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Letter to the Editor

Hepatic manifestations and complications of COVID-19: A systematic review and meta-analysis

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To the Editor

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), was declared a global public health emergency on 30 January 2020. Emerging data suggests that COVID-19 has extrapulmonary manifestations and complications, subsequently leading to multiorgan failure and death. Common cardiovascular and renal complications reported to be associated with COVID-19 include myocardial injury, heart failure, acute kidney injury and electrolyte disturbances.(1, 2) In addition to the observation that older patients, males and those with pre-existing comorbidities such as cardiovascular disease, diabetes, chronic kidney disease and chronic liver disease are at highest risk for severe illness or death,(3, 4) COVID-19 complications have been shown to correlate with the disease severity or mortality.(5, 6) Emerging data also suggests COVID-19 contributes to adverse hepatic manifestations such as acute hepatic injury. Wang and colleagues in their recent published study to investigate characteristics and prognostic factors in 339 elderly patients with COVID-19, a high proportion of severe and critical cases were observed as well as a high fatality rate.(7) Apart from cardiovascular complications such as acute cardiac injury, arrhythmia and cardiac insufficiency, 28.7% of patients were reported to have developed liver enzyme abnormalities. Coronavirus disease 2019 is still evolving; its exact clinical course, severity and complications are still not completely clear. Given the sparse data, the hepatic manifestations and complications of COVID-19 are not clearly defined. In this context, we sought to address the following questions using a systematic meta-analysis: (i) what are the hepatic manifestations and complications of COVID-19?; (ii) what is the prevalence of hepatic manifestations and incidence of hepatic complications?; and (iii) are patients with pre-existing hepatic conditions more susceptible to these complications?

The protocol for this review was registered in the PROSPERO International prospective register of systematic reviews (CRD42020190354) and the review was conducted in accordance with PRISMA and MOOSE guidelines (**Supplementary Materials 1-2**). Published studies reporting on hepatic complications following admission in patients hospitalised with COVID-19 and/or hepatic manifestations during admission were sought MEDLINE, Embase, and The Cochrane library from 2019 to 15 June 2020. Details of the search strategy are reported in **Supplementary Material 3**. The

prevalence of comorbidities (eg, pre-existing chronic liver disease), prevalence of hepatic manifestations and incidence of hepatic complications across studies with their 95% confidence intervals (CIs) were pooled using Freeman-Tukey variance stabilising double arcsine transformation and random-effects models. All statistical analyses employed STATA release MP 16 (StataCorp LP, College Station, TX, USA)

Nineteen retrospective cohort studies comprising of 15,103 patients with COVID-19 were included (**Table 1; Supplementary Materials 4-5**). Fourteen studies were based in China and five in the USA. The average age at baseline ranged from 32 to 71 years.

In pooled analysis of 10 studies, the prevalence of pre-existing chronic liver disease (95% CI) in COVID-19 patients was 1.9% (0.5-3.8) (**Supplementary Material 6**). The prevalence (95% CI) of pre-existing liver cirrhosis (3 studies), hepatitis B (3 studies) and hepatitis C (2 studies) was 0.4% (0.0-1.8), 0.9% (0.1-2.5) and 0.3% (0.2-0.5) respectively (**Supplementary Material 7**). The prevalence (95% CI) of hepatic manifestations on admission: elevated alanine aminotransferase (ALT) (9 studies), elevated aspartate aminotransferase (AST) (8 studies), low albumin (2 studies) and elevated total bilirubin (3 studies) was 26.6% (15.8-39.0), 37.2% (20.3-55.8), 45.6 (40.5-50.8) and 18.2% (10.0-28.1) respectively (**Supplementary Material 8**).

Over hospital stays ranging from 2 to 28 days, the pooled incidence was 69.1% (67.3-70.9) for elevated ALT (2 studies); 34.8% (16.2-56.0) for elevated AST; 11.2% (6.4-17.1) for acute hepatic injury (15 studies) and 7.9% (5.9-10.2) for hypoproteinaemia (n=2 studies) (**Figure 1A**). Subgroup analyses suggested that the incidence of acute hepatic injury was higher in Chinese populations and groups with a higher prevalence of pre-existing chronic liver disease; however, the incidence of acute hepatic injury was similar in older (≥60 years) or younger age (<60 years) groups (**Figure 1B**).

