affects the respiratory system.
- Many case series have reported gastrointestinal (GI) and hepatic manifestations in a proportion of patients.
- Their relationship to severity has not been explored.

What is new in this study?

- In COVID-19, diarrhea is present in 9%, nausea/vomiting in 5%, and pain abdomen in 4%.
- Transaminases are abnormal in approximately 25%, bilirubin in 9%, prothrombin time (PT) in 7%, and low albumin in 60%.
- Up to 20% of patients developed severe clinical course.
- GI and hepatic factors associated with severe clinical course are diarrhea, high aspartate aminotransferase, high alanine aminotransferase, high bilirubin, low albumin, and high PT.

What are the future clinical and research implications of the study findings?

- GI and hepatic involvement should be sought in patients with COVID-19 since it portends severe clinical course.
- Many of these patients require close monitoring and intensive care.
- The pathogenesis of GI and hepatic involvement needs to be explored in future studies.

asymptomatic or mildly symptomatic to severe or critical disease. Although the current estimate of the case fatality rate of COVID-19 is < 5%, up to 15% to 18% of patients may become severe or critically ill, some of them requiring intensive care unit (ICU) care and mechanical ventilation [4].

Since COVID-19 is a new disease, knowledge about this disease is still incomplete and evolving. Apart from the respiratory system involvement, many case series have also reported variable involvement of gastrointestinal (GI) and hepatic systems. However, most of these case series have small sample size, and the data in these are heterogenous and conflicting. In addition, the relationship of GI and hepatic involvement with the severity and outcome of COVID-19 is also not clear.

Hence, this systematic review and meta-analysis was conducted with the following objectives: (1) to study the frequency of GI and hepatic manifestations in COVID-19, and (2) to determine whether GI or hepatic manifestations are associated with severe clinical course of COVID-19.

Methods

Since this is a systematic review and meta-analysis, an institutional review board or an ethics committee approval was not required. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines were consulted during the stages of design, analysis, and reporting of this meta-analysis [5, 6]. The protocol of this meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO) vide registration number CRD42020179482 and is available in full on the NIHR (National Institute for Health Research) website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020179482).

Study selection

Relevant papers in English language were searched in PubMed database using the following keywords: “2019-

nCoV,” “nCoV-2019,” “novel Coronavirus 2019,” “SARS-CoV-2,” “COVID-19,” “coronavirus,” “coronavirus covid-19,” and “corona virus.” Since the first report of COVID-19 disease was published on 31 December 2019 [7], we limited our search to articles published since 1 January 2020. The last search was performed on March 25, 2020. Since there is a high likelihood of duplicate publications on COVID-19 [8], especially, the same set of patients being reported in English as well as Chinese or other languages, we restricted our search to papers published in English language only. For the same reason, we restricted our search to PubMed database only and did not search other databases.

The eligibility criteria for the inclusion of studies were as follows:

- (1) The studies should be in English language.
- (2) The studies should be published in full; studies published only in abstract form (such as conference abstracts) were excluded.
- (3) The study design should be retrospective or prospective, observational, or case-control study with data on GI and/or hepatic manifestations of COVID-19 disease. Interventional studies such as controlled or uncontrolled drug trials were excluded. Case reports, meta-analyses, and systematic reviews were also excluded.
- (4) The participants should be adult patients with COVID-19 disease. Studies describing exclusively pediatric population were excluded; however, studies which had both adult and pediatric patients were included. Studies describing exclusively pregnant women were also excluded.

Data extraction

The following data were extracted from each study: date of online publication, number of patients, study setting, demographic data, comorbidities, presenting symptoms (including GI symptoms), laboratory features (including liver function tests), number of patients having severe and good clinical course. The following criteria were used to identify patients having “severe clinical course”:

1. Patients requiring ICU care
2. Patients developing acute respiratory distress syndrome (ARDS), shock, respiratory failure, or those requiring mechanical ventilation as defined according to the guidance of the WHO for COVID-19 [9]
3. Patients categorized as severe or critical groups according to the diagnostic and treatment guideline for SARS-CoV-2 issued by the National Health Commission of the People’s Republic of China (version 3–5) [10, 11]
4. Patients not surviving

Patients not having any of the features of “severe clinical course” were categorized into “good clinical course.” The baseline clinical and laboratory features of patients with severe clinical course and good clinical course were tabulated separately and compared using meta-analytical tools. For studies with missing data, the corresponding authors of those studies were contacted with a request to provide the missing data.

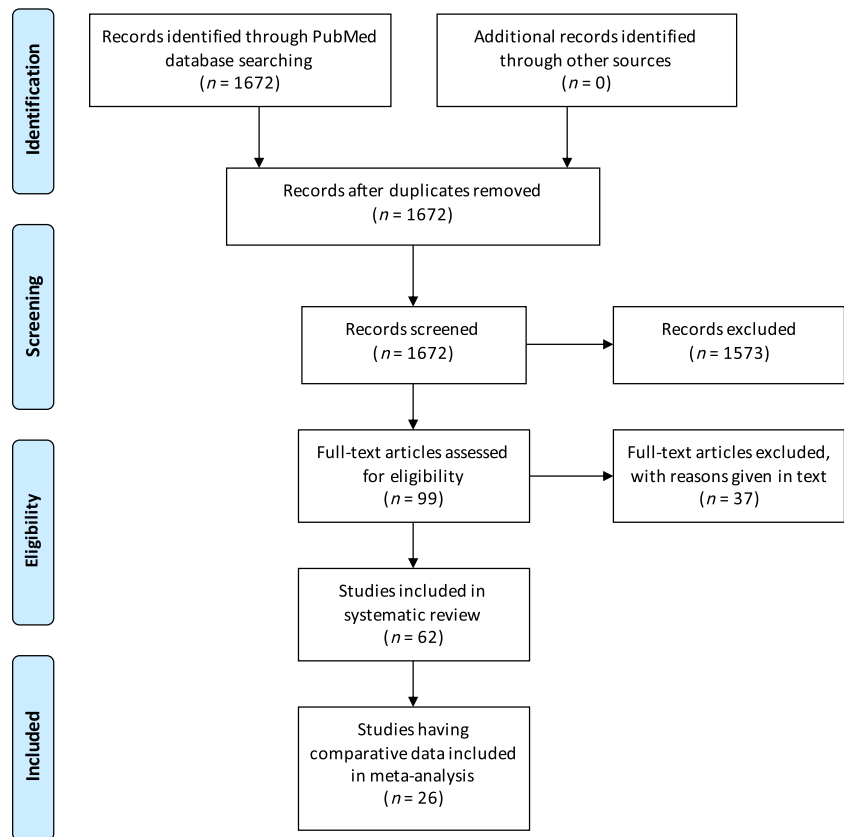
Assessment of quality of studies

For the assessment of quality of studies including risk of bias, the National Institute of Health (NIH) tools were used, which were developed jointly by the National Heart, Lung and Blood Institute (NHLBI) and the Research Triangle Institute International [12]. For the first objective of this systematic review, i.e. to study the GI and hepatic manifestations of COVID-19, the NIH tool for case series was used. It uses nine domains; and based on these, each study was given an overall rating of good, fair, or poor, depending on “yes” response in ≥ 7 domains, 4–6 domains, and < 4 domains, respectively. For the second objective of this meta-analysis, i.e. to determine the GI and hepatic factors associated with severe clinical course of COVID-19, the NIH tool for case-control studies was used. It uses twelve domains, and based on these, each study was given an overall rating of good, fair, or poor, depending on “yes” response in ≥ 8 domains, 6–7 domains, and < 6 domains, respectively.

