Prevalence of liver injury in patients with coronavirus disease 2019 (COVID-19) : a systematic review and meta-analysis

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Abstract

Background and study aims **: The coronavirus disease 2019 (COVID-19) represents a public health emergency of international concern, causing thousands of deaths worldwide. We performed a systematic review with meta-analysis in order to investigate the prevalence of COVID-19-induced liver injury.**

Patients and methods **: We searched MEDLINE, Scopus, Web of Science and the Cochrane Library, for studies reporting laboratory data about COVID-19 patients, with last update on 25th March 2020. The primary outcome was the pooled prevalence of COVID-19-induced liver damage, mainly represented by increase in serum transaminases and bilirubin. The secondary outcome was the description of abnormalities in serum albumin and prothrombin time (PT). We focused on laboratory data only on hospital admission, and adopted random-effects model for meta-analysis.**

Results **: Eleven studies were eligible for meta-analysis. Out of 793 included patients, the pooled prevalence of COVID-19-related liver damage was 22.17% (95% CI 17.64 to 27.07), mostly indicated by hypertransaminasemia. Serum bilirubin was increased in 5.53% (95% CI 3.60 to 7.85) of cases. Abnormal serum albumin was observed in 78.92% (95% CI 39.82 to 99.56), and increased PT value in 19.98% (95% CI 2.49 to 78.23), but these results derived from significantly heterogeneous studies.**

Conclusions **: COVID-19-induced liver injury must not be ignored, as it is observed in one fifth of infected patients. Prospective studies evaluating liver function during the course of COVID-19 are needed to provide a complete overview of hepatic involvement during this viral infection.** (Acta gastroenterol. belg., **2020**, 83, **454-460**).

Key words : COVID-19, liver damage, hypertransaminasemia.

Introduction

The coronavirus disease 2019 (COVID-19) is a pandemic viral infection representing a public health emergency of international concern. First cases were registered in Wuhan (China) in December 2019, then the disease started spreading rapidly throughout the world. According to the World Health Organization situation report of 15th April 2020, the number of infected patients worldwide accounted for 1914916 cases, while reported deaths were 123010 (1). These rates are growing exponentially.

COVID-19 most frequently causes pneumonia, but liver damage has also been reported in some studies, especially in severe cases (2-6). The pathogenesis of COVID-19-induced liver damage has not been completely clarified yet, as data so far available are scanty and controversial. Abnormal liver function blood tests in COVID-19 are mostly transaminases, while alteration of gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) values have been less frequently described.

The suggestion that chronic liver disease might represent a risk factor for fatal COVID-19 course has not been definitely proved yet, as this underlying condition was reported only by few series. However, the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD) and the Belgian Liver and Intestine Advisory Committee (BeLIAC) have recently published recommendations for liver disease patients, as conditions like cirrhosis or previous liver transplantation increase in any case the risk of infection (7-9).

Few systematic reviews have already focused on liver involvement in COVID-19 (10-12), reporting a frequency ranging from 15% to 53% but with a high study heterogeneity. Furthermore, their results did not include all liver laboratory tests, and data might derive from different disease phases.

The aim of this paper was to estimate, through a systematic review and meta-analysis of the published studies, the pooled prevalence of liver injury on hospital admission of patients affected by COVID-19.

Methods

Inclusion Criteria and Outcomes

All available publications regarding COVID-19 adult patients reporting laboratory data were considered in this study. Exclusion criteria were: study population of only pregnant patients, of cases with age < 18 years, or including less than 15 patients; publications not reporting the number of patients with liver impairment during COVID-19; study design as reviews, meta-analyses, recommendations/guidelines, editorials, case reports.

The primary outcome was to estimate the pooled prevalence of COVID-19-induced liver damage on hospital admission, indicated by baseline abnormalities

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of the following liver laboratory tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, ALP, bilirubin.

The secondary outcome was the description of abnormalities in the following liver function tests: serum albumin and prothrombin time (PT).

Search Method

A computerized search was performed screening the following databases: Medline, Scopus, ISI Web of Knowledge and Cochrane Database of Systematic Reviews.