Based on up-to-date published evidence, the common hepatic complications of COVID-19 are liver enzyme abnormalities (particularly the aminotransferases) followed by acute hepatic injury and hypoproteinaemia. Common hepatic manifestations on admission are elevated levels of ALT, AST and total bilirubin as well as low albumin levels. In contrast to a previous study which reported that about 2-11% of patients with COVID-19 have liver comorbidities,(8) the current review suggests that the prevalence estimate of pre-existing chronic liver disease may be lower at 1.9%. Though there

is controversy regarding the causes of liver injury in COVID-19,(8) the following mechanistic pathways have been proposed: (i) drug-induced during treatment; (i) direct injury to the liver due to COVID-19 hepatitis; (ii) COVID-19 induced myositis causing elevations in circulating levels of liver enzymes; (iii) binding of SARS CoV-2 directly to angiotensin-converting enzyme 2 (ACE2) positive rich cholangiocytes and causing liver damage; (iv) hepatic congestion due to high levels of positive end expiratory pressure during mechanical ventilation; and (v) aggravation of liver injury by SARS CoV-2 in patients with pre-existing viral hepatitis.(4) The current findings suggest that patient groups with higher prevalence of pre-existing chronic liver disease have higher incidence of acute hepatic injury.

Patients with pre-existing liver dysfunction appear to have worse outcomes in COVID-19,(8) which has been attributed to their immunocompromised status.(8) Hepatic complications such as acute hepatic injury have also been shown to be associated with increased risk of severe COVID-19 and fatal outcomes.(9) Liver injury is commonly characterised by markedly elevated levels of the aminotransferases and evidence suggests that elevated levels of these enzymes are associated with greater risk of severe disease and mortality.(4) Hepatic dysfunction is associated with systemic disturbances such as activation of the coagulation and fibrinolytic cascades, depressed platelet counts, increased neutrophil counts, decreased lymphocyte counts and increased ferritin levels,(10) which disrupt innate immune regulation. More intensive surveillance of markers of hepatic dysfunction is needed for patients who are admitted, to enable early and individually tailored therapeutic approaches.

Inherent limitations of this review included: (i) low methodological quality and sample sizes of included studies, which was not unexpected given the urgency to report and gain a better understanding of COVID-19; (ii) potential for selective reporting by some of the studies; (iii) definitions of acute hepatic injury were not reported by studies, hence it is unknown if this was consistent across studies; (iv) timing for assessment of hepatic markers may vary between studies, hence estimates may be biased; and (v) the potential possibility of patient overlap given that the majority of studies were conducted from China.(4)

Synthesis of the current literature suggests that liver enzyme abnormalities, acute hepatic injury and hypoproteinaemia are frequent hepatic complications among patients hospitalised with

COVID-19. Intensive monitoring of markers of these complications and management during admission could help in the prediction of favourable outcomes. The causes of these hepatic complications need further elucidation.

Conflict of interest

None.