Statistical analysis

The demographic, clinical, and laboratory data was displayed as n (%) or mean (standard deviation, [SD]). For data with median, interquartile range (IQR), or range, the method described by Wan et al. was used to calculate mean and SD [13]. The meta-analysis was performed using odds ratios (ORs) with 95% confidence intervals (CIs) as the effect sizes of dichotomous data and a p -value of < 0.05 to show a meaningful difference in the outcomes. To obtain ORs from continuous data (i.e. from standardized mean difference), Hasselblad and Hedges’ method was used [14]. To assess the heterogeneity among studies, I^2 statistic was calculated. An I^2 value $> 50\%$ indicated substantial heterogeneity. To take care of heterogeneity among the studies, and to calculate a more conservative result, the ORs were pooled using only the random-effects model. In addition, if the heterogeneity among the studies was $\geq 50\%$, a sensitivity analysis was also performed after removing the outlier studies. Review Manager version 5.3.5 software (The Nordic Cochrane Centre, Copenhagen, Denmark)

Fig. 1 PRISMA flow diagram depicting the flow of information through different phases of the systematic review. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses



and Microsoft Excel (version 16.35) were employed for the meta-analysis and statistical analyses.

Results

Study selection and data collection

Using the keywords “2019-nCoV,” “nCoV-2019,” “novel Coronavirus 2019,” “SARS-CoV-2,” “COVID-19,” “coronavirus,” “coronavirus covid-19,” and “corona virus” and limiting the Entrez date from 1 January 2020, through 25 March 2020, initially 1672 publications in English language were retrieved from the PubMed database, which were screened for relevance (Fig. 1). After carefully going through the abstracts and full texts (if needed), of these publications, only 99 potentially relevant studies were evaluated in detail for potential inclusion. Of these, 37 studies were excluded because of the following reasons: (1) 15 studies did not have any data on GI or hepatic manifestations of COVID-19; (2) 9 studies had overlapping patients with other included studies; (3) 4 studies had only radiological or epidemiological data without any clinical data; (4) 2 studies included only pregnant women; (5) 1 study included only those patients who had GI symptoms and excluded patients without GI symptoms; (6) 1 study included only COVID-19-influenza co-infected patients; (7) 1

study included only cancer patients with COVID-19; and (8) 4 studies had data not relevant to present study. Hence, the remaining 62 studies were included in the systematic review. Of these 62 studies, only 26 had comparative data between severe and good clinical course; hence, these 26 studies were included in the meta-analysis (Fig. 1).

Characteristics and quality of the included studies

The study characteristics of the included 62 studies are given in Table 1. The online publication date of the studies in the PubMed database was from January 24, 2020, through March 25, 2020. Thirty-eight out of 62 (61%) studies were from single centers, while the remaining 24 (39%) were multi-center studies. Most studies (56/62, 90%) were from mainland China, and of the remaining 6 studies, two were from Singapore (3%), and one each (1.6%) from Hong Kong, USA, Australia, and Europe. The total included patients were 8301, and of them, 8076 (97%) were reported from mainland China. The median number of patients included in the studies was 74 (IQR: 34–137). The largest study was by Guan et al. [15], which recruited 1099 patients from 552 hospitals in 30 provinces, autonomous regions, and municipalities of mainland China.

The quality of study was assessed using the NIH tool for case series [12], and the results are shown in Table 1. The scores were as follows: 8/9 (48 studies [77%]); 7/9 (8 studies [13%]); 6/9 (2

Table 1 Characteristics and quality of studies included in systematic review and meta-analysis

First author	PMID	Date of publication	Setting	N	Clinical course		Quality of study	
					Severe	Good	Included in systematic review	Included in meta-analysis
Chan et al. [29]	31986261	24-Jan-20	Single center in Shenzhen, Guangdong Province, China	6			8	
Huang et al. [30]	31986264	24-Jan-20	Single center in Wuhan, Hubei Province, China	41	13	28	8	9
Chen et al. [31]	32007143	30-Jan-20	Single center in Wuhan, Hubei Province, China	99			8	
Song et al. [32]	32027573	06-Feb-20	Single center in Shanghai, China	51			8	
Chang et al. [33]	32031568	07-Feb-20	Three hospitals in Beijing, China	13			8	
Wang et al. [34]	32031570	07-Feb-20	Single center in Wuhan, Hubei Province, China	138	36	102	8	9
Liu et al. [35]	32044814	07-Feb-20	Nine tertiary hospitals in Hubei Province, China	137			8	
Liu et al. [36]	32048163	09-Feb-20	Single center in Shenzhen, Guangdong Province, China	12			8	
Ren et al. [37]	32004165	11-Feb-20	Single center in Wuhan, Hubei Province, China	5			8	
Xu et al. [38]	32075786	19-Feb-20	Seven hospitals in Zhejiang Province, China	62			8	
Zhang et al. [39]	32077115	19-Feb-20	Single center in Wuhan, Hubei Province, China	140	58	82	8	9
Wu et al. [40]	32091414	21-Feb-20	Two hospitals in Chongqing, China	80			8	
Yang et al. [41]	32105632	24-Feb-20	Single center in Wuhan, Hubei Province, China	52	32	20	8	9
Shi et al. [42]	32105637	24-Feb-20	Two centers in Wuhan, Hubei Province, China	81			8	
Xu et al. [43]	32109443	25-Feb-20	Single center in Beijing, China	50	13	37	8	9
Yang et al. [44]	32112884	26-Feb-20	Three tertiary hospitals in Wenzhou City, Zhejiang Province, China	149			8	
Huang et al. [45]	32114074	27-Feb-20	Single center in Wuhan, Hubei Province, China	34			8	
Xu et al. [46]	32107577	28-Feb-20	Single center in Guangdong Province, China	90			8	
Guan et al. [15]	32109013	28-Feb-20	552 hospitals in 30 provinces, autonomous regions, municipalities, China	1099	173	926	8	9
Liu et al. [47]	32118640	28-Feb-20	Three tertiary hospitals in Wuhan, Hubei Province, China	78	11	67	8	9
Wu et al. [48]	32109279	29-Feb-20	Multi-center in Jiangsu Province, China	80			8	
Li et al. [49]	32118615	29-Feb-20	Single center in Chongqing, China	83	25	58	8	9
Cao et al. [50]	32123993	02-Mar-20	Single center in Wuhan, Hubei Province, China	102	18	84	8	9
Zhang et al. [51]	32124995	03-Mar-20	Single center in Jinhua, Zhejiang Province, China	14			5	
Young et al. [52]	32125362	03-Mar-20	Four hospitals in Singapore	18	6	12	8	9
Ruan et al. [53]	32125452	03-Mar-20	Two centers in Wuhan, Hubei Province, China	150	68	82	8	9
Zhao et al. [54]	32125873	03-Mar-20	Four institutions in Hunan Province, China	101	14	87	8	9
Xiong et al. [55]	32134800	03-Mar-20	Single center in Wuhan, Hubei Province, China	42			8	
Xiao et al. [56]	32142773	03-Mar-20	Single center in Guangdong Province, China	73			5	
Hu et al. [57]	32146694	04-Mar-20	Single center in Nanjing, Jiangsu Province, China	24			8	
Zhou et al. [58]	32134681	05-Mar-20	Single center in Wuhan, Hubei Province, China	62			8	
Wang et al. [59]	32139464	05-Mar-20	Single center in Zhengzhou, Henan Province, China	18			6	
Spiteri et al. [60]	32156327	05-Mar-20	WHO European region except UK	38			4	
CNIRST [61]	32156224	11-Mar-20	Multi-center in Australia	71			4	
Zhou et al. [62]	32171076	11-Mar-20	Two hospitals in Wuhan, Hubei Province, China	191	54	137	8	9
Liu et al. [63]	32171866	11-Mar-20	Single center in Hainan Province, China	56			8	
Chen et al. [64]	32171869	11-Mar-20	Single center in Shanghai, China	249	22	227	8	9
Zhao et al. [65]	32161968	12-Mar-20	Two hospitals in Anhui Province, China	19			8	
Chen et al. [66]	32162699	12-Mar-20	Single center in Anhui Province, China	9			8	
Zhu et al. [67]	32167181	13-Mar-20	Two emergency departments in Anhui Province, China	32			8	
Wu et al. [68]	32167524	13-Mar-20	Single center in Wuhan, Hubei Province, China	201	84	117	8	9
Cheng et al. [69]	32174128	14-Mar-20	Single center in Shanghai, China	11			8	
Mo et al. [70]	32173725	16-Mar-20	Single center in Wuhan, Hubei Province, China	155	85	70	8	9