Search strategy was last updated on 25th March 2020. For "disease condition", the following terms were adopted: COVID-19, "Novel coronavirus 2019", "2019 nCoV", "SARS-CoV-2", "coronavirus disease 2019". No language restriction was applied.

Study selection and reference management were conducted using the Endnote program (Endnote X4, Bld 6695), and following the PRISMA Guidelines (13). In the first instance, titles and abstracts were checked in order to evaluate whether the publications dealt with COVID-19 infection. Then, complete full texts were evaluated, and papers considered eligible for qualitative and quantitative analyses were included. The reference lists of all the selected papers were also screened.

Data Extraction

Two independent reviewers (E.M., C.P.) performed the search, study selection and data extraction. The opinion of a third reviewer (G.d.P.) was requested in case of disagreement. Excluded publications were recorded, as well as the reasons for exclusion. In order to avoid the use of duplicated data, in case of studies involving the same hospitals, only the most updated paper and with more details about liver function was analyzed.

The following data were recorded for each study:

- first author
- type of publication

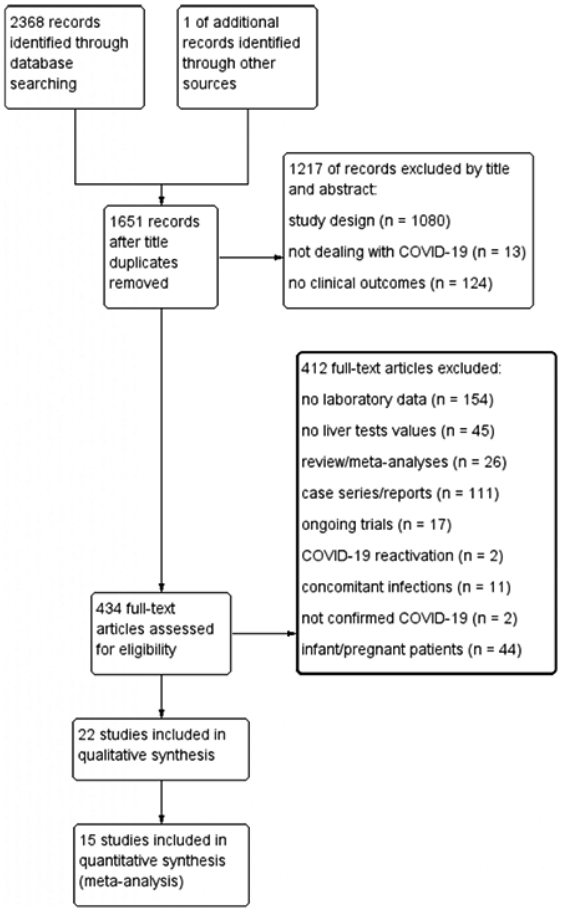
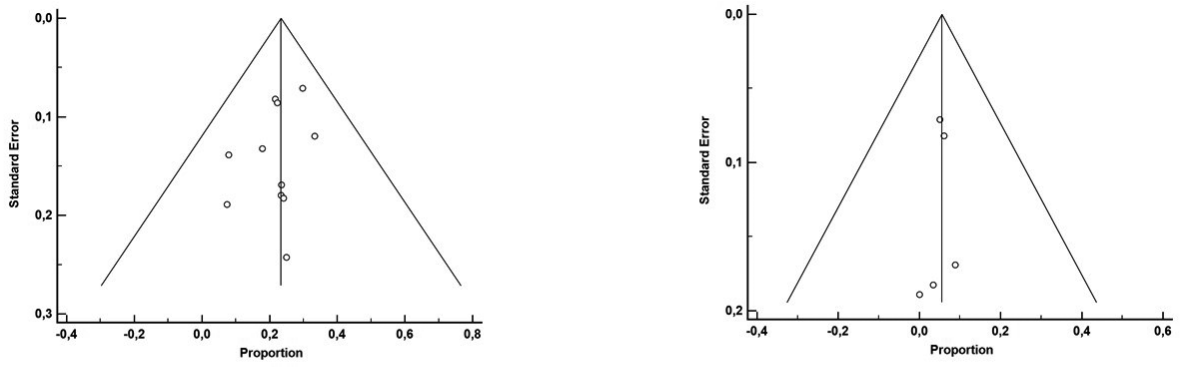


Figure 1. — Study selection sequence to perform the meta-analysis

- Nation/Province/city where diagnosis was performed
- total number of included patients
- number of patients with impaired liver function laboratory tests
- type of impaired liver laboratory test.



