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# Prevalence of acute liver injury and hypertransaminemia in patients with COVID-19: a protocol for a systematic review

Gang Li ,[1] Yongxing Xu ,[2] Yi Tian Yang,[3] Peng Fei Liu [4]

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GL and YX contributed equally.

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For numbered affiliations see end of article.

**Correspondence to**
Dr Yi Tian Yang; yangyitiansdu@126.com and Dr Peng Fei Liu; sfflpf@126.com

## ABSTRACT

**Introduction** COVID-19 has spread rapidly in China and around the world. Published studies have revealed that some patients with COVID-19 had abnormal liver function in laboratory tests. However, the results were inconsistent and the analysis of epidemiological data stratified by the severity of COVID-19 was not available in previous meta-analyses. Furthermore, these meta-analyses were suspected of overestimating the incidence of liver injury in patients with COVID-19 because some studies considered transaminase elevation as liver injury, which might partially result from cardiac and muscle injury. This systematic review aims to enrol published literatures related to COVID-19 without language restriction, analyse the data based on the severity of the COVID-19 and explore the impact of varied definitions of liver injury on the incidence of liver injury.

**Methods and analysis** We have conducted a preliminary search on PubMed and Excerpta Medica Database on 13 April 2020, for the studies published after December 2019 on the prevalence of acute liver injury and hypertransaminemia in patients with COVID-19. Two reviewers will independently screen studies, extract data and assess the risk of bias. We will estimate the pooled incidence of hypertransaminemia and acute liver injury in patients with COVID-19 by using the random-effects model. The $I^2$ test will be used to identify the extent of heterogeneity. Publication bias will be assessed by funnel plot and performing the Begg's and Egger's test if adequate studies are available. We will perform a risk of bias assessment using the Joanna Briggs Institute's critical appraisal checklist.

**Ethics and dissemination** Since this study will be based on the published data, it does not require ethical approval. The final results of this study will be published in a peer-reviewed journal.

**PROSPERO registration number** CRD42020179462.

## Strengths and limitations of this study

- This systematic review and meta-analysis will evaluate the prevalence of acute liver injury and hypertransaminemia in patients with COVID-19, based on the severity of the COVID-19.
- The definitions of liver injury have a major impact on the results, so we will perform a subgroup analysis to explore the impact of different definitions of liver injury on the incidence of liver injury in patients with COVID-19.
- No language limitation in this research is another strength, compared with previous studies, which will avoid language bias.
- Because clinical research on COVID-19 is ongoing rapidly, some latest studies on this will not be included.

## INTRODUCTION

In December 2019, a novel coronavirus was found in Wuhan. The virus could cause pneumonia, and was named COVID-19 by WHO.[1] The disease is spreading rapidly around the world. As of 12 June 2020, the number of confirmed cases is more than 7.4 million, and the number of deaths has exceeded 400 000 around the world.[2] Under this severe situation, strict measures have been taken around the world. Unfortunately, there are no specific treatments for the patients with COVID-19, who are just receiving supportive treatment. In the next few months, the global number of infections and deaths will probably rise.[3]

Published literatures proved that some patients with COVID-19 had abnormal liver function.[4 5] In addition to lungs, acute liver injury could occur in patients with COVID-19.[6–8] Although some published meta-analysis discussed this point in their studies,[9–12] most of which only estimated weighted mean difference or standardised mean difference of liver function measures in patients with COVID-19 with or without severe disease and did not report the incidence of transferase elevation and liver injury.[9–11] The meta-analysis conducted by Mao *et al* reported the prevalence of transaminase elevation and liver injury, nevertheless, they failed to perform analysis stratified by the severity of COVID-19 when conducting the pooled analysis of the overall prevalence of abnormal liver

chemistry and liver injury.[12] Besides, Mao *et al* considered the transaminase more than the upper limit of normal value as liver injury, which, from our point of view, is not rigorous. The elevation of transaminase also might be associated with myocardial or muscle injury caused by this viral infection.[13 14] In this case, the prevalence of liver injury might be overestimated.[14] In addition, articles published in English were only included in some meta-analysis, which might lose some studies presented in other languages.[12 15 16] In our opinion, the search strategy without language restriction in the meta-analysis is more appropriate. Therefore, we aim to conduct a meta-analysis of clinical studies on the COVID-19 without language restriction to comprehensively explore the prevalence of transaminase elevation and liver injury in patients with COVID-19. We will also analyse the data based on the severity of the COVID-19 to further discuss the incidence of liver injury and transaminase elevation in different populations. Meanwhile, we will explore the impact of varied definitions of liver injury on the incidence of liver injury.