Table 1 (continued)

First author	PMID	Date of publication	Setting	N	Clinical course		Quality of study	
					Severe	Good	Included in systematic review	Included in meta-analysis
Wang et al. [71]	32176772	16-Mar-20	Single center in Wuhan, Hubei Province, China	69	14	55	8	9
Wang et al. [72]	32179910	17-Mar-20	Single center in Shenzhen, Guangdong Province, China	55			8	
Han et al. [73]	32181672	17-Mar-20	Single center in Wuhan, Hubei Province, China	108			7	
Qian et al. [74]	32181807	17-Mar-20	Five hospitals in Zhejiang Province, China	91	9	82	8	9
Gao et al. [75]	32181911	17-Mar-20	Single center in Fuyang, Anhui Province, China	43	15	28	8	9
Shi et al. [76]	32188484	18-Mar-20	Multi-center in Zhejiang Province, China	487	49	438	7	8
Arentz et al. [77]	32191259	19-Mar-20	Single center in Washington State, USA	21	21	0	7	
Wang et al. [78]	32191587	19-Mar-20	Single center in Wuhan, Hubei Province, China	90			7	
Wu et al. [79]	32199469	19-Mar-20	Single center in Zhuhai, Guangdong Province, China	74	18	56	7	
Liu et al. [80]	32199493	19-Mar-20	Single center in Nanchang, Jiangxi Province, China	76	30	46	6	9
Zhang et al. [81]	32205284	20-Mar-20	Multi-center in Zhejiang Province, China	645	64	581	8	9
Deng et al. [82]	32209890	20-Mar-20	Two tertiary hospitals in Wuhan, Hubei Province, China	225	109	116	8	8
Wan et al. [83]	32198776	21-Mar-20	Multi-center in Chongqing, China	135	40	95	8	9
Zhou et al. [84]	32209382	21-Mar-20	Single center in Wuhan, Hubei Province, China	34	8	26	7	9
To et al. [85]	32213337	23-Mar-20	Two hospitals in Hong Kong	23	10	13	7	9
Jin et al. [86]	32213556	24-Mar-20	Multi-center in Zhejiang Province, China	651	64	587	8	
Sun et al. [87]	32211755	25-Mar-20	Single center in Singapore	54			7	
Shi et al. [88]	32211816	25-Mar-20	Single center in Wuhan, Hubei Province, China	416			8	
Lian et al. [89]	32211844	25-Mar-20	Multi-center in Zhejiang Province, China	788	78	710	8	
				8301	1241/6210 (20%)	4969/6210 (80%)		

PMID PubMed identification number, N number

Table 2 Demographic data and clinical presentation of patients

First author	N	Age		Gender		Comorbidities		General symptoms				Gastro-intestinal symptoms			
		Mean	SD	Male	Male%	Any	CLD	Fever	Cough	Sputum	Dyspnea	Diarrhea	Nausea	Vomiting	Pain abdomen
Chan et al. [29]	6	46.2	22.5	3	50	4	–	5	4	1	0	2	–	–	–
Huang et al. [30]	41	49.3	13.1	30	73	13	1	40	31	(11/39)	(22/40)	(1/38)	–	–	–
Chen et al. [31]	99	55.5	13.1	67	68	50	–	82	81	–	31	2	1	–	–
Song et al. [32]	51	49.0	16.0	25	49	11	1	49	24	10	7	5	3	–	–
Chang et al. [33]	13	38.7	11.6	10	77	–	–	12	6	2	–	1	–	–	–
Wang et al. [34]	138	55.3	19.5	75	54	64	4	136	82	37	43	14	14	3	3
Liu et al. [35]	137	54.2	12.1	61	45	27	–	112	66	6	26	11	–	–	–
Liu et al. [36]	12	53.7	18.0	8	67	7	0	10	11	–	–	2	2	–	–
Ren et al. [37]	5	53.6	9.5	3	60	2	1	5	5	1	4	0	–	–	–
Xu et al. [38]	62	41.7	15.2	35	56	20	7	48	50	35	2	3	–	–	–
Zhang et al. [39]	140	56.5	11.8	71	51	90	8	(110/120)	(90/120)	–	(44/120)	(18/139)	(24/139)	(8/139)	–
Wu et al. [40]	80	44.0	11.0	42	53	15	–	61	58	11	7	7	–	–	7
Yang et al. [41]	52	59.7	13.3	35	67	21	–	51	40	–	33	–	2	–	–
Shi et al. [42]	81	49.5	11.0	42	52	21	7	59	48	15	34	3	4	–	–
Xu et al. [43]	50	43.9	16.8	29	58	–	–	43	20	7	4	1	–	–	–
Yang et al. [44]	149	45.1	13.4	81	54	–	8	114	87	48	2	11	2	–	–
Huang et al. [45]	34	56.2	17.1	14	41	16	1	32	17	8	5	5	–	–	–
Xu et al. [46]	90	51.0	13.8	39	43	45	–	70	57	11	–	5	5	–	–
Guan et al. [15]	1099	46.7	17.1	640	58	261	23	975	745	370	205	42	55	–	–
Liu et al. [47]	78	42.7	18.1	39	50	–	–	57	34	–	–	–	–	–	–
Wu et al. [48]	80	46.1	15.4	39	49	38	1	63	51	–	30	1	1	–	–
Li et al. [49]	83	45.5	12.3	44	53	15	–	72	65	15	9	7	–	–	7
Cao et al. [50]	102	52.7	22.6	53	52	47	2	83	50	–	–	11	–	–	–
Zhang et al. [51]	14	46.8	20.2	7	50	–	–	13	10	–	–	0	0	–	–
Young et al. [52]	18	49.5	11.5	9	50	5	–	13	15	–	2	3	–	–	–
Ruan et al. [53]	150	57.7	12.5	102	68	77	4	127	110	54	110	–	–	–	–
Zhao et al. [54]	101	44.4	11.6	56	55	30	–	79	63	–	1	3	2	–	–
Xiong et al. [55]	42	49.5	14.1	25	60	13	–	36	27	–	8	10	–	–	–
Xiao et al. [56]	73	41.2	16.2	41	56	–	–	–	53	–	–	26	–	–	–
Hu et al. [57]	24	36.2	29.9	8	33	–	0	5	2	–	–	–	–	–	–
Zhou et al. [58]	62	52.8	12.2	39	63	–	–	54	28	28	15	9	–	–	–
Wang et al. [59]	18	41.0	20.9	10	56	6	–	17	10	–	4	3	1	–	–
Spiteri et al. [60]	38	41.8	18.5	25	66	(2/7)	(0/7)	(20/31)	(14/31)	–	(2/31)	(1/31)	(1/31)	–	–
CNIRST [61]	71	46.0	19.8	36	51	–	–	(22/34)	(24/34)	–	(3/34)	(9/34)	(2/34)	–	–