Supplementary Figure 1. — Funnel plots of meta-analyses for :
a) COVID-19-induced liver injury ; b) increase in bilirubin during COVID-19.

Table 1. — **Qualitative analysis of the studies : demographics and liver injury at study admission**

First author	Type of study	Nation (City, Province)	*N*	Gender (male), *n* (%)	Age [years; mean (range)	Chronic liver disease, *n* (%)	Liver injury, *n* (%)
Guan W.J. †	Retrospective, multicenter	China	1099 ‡	637 (57.9)	47	23 (2.1)	244 (22.2)
Cao B.	Randomized, open-label, controlled trial	China (Wuhan, Hubei)	199	120 (60.3)	Median 58	0	80 (40.2)
Wu C.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**198**	**128 (63.7)**	**- (21-83)**	**7 (3.5)**	**59 (29.8)**
Liu M.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**30**	**10 (33.3)**	**35**	**0**	**7 (23.3)**
Chen L.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**29**	**21 (72.4)**	**56 (26-79)**	**2 (6.9)**	**7 (24.1)**
Zhou F.	Retrospective, multicenter	China (Wuhan, Hubei)	189	119 (62.3)	56	Not reported	59 (31.2)
Huang C.	Prospective, unicenter	China (Wuhan, Hubei)	41	30 (73.2)	49 (41-58)	1 (2.4)	15 (36.6)
Wang Z.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**69**	**32 (46.4)**	**Median 42**	**1 (1.4)**	**23 (33.3)**
Shi H.	Retrospective, multicenter	China (Wuhan, Hubei)	81	42 (51.8)	Not reported	7 (8.6)	43 (53.1)
Huang Y.	**Retrospective, unicenter**	**China (Wuhan, Hubei)**	**34**	**14 (41.2)**	**56.24**	**1 (2.9)**	**8 (23.5)**
Chen N.S.	Retrospective, unicenter	China (Wuhan, Hubei)	99	67 (67.7)	55.5 (21-82)	0	≥ 35 (35.0)
Zhang X.	Retrospective, unicenter	China (Hangzhou, Zhejiang)	645	295 (51.5)	Not reported	2 (0.3)	81 (12.5) (no details)
Xu X.W.	Retrospective, multicenter	China (Zhejiang)	62	35 (56.4)	Median 41	7 (11.3)	10 (16.1)
Yang W. †	Retrospective, multicenter	China (Zhejiang)	149	81 (54.4)	45.1	Not reported	27 (18.1)
Qian G.Q.	Retrospective, multicenter	China (Zhejiang)	91 ‡	37 (40.7)	Not reported	0	9 (9.9)
Fan Z.	**Retrospective, unicenter**	**China (Shangai)**	**148 ‡**	**75 (50.7)**	**50 (15-88)**	**0**	**32 (21.6)**
Wan S.	**Retrospective, unicenter**	**China (Chongqing)**	**135**	**72 (53.3)**	**47**	2 (1.5)	30 (22.2)
Wu J.	Retrospective, multicenter	China (Jiangsu)	80 ‡	39 (48.7)	46.1	1 (1.2)	3 (3.7)
Xu T.	**Retrospective, unicenter**	**China (Changzhou, Jiangsu)**	**51**	**25 (49.0)**	**Not reported**	0	4 (7.8)
Hu Z.	**Retrospective, unicenter**	**China (Nanjing)**	**24 ‡**	**9 (37.5)**	**46.5 (23-95)**	0	2 (8.3)
Liu K.	**Retrospective, unicenter**	**China (Hainan)**	**56**	**31 (55.3)**	**Not reported**	1 (1.8)	10 (17.8)
Wang L.	**Retrospective, unicenter**	**China (Zhengzhou, Henan)**	**16 ‡**	**10 (55.6)**	**39**	0	4 (25.0)

References in bold have been included in meta-analysis. † Involving multiple Chinese Provinces. ‡ Including children and/or pregnant patients.