Acknowledgements

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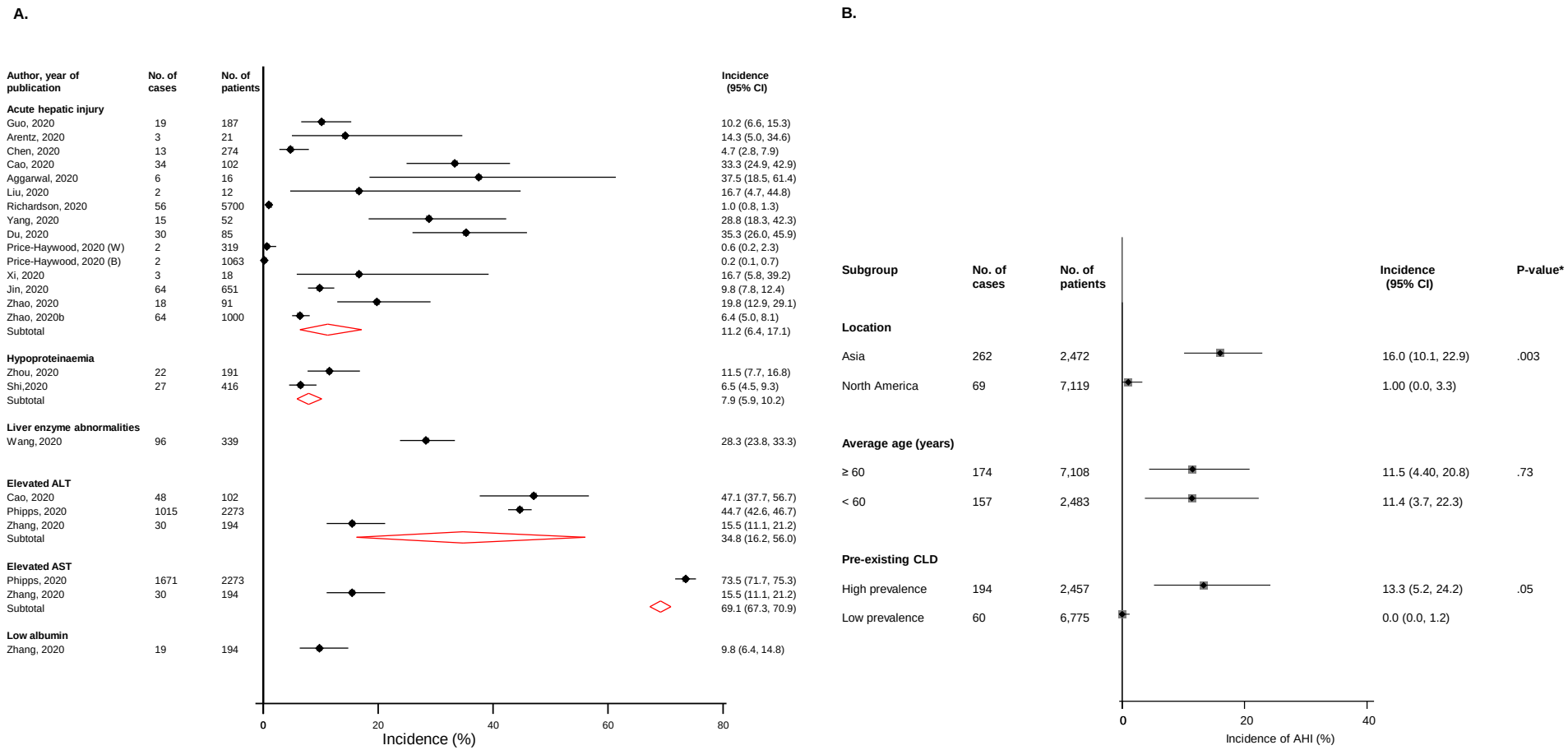
Table 1. Characteristics of included studies