Table 2 (continued)

First author	N	Age		Gender		Comorbidities		General symptoms				Gastro-intestinal symptoms			
		Mean	SD	Male	Male%	Any	CLD	Fever	Cough	Sputum	Dyspnea	Diarrhea	Nausea Vomiting	Pain abdomen	
Zhou et al. [62]	191	56.3	15.7	119	62	91	–	180	151	44	56	9	7	–	
Liu et al. [63]	56	52.1	14.7	31	55	–	1	44	21	21	4	–	10	–	
Chen et al. [64]	249	50.3	20.9	126	51	90	2	217	91	–	19	8	–	–	
Zhao et al. [65]	19	43.7	23.2	11	58	3	1	15	9	–	–	1	–	–	
Chen et al. [66]	9	42.1	15.3	5	56	0	–	8	7	–	0	2	–	0	
Zhu et al. [67]	32	44.3	13.2	15	47	–	2	27	21	5	–	1	–	–	
Wu et al. [68]	201	51.3	12.7	128	64	–	7	188	163	83	80	–	–	–	
Cheng et al. [69]	11	50.4	15.5	8	73	–	–	8	7	3	1	1	–	–	
Mo et al. [70]	155	54.0	18.0	86	55	71	7	126	97	–	50	7	3	3	
Wang et al. [71]	69	46.3	20.4	32	46	25	1	60	38	20	20	10	3	–	
Wang et al. [72]	55	42.2	14.7	22	40	–	1	7	7	–	–	–	–	–	
Han et al. [73]	108	45.0	13.6	38	35	–	–	94	65	–	–	15	–	–	
Qian et al. [74]	91	47.8	15.4	37	41	–	–	65	55	30	10	21	11	–	
Gao et al. [75]	43	43.7	12.1	26	60	–	–	–	–	–	–	–	–	–	
Shi et al. [76]	487	46.0	19.0	259	53	–	22	–	–	–	–	–	–	–	
Arentz et al. [77]	21	70.0	13.0	11	52	18	1	11	11	–	17	–	–	–	
Wang et al. [78]	90	45.0	14.0	33	37	–	–	55	20	–	–	6	–	2	
Wu et al. [79]	74	43.5	3.8	39	53	–	–	45	37	–	9	26	–	–	
Liu et al. [80]	76	48.3	15.7	48	63	–	–	63	35	–	9	2	2	–	
Zhang et al. [81]	645	45.3	14.3	328	51	(177/468)	(25/620)	540	425	225	26	53	22	–	
Deng et al. [82]	225	55.4	19.0	124	55	127	–	189	85	49	99	33	–	–	
Wan et al. [83]	135	46.0	14.2	72	53	43	2	120	102	12	18	18	4	–	
Zhou et al. [84]	34	64.7	8.8	17	50	–	–	–	–	–	–	–	–	–	
To et al. [85]	23	58.4	11.6	13	57	11	–	22	5	–	4	2	1	–	
Jin et al. [86]	651	45.2	14.4	331	51	178	25	545	435	227	27	–	–	–	
Sun et al. [87]	54	44.8	13.9	29	54	5	0	–	36	13	7	20	–	–	
Shi et al. [88]	416	61.0	12.5	205	49	–	4	334	144	23	117	16	–	–	
Lian et al. [89]	788	45.8	14.9	407	52	218	31	636	506	265	37	88	–	–	
	8301	48.7	16.5	4443	54%	1957	200	6274	4651	1690	1263	555	182	30	
						/5785	/6183	/7546	/7673	/5894	/6962	/6401	/3629	/694	
						(34%)	(3%)	(83%)	(61%)	(29%)	(18%)	(9%)	(5%)	(4%)	

N number, SD standard deviation, CLD chronic liver disease

studies [3%]; 5/9 (2 studies [3%]); and 4/9 (2 studies [3%]). Thus, 56 studies (90%) were of good quality (scores of ≥ 7) and the remaining 6 studies (10%) were of fair quality (scores 4–6). None of the included study was judged poor.

Twenty-six studies (4676 patients), which were included in the meta-analysis, were evaluated for quality by NIH tool for case-control studies [12] (Table 1). The scores were as follows: 9/12 (24 studies [92%]) and 8/12 (2 studies [8%]). Thus, all the studies were of good quality with scores ≥ 8 . Out of the twelve domains assessed by this tool, the three domains in which all the studies were given “0” score were sample size justification, blinding of assessors, and adjusting for confounding variables.

Demographic data and clinical presentation of patients

Table 2 shows the clinical presentation of the included patients. The total number of patients was 8301, and of these, 4443 (54%) were males. Thus, the male to female ratio was approximately 1.2:1. The pooled mean age of patients was 48.7 ± 16.5 years.

Table 2 also shows the clinical presentation and underlying comorbidities of the included patients. Thirty-

four percent (1957/5785) of patients had one or more of some chronic underlying comorbidity such as hypertension, diabetes, cardiovascular disease, and chronic kidney disease (individual data not shown). Notably, chronic liver disease (including chronic hepatitis B or C, non-alcoholic steatohepatitis [NASH], or cirrhosis) was present in just 3% (200/6183) of patients.

Of the presenting symptoms, fever was the most common, present in 83% (6274/7546) of patients, followed by cough in 61% (4651/7673), expectoration (sputum) in 29% (1690/5894), and dyspnea in 18% (1263/6962) patients. Among the GI symptoms, diarrhea was the most common, present in 9% (555/6401), followed by nausea/vomiting in 5% (182/3629) and abdominal pain in just 4% (30/694) patients (Table 2).