As publications reported laboratory values with different modalities and normal ranges, data about the outcomes were recorded as dichotomous variables (presence or absence of the abnormal laboratory value).

As far as the primary outcome concerns, when the total amount of patients with liver damage was not clearly stated in publication, we considered for the analysis the laboratory test which was more frequently impaired in the study population.

Risk of Bias

Study quality was evaluated by two authors (E.M. and C.P.) independently, and a third author (G.d.P.) resolved disagreements. The MINORS criteria (14) were adopted for non-randomized studies, while randomized controlled studies (RCTs) were defined as being at "low risk of bias" if classified as adequate in sequence generation, allocation concealment, blinding, incomplete data outcomes and selective reporting.

Statistical Method

Single-arm meta-analyses were performed using the random-effects model. Heterogeneity was estimated by Cochran Q test, with significance set at P value < 0.10.

An I^2 of ≥ 50% was considered representative of significant heterogeneity.

Table 2. — **Liver function blood tests in COVID-19: prevalence of patients with impaired laboratory values**

First author	ALT, *n* (%)	AST, *n* (%)	Albumin, *n* (%)	Bilirubin, *n* (%)	GGT, *n* (%)	ALP, *n* (%)	PT, *n* (%)
Guan W.J.	158/741 (21.3)	168/757 (22.2)	-	76/722 (10.5)	-	-	-
Cao B.	80 (40.2)	40 (20.1)	-	-	-	-	-
Wu C.	**42 (21.2)**	**59 (29.8)**	**195 (98.5)**	**10 (5.0)**	**-**	**-**	**4 (2.0)**
Liu M.	**7 (23.3)**	**7 (23.3)**	**-**	**-**	**-**	**-**	**-**
Chen L.	**5 (17.2)**	**7 (24.1)**	**15 (51.7)**	**1 (3.4)**	**-**	**-**	**-**
Zhou F.	59 (31.2)	-	-	-	-	-	11/182 (6.0)
Huang C.	-	15 (36.6)	-	-	-	-	-
Wang Z.	**23 (33.3)**	**19 (27.5)**	**-**	**-**	**-**	**-**	**-**
Shi H.	-	43 (53.1)	-	-	-	-	-
Huang Y.	**8 (23.5)**	**7 (20.6)**	**25 (73.5)**	**3 (8.8)**	**-**	**-**	**17 (50.0)**
Chen N.S.	35 (35.0)	-	97 (98.0)	18 (18.0)	-	-	5 (5.0)
Xu X.W.	-	10 (16.1)	-	-	-	-	-
Yang W.	**18 (12.1)**	**27 (18.1)**	**9 (6.0)**	**4 (2.7)**	**-**	**-**	**17 (11.4)**
Qian G.Q.	**7 (7.7)**	**9 (9.9)**	**43 (47.2)**	**-**	**-**	**-**	**-**
Fan Z.	**27 (18.2)**	**32 (21.6)**	**-**	**9 (6.1)**	**26 (17.6)**	**6 (4.0)**	**-**
Wan S.	**-**	**30 (22.2)**	**-**	**-**	**-**	**-**	**-**
Wu J. 2	**3 (3.7)**	**3(3.7)**	**2 (2.5)**	**1 (1.2)**	**-**	**-**	**3 (3.7)**
Xu T.	**4 (7.8)**	**4 (7.8)**	**-**	**-**	**-**	**-**	**-**
Hu Z.	**2 (7.4)**	**0 (0)**	**-**	**0 (0)**	**-**	**-**	**-**
Wang L.	**4 (25.0)**	**4 (25.0)**	**-**	**-**	**-**	**-**	**-**

References in bold have been included in meta-analysis. ALT : alanine aminotransferase ; AST : aspartate aminotransferase ; GGT : gamma-glutamyl transpeptidase ; ALP : alkaline phosphatase ; PT: prothrombin time.