Author, year of publication	Source of data	Country	Dates of data collection	Mean/median age (years)	Male %	Hospitalisation (days)	No. of patients	Hepatic complications	NOS
Aggarwal, 2020	UnityPoint Clinic	USA	March - April 2020	67.0	75.0	2.0	16	Acute hepatic injury	4
Arentz, 2020	Evergreen Hospital in Kirkland, Washington	USA	Feb - March 2020	70.0	52.0	5.2	21	Acute hepatic injury	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62.0	13.0	274	Acute hepatic injury	4
Cao, 2020	Zhongnan Hospital of Wuhan University	China	Jan - Feb 2020	54.0	52.0	11.0	102	Acute hepatic injury; liver enzyme abnormalities	4
Du, 2020	Hannan Hospital and Wuhan Union Hospital	China	Jan - Feb 2020	65.8	72.9	10.1	85	Acute hepatic injury	4
Guo, 2020	Seventh Hospital of Wuhan City	China	Jan - Feb 2020	58.5	48.7	16.3	187	Acute hepatic injury	5
Jin, 2020	Zhejiang province	China	Jan – Feb 2020	45.2	50.8	NR	651	Acute hepatic injury	6
Liu, 2020	Shenzhen Third People's hospital	China	Dec 2019 - Jan 2020	61.0	66.7	8.6	12	Hepatic insufficiency	4
Phipps, 2020	New York-Presbyterian network	USA	March – April 2020	65.0	57.0	6.0	2,273	Liver enzyme abnormalities	6
Price-Haywood, 2020 (W)	Ochsner Health in Louisiana	USA	March – April, 2020	55.5	45.7	7.0	1,030	Acute hepatic injury	6
Price-Haywood, 2020 (B)	Ochsner Health in Louisiana	USA	March – April, 2020	53.6	37.7	6.0	2,451	Acute hepatic injury	6
Richardson, 2020	Hospitals in New York	USA	March - April 2020	63.0	60.3	4.5	5,700	Acute hepatic injury	4
Shi,2020	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	64.0	49.3	NR	416	Hypoproteinaemia	6
Wang, 2020	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	71.0	49.0	28.0	339	Liver enzyme abnormalities	4
Xi, 2020	Fourth People's Hospital of Qinghai Province; Third People's Hospital of Xining	China	Jan – April 2020	32.0	67.0	13.5	18	Acute hepatic injury	4
Yang, 2020	Wuhan Jin Yin-tan hospital	China	Dec 2019 - Jan 2020	59.7	67.0	10.0	52	Liver dysfunction	4
Zhang, 2020	Huanggang Central Hospital; The Second Affiliated Hospital of Shandong First Medical University	China	Jan – Feb 2020	48.3	55.7	10.2	194	Low albumin; elevated aminotransferases	4
Zhao, 2020	Jingzhou Central Hospital	China	Jan – Feb 2020	46.0	53.8	NR	91	Acute hepatic injury	4
Zhao, 2020b	Shouyi and East districts of Renmin Hospital of Wuhan University	China	Jan – Feb 2020	61.0	46.6	7.0	1000	Acute hepatic injury	4
Zhou, 2020	Jinyintan Hospital & Wuhan Pulmonary Hospital	China	Dec - Jan 2020	56.0	62.0	11.0	191	Hypoproteinaemia	5

B, blacks; NOS, Newcastle Ottawa Scale; NR, not reported; W, whites

Fig. 1 (A) Incidence of hepatic complications in COVID-19 patients; (B) Incidence of acute hepatic injury in COVID-19 patients, by clinically relevant characteristics



AHI, acute hepatic injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval (bars); CLD, chronic liver disease; *, *p*-value for meta-regression

SUPPLEMENTARY MATERIAL

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	MOOSE checklist
Supplementary Material 3	MEDLINE literature search strategy
Supplementary Material 4	Selection of studies included in the meta-analysis
Supplementary Material 5	Reference list of included studies
Supplementary Material 6	Prevalence of pre-existing chronic liver disease in COVID-19 patients
Supplementary Material 7	Prevalence of other pre-existing hepatic conditions in COVID-19 patients
Supplementary Material 8	Prevalence of hepatic manifestations on admission in COVID-19 patients

Supplementary Material 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Supplementary material 4
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figure 1; Supplementary material 6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Page 5

Supplementary Material 2. MOOSE checklist

Hepatic manifestations and complications of COVID-19: A systematic review and meta-analysis

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Hepatic manifestations of COVID-19 are not clearly defined.
√	Hypothesis statement	(i) What are the hepatic manifestations and complications associated with COVID-19? (ii) What is the prevalence of hepatic manifestations and incidence of hepatic complications? (iii) Are patients with pre-existing hepatic conditions more susceptible to these hepatic complications?
√	Description of study outcomes	Hepatic complications
√	Type of exposure	Prevalence and incidence estimates
√	Type of study designs used	Observational cohort designs and clinical studies
√	Study population	Adult patients with COVID-19
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 15 June 2020 The detailed search strategy can be found in Supplementary material 3
√	Databases and registries searched	MEDLINE, Embase and The Cochrane Library
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Results
√	Description of statistical methods in sufficient detail to be replicated	Described in methods section
√	Provision of appropriate tables and graphics	Table 1; Figure 1; Supplementary materials 6-8
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Supplementary materials 6-8
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves studies with limited information.