Liver function tests of patients

Only 23 studies had data on liver function tests (Table 3). The transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were elevated in 25% (559/2226) and 23% (477/2107) patients,

Table 3 Liver function tests of patients

First author	<i>N</i>	High AST	High ALT	High bilirubin	Low albumin	High PT
Chan et al. [29]	6	0	0	0	0	0
Huang et al. [30]	41	15	–	–	–	–
Chen et al. [31]	99	35	28	18	97	5
Liu et al. [36]	12	2	2	0	6	–
Ren et al. [37]	5	–	1	–	–	1
Xu et al. [38]	62	10	–	–	–	–
Yang et al. [41]	52	15	15	–	–	–
Shi et al. [42]	81	43	–	–	–	–
Yang et al. [44]	149	27	18	4	9	17
Huang et al. [45]	34	7	8	3	25	17
Guan et al. [15]	1099	(168/757)	(158/741)	(76/722)	–	–
Wu et al. [48]	80	3	3	1	2	0
Ruan et al. [53]	150	(54/147)	(43/146)	(18/147)	(114/148)	–
Hu et al. [57]	24	0	2	0	–	–
Wang et al. [59]	18	(4/16)	(4/16)	–	–	–
Zhou et al. [62]	191	–	(59/189)	–	–	(11/182)
Zhao et al. [65]	19	(5/18)	(5/18)	–	–	–
Wu et al. [68]	201	(59/198)	(43/198)	(10/198)	(195/198)	(4/195)
Mo et al. [70]	155	54	54	–	–	–
Wang et al. [71]	69	19	23	–	–	–
Qian et al. [74]	91	9	7	–	43	–
Wan et al. [83]	135	30	–	–	–	–
To et al. [85]	23	–	4	–	–	–
		559/2226 (25%)	477/2107 (23%)	130/1471 (9%)	491/817 (60%)	55/750 (7%)

AST aspartate aminotransferase, ALT alanine aminotransferase, PT prothrombin time, *N* number

respectively. Serum bilirubin was elevated in 9% (130/1471), and prothrombin time (PT) was elevated in just 7% (55/750) patients. Very few studies had data on serum albumin; however, it was below the normal range in 60% (491/817) patients.

Clinical outcome

Since, at the time of publication of most of these studies, many of the included patients were still admitted in the hospital, with many in the ICUs, it was not possible by many studies to provide the mortality data. However, many studies did classify the patients into severe and non-severe groups based on pre-defined criteria [9–11]. Overall, 30 studies reported that 80% (4969/6210) of their patients had good clinical course, while the remaining 20% (1241/6210) patients had severe clinical course based on pre-defined severity criteria [9–11], including admission to ICU, development of ARDS, ventilatory requirement, or mortality (Table 1).

Factors associated with severe clinical course: age and comorbidity

Age was compared between patients with severe clinical course and good clinical course in 26 studies. The mean age in patients with severe clinical course was found to be significantly higher than in patients with good clinical course (60 ± 16 vs. 46 ± 16 years; *p* < 0.01). The pooled OR of patients of

advanced age (≥ 60 years) having severe clinical course was 3.96 (95% CI, 3.24–4.84; *p* < 0.01) (Fig. 2). The heterogeneity among the studies was substantial with an *I*² of 95%. A sensitivity analysis after removing 7 outlier studies revealed a higher pooled odds ratio of 4.19 (95% CI, 3.18–5.53; *p* < 0.01) and an acceptable *I*² of 42%.

Presence of any comorbidity was assessed as a factor associated with severe clinical course in 16 studies. The pooled OR of 3.88 (95% CI, 2.92–5.13; *p* < 0.01) suggested that the presence of any comorbidity was significantly associated with severe clinical course (Fig. 3). The heterogeneity among studies was acceptable with an *I*² of 42%.

GI and hepatic factors associated with severe clinical course

Presence of underlying chronic liver disease, as a factor associated with severe clinical course, was assessed in 10 studies, and it was not found to be significantly associated (pooled OR 1.07 [95% CI, 0.55–2.09; *p* = 0.83]) (Fig. 4). There was no heterogeneity among the studies (*I*² = 0%).

Among the GI symptoms, diarrhea was found in 9% of cases. Whether it was associated with severe clinical course was assessed in 16 studies. A pooled OR of 2.00 (95% CI, 1.37–2.91; *p* < 0.01) indicated that it was significantly associated with severe clinical course (Fig. 5). There was non-significant heterogeneity among studies with an *I*² of 22%.

Transaminases, AST and ALT values, were reported to be associated with severe clinical course by many individual

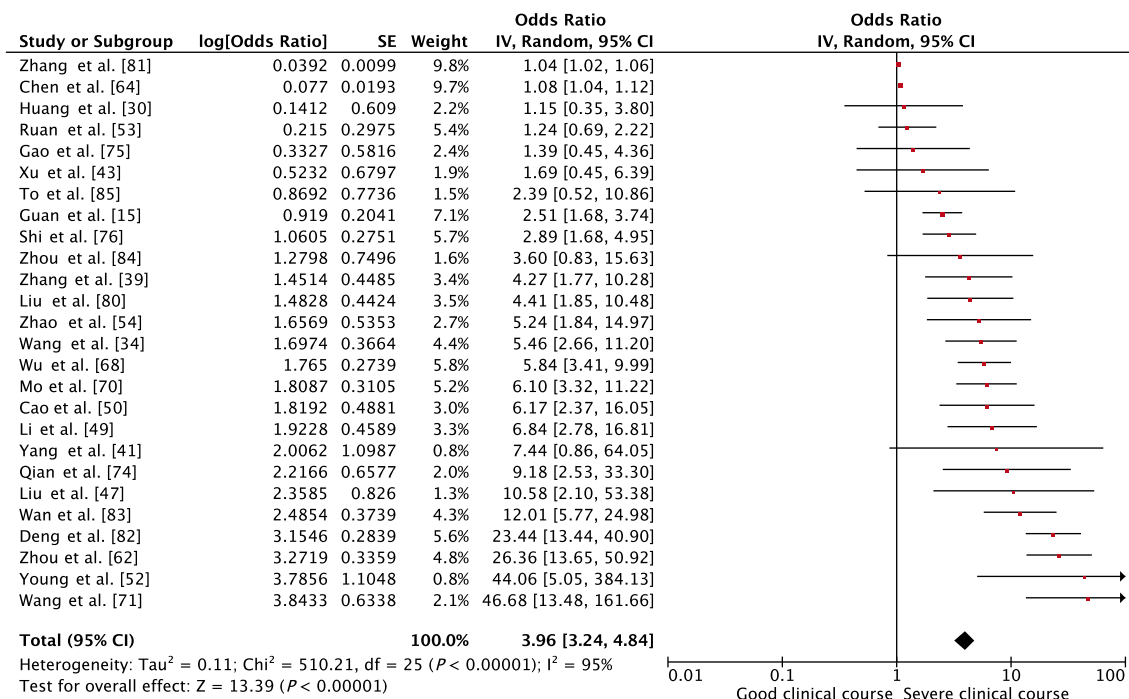


Fig. 2 Forest plot showing pooled odds ratio for patients with higher age (≥ 60 years) developing severe clinical course