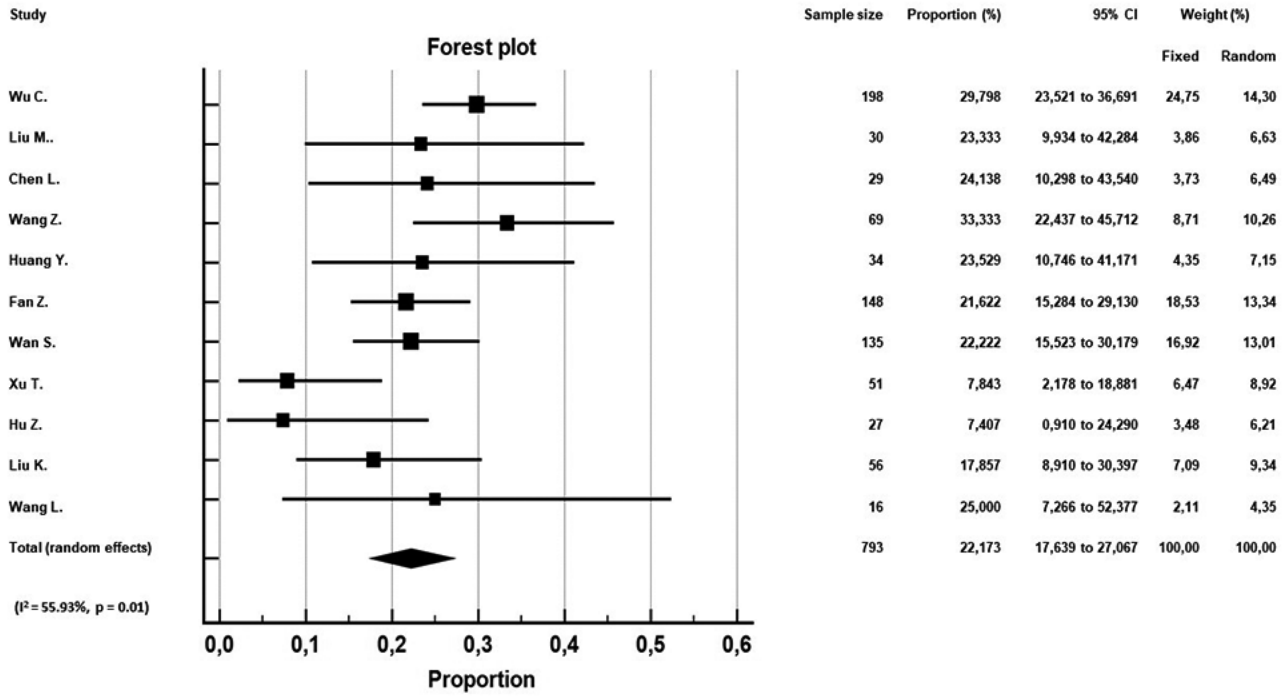


Figure 2. — COVID-19-induced liver injury: forest plot of overall population.

For sensitivity analysis, we investigated the influence of different patients' recruitment (unicenter or multicenter study), and potential bias due to inclusion criteria (15-17).

As software program, we adopted Medcalc 15.6.1 (www.medcalc.be).

Results

Search Results

Database searches provided 2368 references: 1532 by Medline, 570 by Scopus, 249 by Isi web of science,