## METHODS

The development of this protocol was done according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols as illustrated in the online supplementary file 1.[17] This protocol was previously registered with the International Prospective Register of Systematic Reviews, a platform for the international registration of prospective systematic reviews and assigned the registration number CRD42019120201.

### Criteria for considering studies for this review and prespecified outcomes

The published observational studies reporting the incidence of hypertransaminemia or acute liver injury will be included. Single-case studies and randomised controlled trials will be excluded. Studies with less than 10 participants will be also excluded.

The incidence of acute liver injury in patients with COVID-19 will be the main outcome. Incidence of elevated alanine transaminase (ALT) and aspartate aminotransferase (AST) in patients with COVID-19 will be additional outcome. Acute liver injury and elevated ALT and AST will be defined by the specific studies.

### Search methods for identification of relevant studies

We have conducted a search on PubMed and Excerpta Medica Database electronic databases on 13 April 2020, with no language restriction using relevant text words and medical subject headings as follows: severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, sars cov 2, 2019-nCoV, 2019 novel CoV, 2019 novel coronavirus, corona virus disease 2019, coronavirus disease 19, coronavirus disease 2019, COVID-19, COVID-2019 and novel coronavirus-infected pneumonia. The reference list of the eligible articles and relevant reviews will be manually searched to identify additional studies. The search strategy for some databases is illustrated in the online supplementary file 2.

### Records and data management

All citations identified by our search strategy will be exported to EndNote X9, a bibliographic management software and duplicates will be removed. The screening of remaining citations will be conducted by using Endnote X9, too. The data extraction will be performed on Microsoft Excel 2016 and a standardised excel sheet is designed for data collection (online supplementary file 3).

### Study selection and data extraction

Two independent reviewers will assess the eligibility of studies in the stages of title and abstract, and full-text study selection (online supplementary file 4). In the title and abstract screening stage, two authors will independently screen initial subsets of studies. Subsequently, full-text records of the selected abstracts will be retrieved. Full-text records selected for inclusion by both the authors will be included in the review. Any disagreements during this stage will be resolved through discussion. In the case, if non-English studies will be selected for inclusion in the review, Google Translate will be used to translate into English.[18–20] Moreover, to avoid errors, the studies will be rechecked by official translators and then assessed for the final selection. Students from the Peking University will also provide support in translating non-English articles. We will record the selection process with reasons for exclusion.

To avoid double counting, we will look for similarities between studies of the same author or group to ensure they are not the same sample. When there are multiple studies from the same cohort, the study with the largest sample size will be used. If the sample size does not vary, the most recent paper will be used.

Two authors will independently extract data, including study characteristics, incidence and definition of acute liver injury, and incidence of elevated ALT and AST in patients with COVID-19 using a standardised excel spreadsheet (online supplementary file 3). Data about the risk factors of acute liver injury and the impact of acute liver injury on the severity of COVID-19 disease and prognosis will also be collected if available. In the case where non-English studies are selected for inclusion in the review, Google Translate will be used to allow for data extraction.