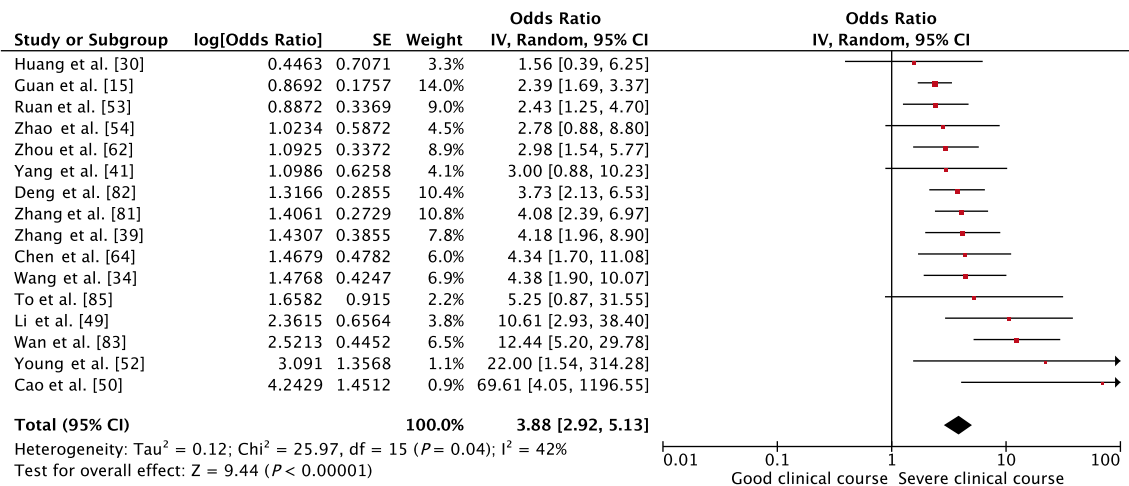


Fig. 3 Forest plot showing pooled odds ratio for patients having any comorbidity developing severe clinical course

studies. AST was evaluated in 15 studies, and higher than normal values of AST was found to be significantly associated with severe clinical course (pooled OR 1.40 [95% CI, 1.25–1.56]; *p* < 0.01) (Fig. 6). The heterogeneity among studies was substantial (I² of 91%) so a sensitivity analysis was done after removing four outlier studies, which again revealed a significant pooled OR of 2.45 (95% CI, 1.83–3.28; *p* < 0.01) and an acceptable I² of 31%. ALT was evaluated in 16 studies, and higher than normal values of ALT was found to be significantly associated with severe clinical course (pooled OR 1.57 [95% CI, 1.22–2.04; *p* < 0.01]) (Fig. 7). Since the heterogeneity among the studies was high (I² 68%), a sensitivity analysis was done after removing one outlier study, which still revealed a significant pooled OR of 1.68 (95% CI, 1.39–2.04; *p* < 0.01) and an I² of just 8%.

Serum bilirubin was assessed in 7 studies, and higher than normal values of serum bilirubin was found to be significantly associated with severe clinical course with a pooled OR of 2.38 (95% CI, 1.76–3.22; *p* < 0.01) (Fig. 8). The heterogeneity among the studies was non-significant with an I² of 25%.

Serum albumin was assessed in 10 studies, and lower than normal values of serum albumin was found to be significantly associated with severe clinical course with

a pooled OR of 3.40 (95% CI, 2.35–4.92; *p* < 0.01) (Fig. 9). Since the heterogeneity among studies was substantial with an I² of 93%, a sensitivity analysis was done after removing two outlier studies, which again revealed a significant pooled OR of 5.09 (95% CI, 3.75–6.91; *p* < 0.01) and an acceptable I² of 25%.

PT as a factor associated with severe clinical course was evaluated in 8 studies. Higher than control values of PT was found to be significantly associated with severe clinical course with a pooled OR of 2.95 (95% CI, 1.61–5.38; *p* < 0.01) (Fig. 10). Since the heterogeneity among studies was significant with an I² of 69%, a sensitivity analysis was done after removing one outlier study, which again showed a significant pooled OR of 3.81 (95% CI, 2.68–5.41; *p* < 0.01) and non-significant I² of 13%.

Discussion

To summarize the results of this systematic review and meta-analysis, the mean age of patients with COVID-19 is 48.7 ± 16.5 years with a male to female ratio of 1.2:1. Common symptoms and their frequency are fever

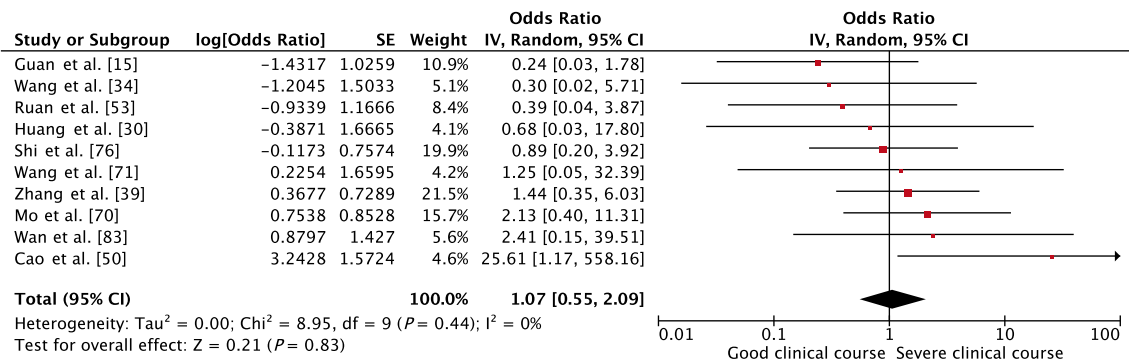


Fig. 4 Forest plot showing pooled odds ratio for patients with chronic liver disease developing severe clinical course

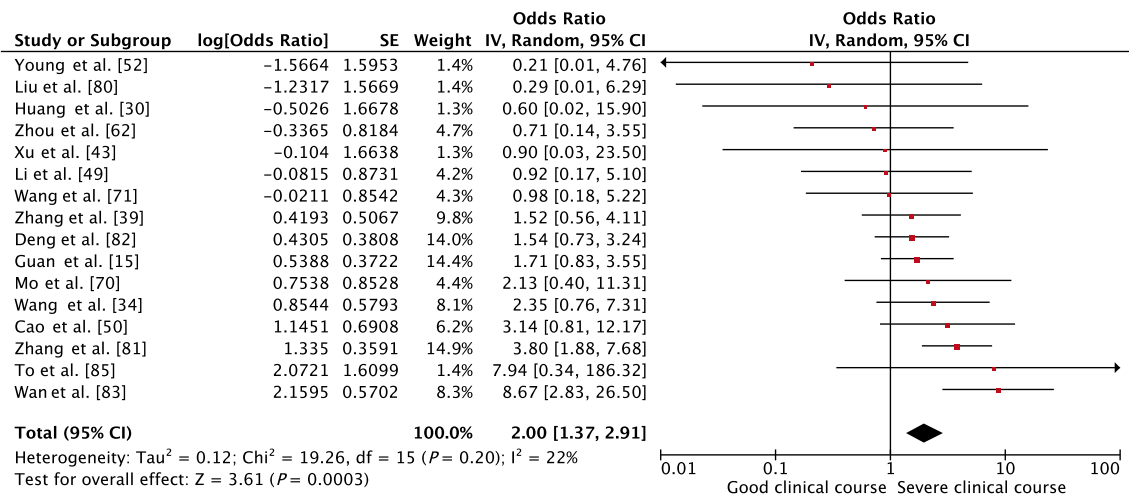


Fig. 5 Forest plot showing pooled odds ratio of diarrhea being associated with severe clinical course

(83%), cough (61%), expectoration (29%), and dyspnea (18%). Among the GI symptoms, diarrhea was the most common, present in 9%, followed by nausea/vomiting in 5%, and pain abdomen in just 4% of patients. Transaminases were abnormal in approx. 25%, serum albumin was low in 60%, bilirubin was high in 9%, and prothrombin time was abnormal in 7%. Twenty percent of patients developed severe clinical course, and two of the most common factors associated with severe clinical course are age ≥ 60 years (OR approximately [approx.] 4) and underlying chronic comorbidity (OR approx. 4). However, underlying chronic liver disease was not associated with severe clinical course. Presence of diarrhea was associated with severe clinical course (OR 2). Liver function abnormalities were associated with severe clinical course: high AST (OR approx. 2), high ALT (OR approx. 1.7), high bilirubin (OR approx. 2), low albumin (OR approx. 5), and high PT (OR approx. 4).