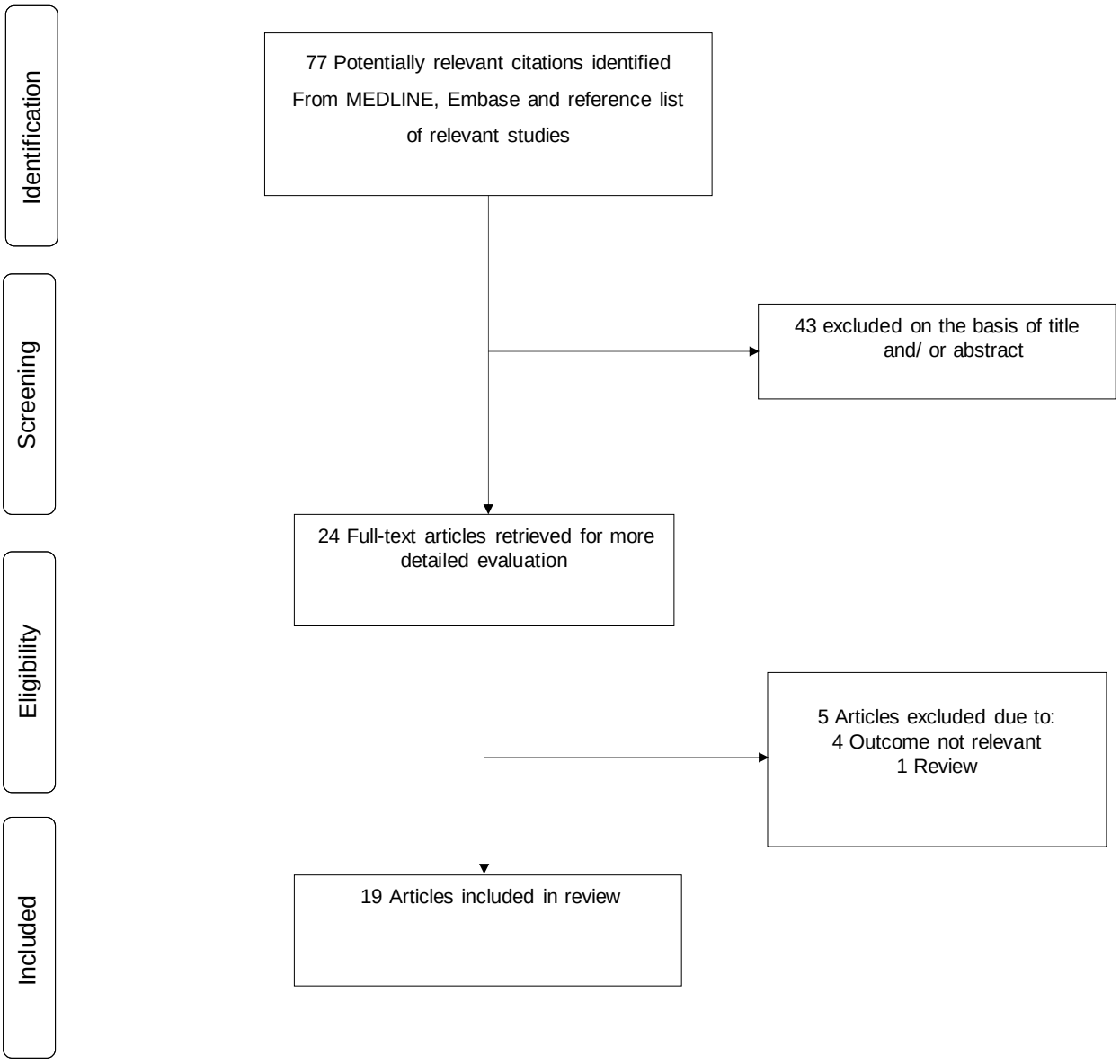
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in ‘Methods’ section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend large-scale studies when more data becomes available
√	Disclosure of funding source	In “Acknowledgement” section

Supplementary Material 3: MEDLINE literature search strategy

1 COVID-19.mp. (7239)
2 SARS-CoV-2.mp. (2017)
3 exp Liver Diseases/ (549145)
4 acute liver injury.mp. (2471)
5 acute hepatic injury.mp. (366)
6 liver dysfunction.mp. (7648)
7 exp Liver Cirrhosis/ (88730)
8 chronic liver disease.mp. (15325)
9 exp Hypoproteinemia/ (2827)
10 1 or 2 (7412)
11 3 or 4 or 5 or 6 or 7 or 8 or 9 (559902)
12 10 and 11 (24)
13 limit 12 to (english language and humans and yr="2019 -Current") (15)

Each part was specifically translated for searching alternative databases.