### Assessing the risk of bias

The risk of bias of the included studies will be assessed independently by two reviewers. Any disagreement will be discussed by consultation. The risk of bias assessment will be used the Joanna Briggs Institute's critical appraisal checklist.[21]

### Statistical analysis

In this study, we will estimate the pooled incidence of hypertransaminemia and acute liver injury by using random-effects model.[22] Forest plots will be generated

displaying prevalence with the corresponding 95% CI. The heterogeneity between studies will be investigated statistically using the $X^2$ test and $I^2$ statistic. $I^2$ values of 25, 50 and 75% correspond to low, medium and high levels of heterogeneity, respectively.[23] If heterogeneity exists and there are a substantial number of studies, subgroup analyses will be undertaken based on the severity of COVID-19 disease, participants (adult vs children) and liver injury definitions. Based on previous studies,[24–27] we adopted a relatively strict definition of acute liver injury that is ALT and/or AST higher than threefold of the upper limit unit (ULN), or alkaline phosphatase and/or total bilirubin (TBIL) higher than twofold of the ULN. If studies considered ALT and/or AST, or alkaline phosphatase and/or TBIL higher than the ULN as liver injury, we think these definitions were not strict or rigorous. We will explore the impact of different liver injury definitions on the incidence of liver injury in our meta-analysis by subgroup analysis. We will perform sensitivity analysis by the Duval and Tweedie non-parametric 'trim-and-fill' procedure.[28]

Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.[29 30] A two-sided $p<0.05$ will be regarded as significant for all analyses. All analyses will be calculated using Stata software (V.15.0; StataCorp). When there are insufficient clinically homogeneous trials to perform a meta-analysis, we will present a narrative synthesis.

### Patient and public involvement

Patients were not involved in any stage of the study including but not limited to development of the research question, outcome measure and study design. Data will be collected from published studies available in the underlined electronic databases.

### Ethics and dissemination

Since this work relies on published data, there is no requirement for ethical approval. The findings from the review will be disseminated in a scientific peer-reviewed journal and academic reports.

## DISCUSSION

The protocol reveals an explicit plan of a systematic review to identify and analyse the studies focusing on the acute liver injury and hypertransaminemia in patients with COVID-19. Although previous meta-analyses performed pooled incidence of acute liver injury and hypertransaminemia, these studies failed to analyse the incidence based on the severity of COVID-19.[12 15] The prevalence of increased aminotransferases and liver injury is affected by the proportion of patients with severe COVID-19 included. Hence, assessing the prevalence of liver injury based on the severity of COVID-19 is more valuable.

The definitions of liver injury have a major impact on the incidence of liver injury in patients with COVID-19. Currently, there is still no uniform definition of acute liver injury. Some studies defined transaminase higher than the upper limit of normal value as acute liver injury.[12] Because transaminase elevation might partially result from cardiac and muscle injury,[14] we think this definition is not rigorous. Based on previous studies,[24–27] we adopted that ALT and/or AST higher than threefold of the ULN, or alkaline phosphatase and/or TBIL higher than twofold of the ULN as a strict definition. Under different definitions, the prevalence of liver injury in patients with COVID-19 will be analysed and compared, to investigate whether the incidence of liver injury is overestimated in patients with COVID-19.

In summary, compared with previous studies, the novelty of our work is as follows. First, we will analyse the data based on the severity of the COVID-19 to further discuss the incidence of liver injury and transaminase elevation in different populations. Second, the definitions of liver injury have a significant impact on the results, thus, we will carry out subgroup analyses to explore the impact of the varied definitions of liver injury on the incidence of liver injury in patients with COVID-19. Third, the absence of language restriction of studies could enrol more relative studies in our analysis. Ultimately, we will also try to verify the robustness of the result by sensitivity analysis.

**Author affiliations**
[1]Department of General Surgery, Peking University Third Hospital, Beijing, China
[2]Department of Nephrology, PLA Strategic Support Force Characteristic Medical Center, Beijing, China
[3]Department of Anesthesiology and Perioperative Medicine, Henan Provincial People's Hospital, Zhengzhou, Henan, China
[4]Department of Anesthesiology, Capital Medical University Affiliated Beijing Shijitan Hospital, Beijing, China

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**ORCID iDs**
Gang Li http://orcid.org/0000-0003-3601-3914
Yongxing Xu http://orcid.org/0000-0003-1216-235X
Peng Fei Liu http://orcid.org/0000-0001-8098-8925

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