The strength of this systematic review and meta-analysis is that it included a large number of studies: 62 studies involving 8301 patients for the data on demographic and clinical features (especially GI and hepatic) and 26 studies involving 4676 patients for meta-analysis of GI and hepatic factors associated with severe clinical course. This is one of the first meta-analyses on factors associated with severe clinical course. The results of our study show that, even though COVID-19 is a disease of predominantly respiratory system, however, the involvement of the digestive system is also common, and it portends severe clinical course, including ICU requirement, or even mortality.

Our study showed that although GI symptoms are not very common, they can still occur in up to 10% of patients. However, it is still unclear how the SARS-CoV-2 virus induces GI symptoms and whether SARS-CoV-2 can be transmitted through the GI tract [16]. The SARS-CoV-2 virus has been documented in fecal samples as well as in intestinal mucosa of infected patients,

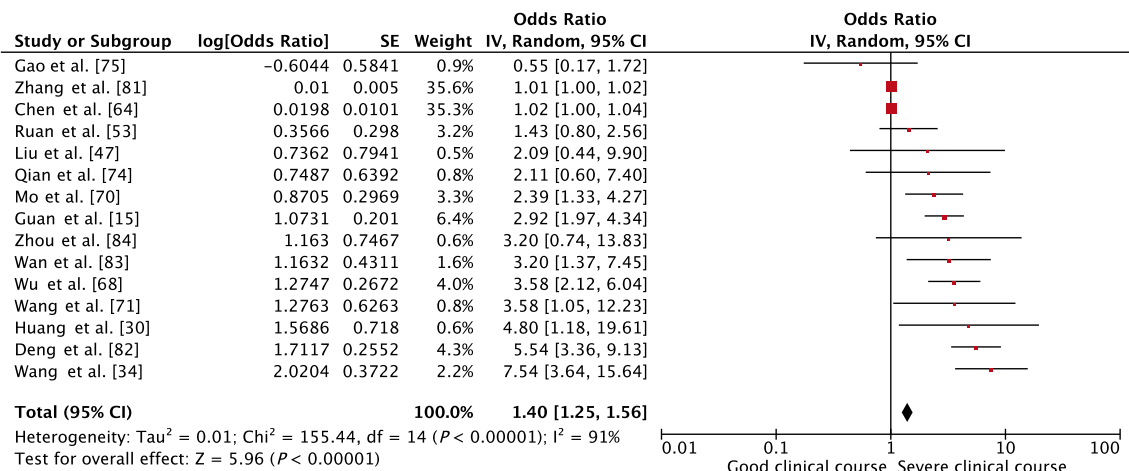


Fig. 6 Forest plot showing pooled odds ratio of higher than normal values of aspartate aminotransferase being associated with severe clinical course

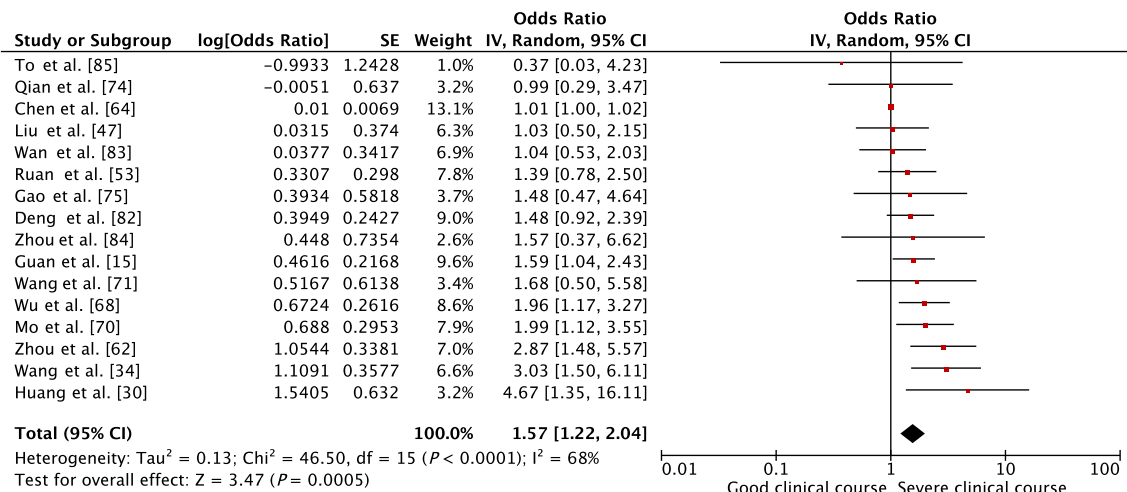


Fig. 7 Forest plot showing pooled odds ratio of higher than normal values of alanine transaminase being associated with severe clinical course

and this may indicate that GI symptoms are a result of invasion of GI tract by SARS-CoV-2 as an alternative route of infection. SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2) as a viral receptor to enter host cells [17], and these receptors are not only highly expressed in the small intestine, especially in the proximal and distal enterocytes [18], but also an important regulator of intestinal inflammation [19]. The SARS-CoV-2 infection of the ACE2-expressing enterocytes leads to mucosal inflammation, malabsorption, unbalanced intestinal secretion, and activation of the enteric nervous system, resulting in diarrhea. Other indirect mechanisms of GI involvement in COVID-19 could be damage of the GI mucosa through a chain of inflammatory responses; drugs-induced (especially antibiotics) diarrhea; and changes in the composition and function of intestinal microbiota that mutually affect the respiratory tract through immune regulation, the so-called “gut-lung axis” [20, 21]. Whatever be the mechanism of GI involvement, the implication of diarrhea and prolonged fecal shedding of SARS-CoV-2 viral particles (even after clinical recovery), is the potential for fecal-oral transmission of COVID-19, especially in countries with poor sanitation [22, 23]. Hence, a negative stool sample

should be a mandatory criterion before discharging a patient from the hospital.