Supplementary Material 4: Selection of studies included in the meta-analysis



Supplementary Material 5: Reference list of included studies

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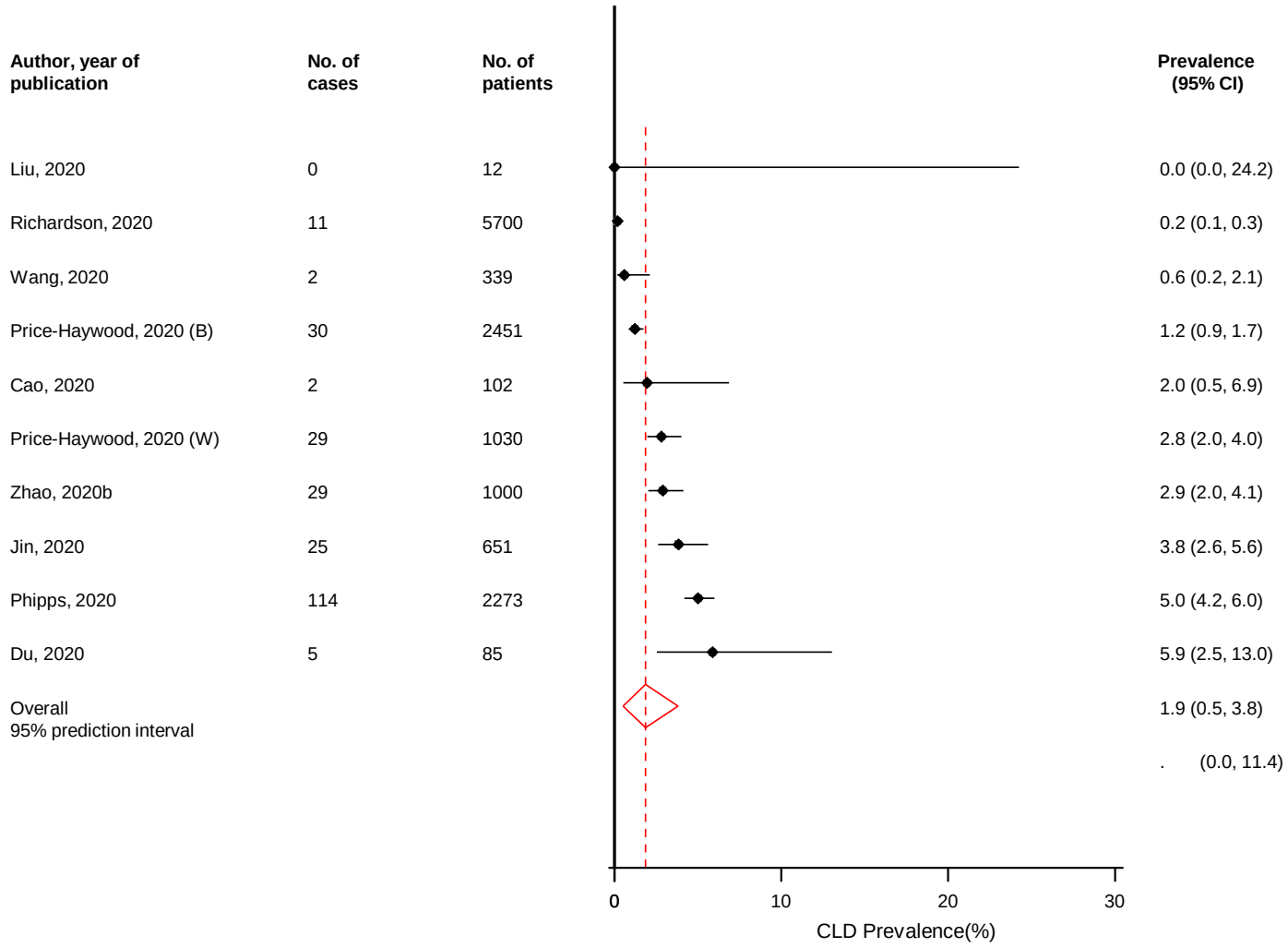
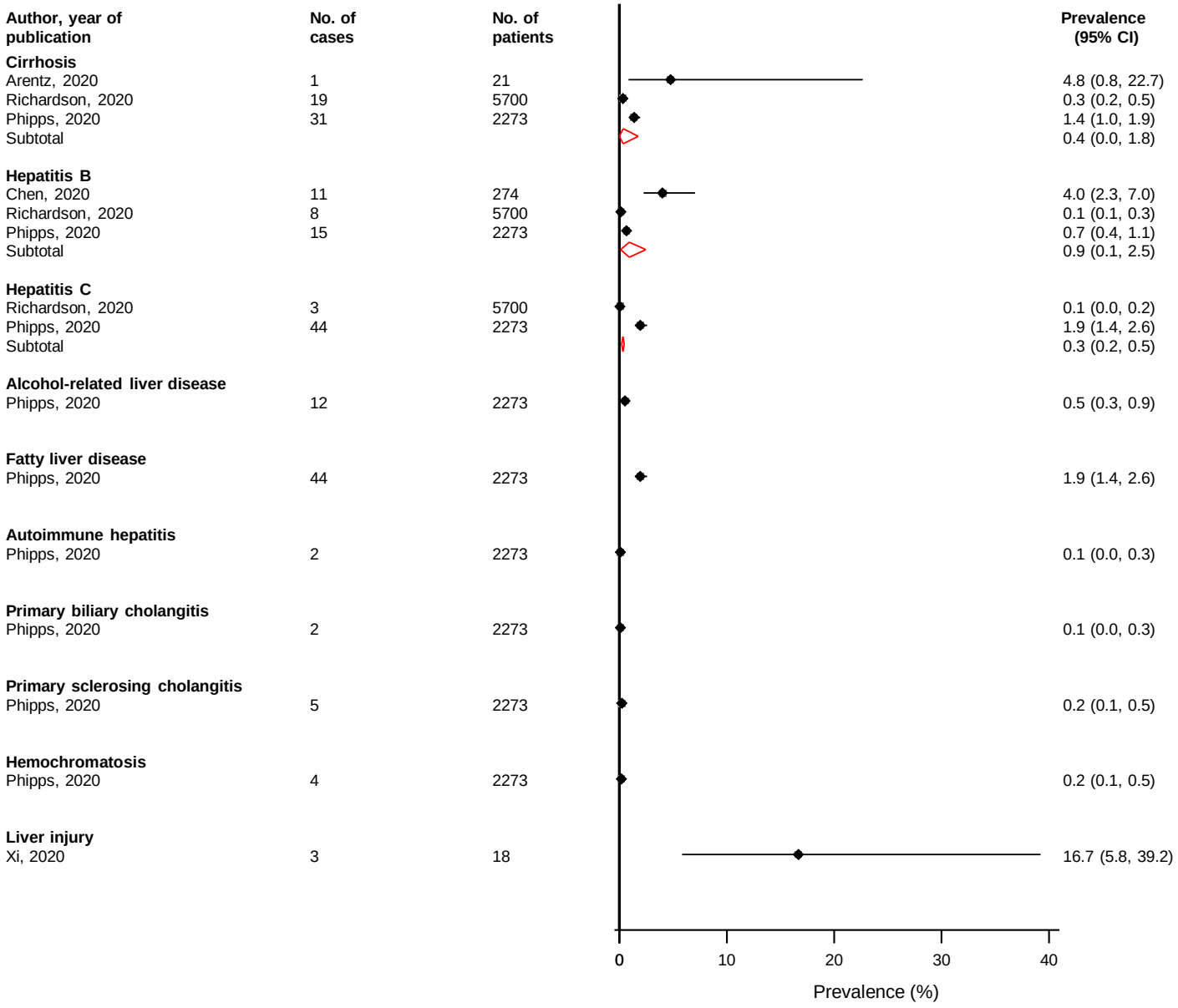
Supplementary Material 6: Prevalence of pre-existing chronic liver disease in COVID-19 patients