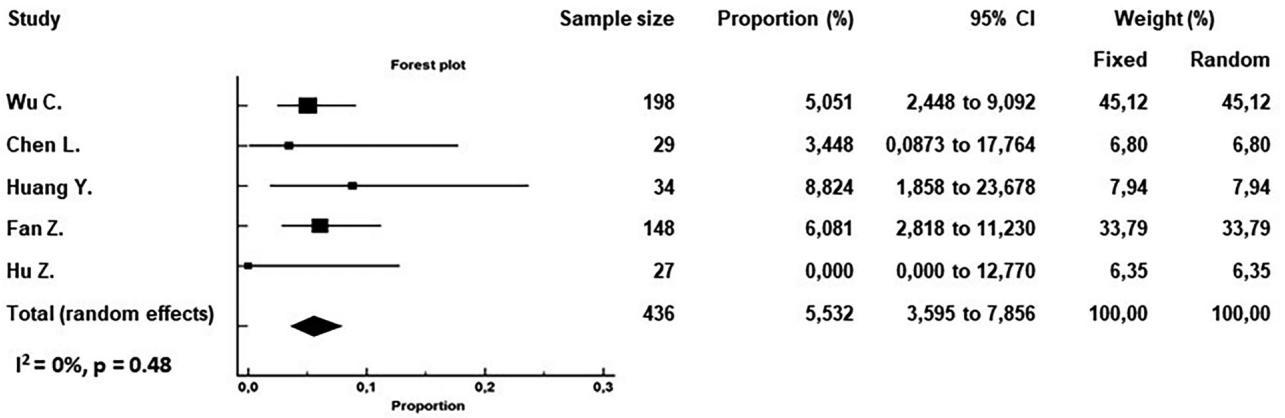


Figure 3. — COVID-19-induced liver injury : forest plot of increased bilirubin.

and 17 by the Cochrane Library (Figure 1). Two "special collection" documents obtained by the Cochrane Library (including 37 systematic reviews) were excluded, as not dealing with COVID-19 infection. Screening the references of included publications, one additional publication was evaluated (3).

After excluding title duplicates, 1651 references were screened, and 1217 of these did not respond to inclusion criteria. Full texts of 434 publications were evaluated, and 22 were included in qualitative analysis (2-4,15-33). Demographics and laboratory values are reported in Table 1 and 2.

After excluding 7 additional papers due to risk of data duplication (2,4,21,22,24,26,28), 15 studies were considered eligible for meta-analysis.

Risk of bias

Risk of bias assessment for non-randomized studies is detailed in Supplementary Table 1.

As far as quality of RCT by Cao B. *et al.* (4) concerns, allocation concealment and blinding of participants were inadequate. However, we considered these limitations justified by the emergency nature of the trial.

Primary outcome : COVID-19-induced liver injury

We performed the meta-analysis with 15 studies, and it showed a prevalence of COVID-19-induced liver injury of 18.18% (95% CI 13.81 to 23.01). Heterogeneity was however significantly high ($I^2 = 80.55\%$, $p < 0.01$).

Performing sensitivity analysis, we excluded 3 references due to multicenter recruitment (15-17). We also evaluated the inclusion criteria of all the remaining publications, removing from the analysis one further study recruiting only COVID-19 patients with chest CT abnormalities (27).

Eleven studies were then included in the meta-analysis. Considering a total amount of 793 patients, the pooled prevalence of COVID-19-related liver injury was 22.17% (95% CI 17.64 to 27.07). A mild heterogeneity of the included studies was observed ($I^2 = 55.93\%$, $p = 0.01$) (Figure 2). Funnel plot is shown in Supplementary Figure 1a.

Almost all the patients with COVID-19-induced liver damage presented hypertransaminasemia, as only one study provided no details of impaired laboratory values (32).

Focusing on the other laboratory tests, GGT and ALP values were reported only in Fan Z. *et al.*(3). In details, GGT was increased in 26/148 cases (17.6%) and ALP in 6/148 (4.0%) (Table 2).

Bilirubin values were reported by 5 studies, and abnormalities were observed in 5.53% (95% CI 3.60 to 7.85; $I^2 = 0\%$, $p = 0.48$) of the total population (Figure 3, Supplementary Figure 1b).

Secondary outcome: other liver function tests in COVID-19

Serum albumin was reduced in 78.92% (95% CI 39.82 to 99.56) of cases, and increased PT value in 19.98 (95% CI 2.49 to 78.23). As data about these laboratory tests were respectively reported only by 3 and 2 studies included in the meta-analysis, forest and funnel plots are not shown in the manuscript.

Discussion

The present study investigates the COVID-19-induced liver injury by performing a systematic review and meta-analysis. According to published data, considering a population of 793 patients, the pooled prevalence of COVID-19-related liver damage at hospital admission was 22.17% (95% CI 17.64 to 27.07; $I^2 = 55.93\%$, $p = 0.01$), mainly characterized by hypertransaminasemia. Additional impaired liver blood test was bilirubin (5.53%; 95% CI 3.60 to 7.85; $I^2 = 0\%$, $p = 0.48$), while data about alterations in serum GGT and ALP levels were too scanty to draw any conclusion (3).