The pathogenesis of hepatic involvement may also be multi-factorial. It has been shown previously that cholangiocytes may too express ACE2 receptors [24]; and so it has been speculated that SARS-CoV-2 infection might cause bile duct involvement rather than hepatocellular involvement. However, significant increases in circulating levels of serum gamma-glutamyl transferase, alkaline phosphatase, or bilirubin have been rarely reported in COVID-19 patients. In addition, liver histopathologic features from COVID-19 patients also did not show any significant damage in hepatocytes or bile duct cells. For this reason, it is hypothesized that COVID-19-related liver dysfunction is more likely due to secondary liver damage rather than primary cholangiocyte or hepatocyte damage by SARS-CoV-2. The secondary mechanisms of COVID-19-related liver dysfunction could be systemic inflammatory response syndrome (SIRS); sepsis; hypoxia-reperfusion dysfunction; and drug-induced liver injury (DILI) as a result of hepatotoxic drugs used to treat COVID-19 [25]. SIRS is a result of sudden initiation of an inflammatory cascade due to the activation of both natural and cellular immunity triggered by COVID-19 in-

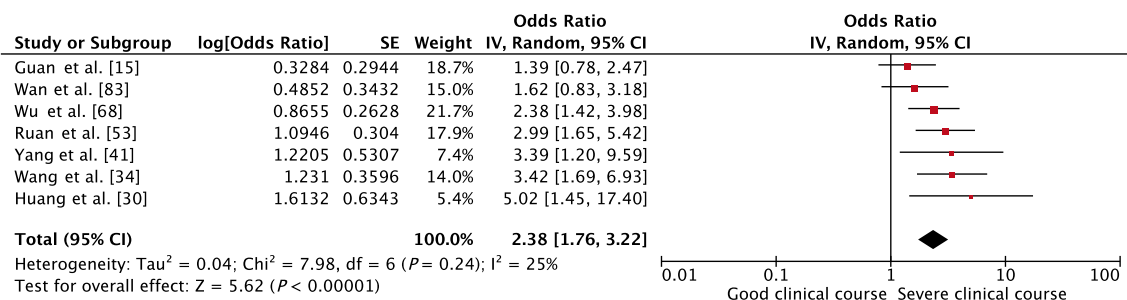


Fig. 8 Forest plot showing pooled odds ratio of higher than normal values of serum bilirubin being associated with severe clinical course

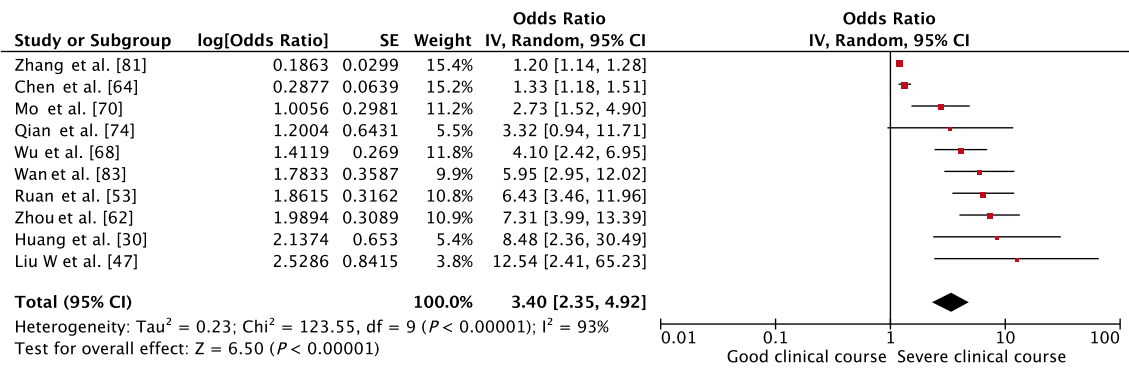


Fig. 9 Forest plot showing pooled odds ratio of lower than normal values of serum albumin being associated with severe clinical course

fection. Hyperactivated immune responses and cytokine storm-related systemic inflammation in SARS-CoV-2 infection can affect and damage many organs, including the gut and liver [26]. In addition to SIRS, sepsis is also not uncommon in severe and critical COVID-19 cases. The pathophysiology of sepsis-related liver injury includes cholestasis due to altered bile metabolism, hepatocellular injury due to drug toxicity, or overwhelming inflammatory hypoxic liver injury due to ischemia and shock [27]. Furthermore, severe hypoxia and hypovolemia could be the major causes of ischemic liver injury in COVID-19 cases with hypotension and shock. Ischemic hepatic injury is associated with metabolic acidosis, calcium overloading, and changes of mitochondrial membrane permeability, and has thus far usually manifested as high aminotransferase concentrations in serum [26]. In addition, many patients with COVID-19 have a history of simultaneous use of multiple antiviral, antimalarial, and antibiotic drugs, which are potentially hepato-toxic, such as oseltamivir, abidol, lopinavir/ritonavir, hydroxychloroquine, and azithromycin. Thus, DILI may be an additional factor in liver function derangement [28].

Our meta-analysis had a few limitations. The first limitation was that several of the identified factors may be confounding variables, and which of these factors are independently associated with severe clinical course could not be determined. Since our meta-analysis included only retrospective case series with a lot of heterogeneity, identification of independent factors was not possible. Only a well-designed prospective study can identify

independent factors associated with severe clinical course or mortality. The second limitation was the non-uniformity of the clinical endpoint. It may be argued that clubbing studies that compared patients with and without ICU admission with studies that used mortality as endpoint may not be statistically justified. However, in the present circumstances, when many of the included patients are still admitted and sufficient follow-up time has still not elapsed to determine their final outcome, using a composite endpoint of “severe clinical course” seems to be the most acceptable endpoint in our meta-analysis. The third limitation is that most studies in this meta-analysis are from China. COVID-19 is now a global disease; however, at the time of data extraction and analysis very few non-China studies were published. This meta-analysis will need updating when more studies from other countries become available.

In conclusion, our systematic review and meta-analysis has shown that, even though GI and hepatic manifestation are not very common in COVID-19, their presence portends a severe clinical course. GI symptoms, especially diarrhea, should be enquired from patients because it not only indicates severe disease, these patients are more likely to have fecal shedding of virus with potential infectivity to others. In addition, liver function tests in COVID-19 patients need to be monitored, which are likely to be abnormal in up to one-fourth of patients, especially those with severe clinical course.

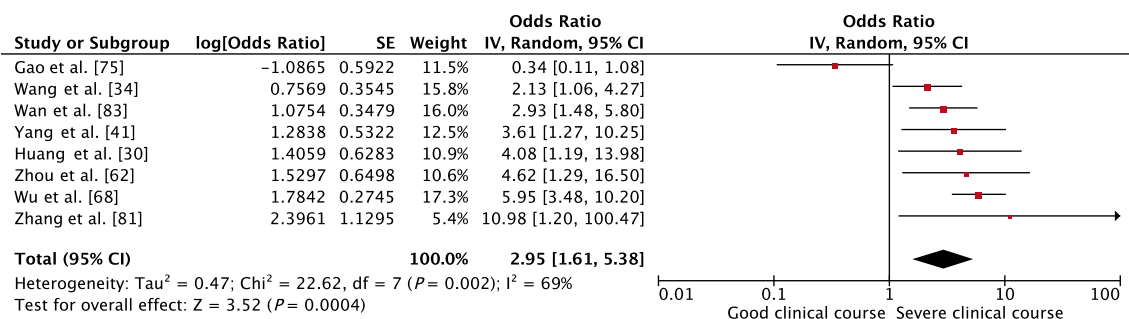


Fig. 10 Forest plot showing pooled odds ratio of higher than normal values of prothrombin time being associated with severe clinical course

Compliance with ethical standards

Conflict of interest AK, AA, PS, SAA, NB, VS, SK, and AS declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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