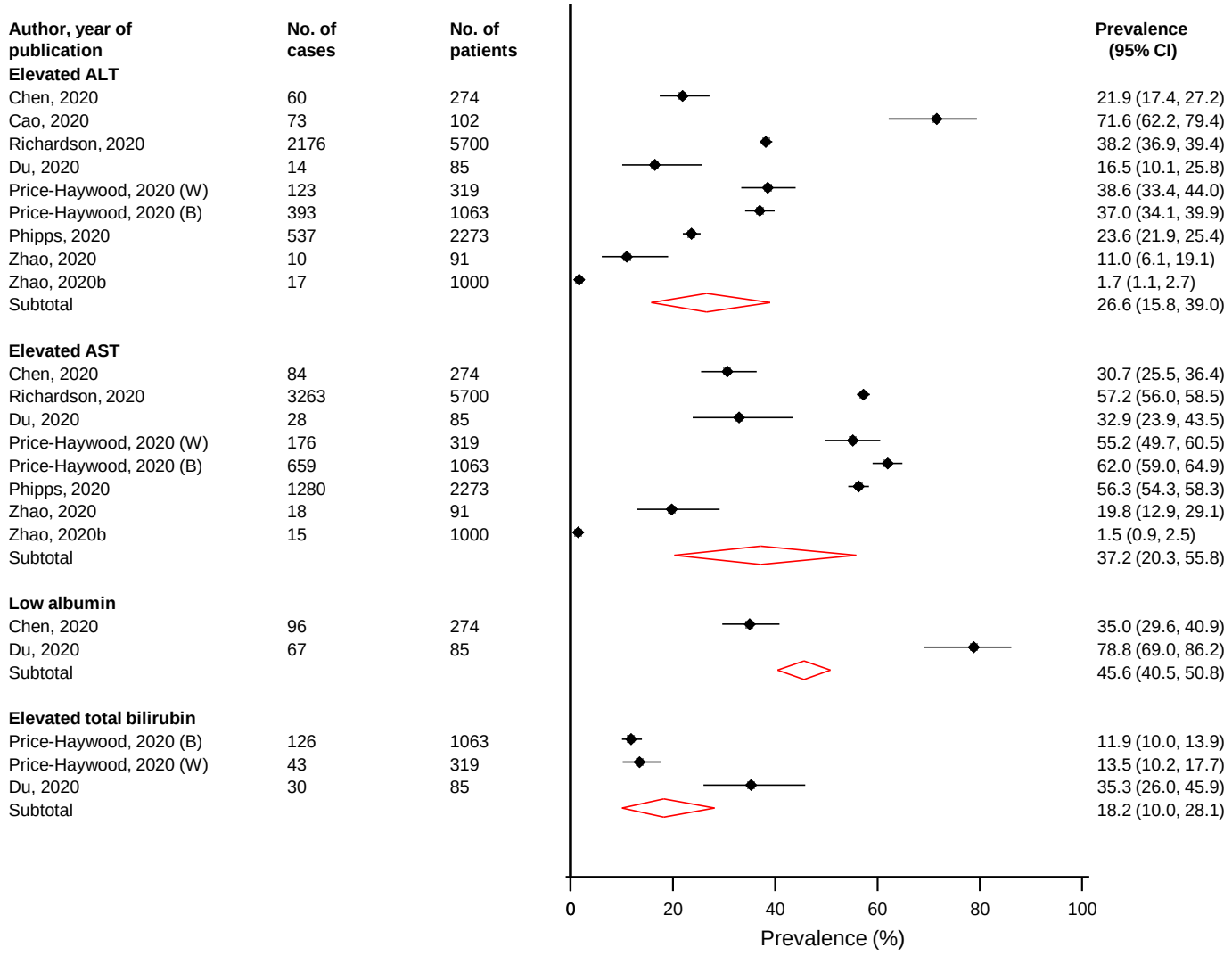
B, black; CI, confidence interval (bars); CLD, chronic liver disease; W, white

Supplementary Material 7: Prevalence of other pre-existing hepatic conditions in COVID-19 patients



CI, confidence interval (bars)

Supplementary Material 8: Prevalence of hepatic manifestations on admission in COVID-19 patients



ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, black; CI, confidence interval (bars); W, white