The clinical relevance of COVID-19 liver impairment has been proved by a previous meta-analysis, showing an increased level of transaminases as a sign of disease progression (6). However, the underlying pathogenetic mechanisms still need to be clarified. This manifestation

might be explained considering that COVID-19 exploits angiotensin-converting enzyme 2 (ACE2) as receptor for entry process, and that ACE2-mRNA is also expressed in bile duct cells (34). Besides direct viral-induced injury, mechanical ventilation and some drugs adopted against the infection might also contribute to liver injury in these patients (34,35). Other hypotheses involve immune-mediated inflammation, such as cytokine storm, virally induced cytotoxic T cells, the induction of a dysregulated innate immune response and pneumonia-associated hypoxia (5,35).

Few systematic reviews focusing on liver involvement in COVID-19 have already been published (10-12) reporting a frequency ranging from 15% to 53%, but one of these meta-analysis did not report a pooled prevalence (11). Although presenting a significantly high study heterogeneity, sensitivity analysis was missing in these publications, and the risk of data duplication was not completely taken into account. Furthermore, their results did not include all liver laboratory tests, and data might derive from different disease phases and were not restricted to hospital admission values. The strong point of the present meta-analysis is instead that, in order to provide the real estimate of the COVID-19-induced liver injury by excluding any potential confounding factors, we have focused only on the baseline laboratory values at hospital admission. Furthermore, we have tried to avoid data duplication due to inclusion in the meta-analysis of studies reporting data from the same patients, as suggested by Bauchner H. *et al*. (36). In order to limit this bias, we have performed a careful check of all the hospitals involved in the analyzed studies, and when data derived from the same institution we considered only the paper with the largest population and/or with more details about liver function tests.

Although the adopted selection criteria, heterogeneity was observed in our meta-analysis and might be due to several reasons. We consider as the major responsible the different study design of analyzed publications, together with the limited quality of included studies (Supplementary Table 1). For this reason, we performed a sensitivity analysis and could reduce heterogeneity (I^2 = 55.93% vs. 80.55%), but a complete resolution of bias was not feasible. The validity of meta-analysis increases indeed when only RCTs are included. As most of the available clinical data about COVID-19 patients are provided by observational studies, this limit is hard to be overcome at the moment.

The suggestion that chronic liver disease (i.e., liver fibrosis, chronic viral hepatitis) might represent a risk factor for fatal COVID-19 course has not been definitely proved yet. EASL, AASLD and BeLIAC have however published recommendations for chronic liver disease patients, providing healthcare professionals useful tools to manage hepatic patients in this challenging situation (7-9). Some cases included in our study were affected by chronic liver disease, with potential risk of overestimation of COVID-19-related liver damage. Although it is impossible to exclude this subgroup from meta-analysis, they represent only a minority of the population (14/793) (Table 1), and we suppose they might not significantly affect results.

The present study has other additional potential limitations. Our primary outcome was mainly based on transaminase levels, but non-liver organ injury might be a confounding factor for transaminase elevations, for example in case of heart or muscle injury. Same consideration regards serum albumin, which was reduced in the majority of patients (78.92%; 95% CI 39.82 to 99.56), also due to hypercatabolic status and/or insufficient nutritional intake. Additionally, PT value might for example be influenced by the use of oral anticoagulant therapy. This potential bias is hard to be overcome. We have tried to limit the risk of an overestimation of COVID-19 liver injury by excluding from the analysis other liver laboratory tests (such as lactate dehydrogenase), which even more frequently are influenced by other mechanisms.

Another limitation is the lack of a correlation between COVID-19 severity and impaired liver function, which had been suggested by a previous meta-analysis reporting AST value > 40 U/L as a negative prognostic factor for poor outcome (6). Unfortunately, we could not explore this correlation in the present systematic review, as only a minority of included publications differentiated data according to disease severity.

In conclusion, the present meta-analysis shows that COVID-19-induced liver injury involves more than one fifth of cases at hospital admission. Liver damage is most frequently indicated by increased serum transaminase levels in these patients. Prospective studies evaluating liver function during the course of COVID-19 are needed, in order to provide a complete overview of hepatic involvement during this viral infection.

Conflict of interest

Authors have no conflicts of interest to declare.

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