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Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis

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Abstract. – OBJECTIVE: Liver involvement of SARS-CoV-2 infection has been reported in several papers, but without homogeneous findings. We aimed to systematically review the prevalence of liver involvement in patients with SARS-CoV-2 infection at their hospital admission, and its correlation with disease severity and clinical outcomes in patients with or without pre-existing chronic liver disease.

MATERIALS AND METHODS: We systematically searched PubMed, Embase, Web of Science, Medline, PMC, clinical trial registries, and other Coronavirus family publications for studies reporting data on SARS-CoV-2 infection or COVID-19 and liver function tests (LFTs) alterations, as well as clinical course of patients with chronic liver disease or cirrhosis. Case reports, preprints, editorials, reviews were excluded. We also revised literature to describe the background of liver involvement during SARS-CoV-2 infection.

RESULTS: 36 studies, including 20724 patients with SARS-CoV-2 infection, were included. The pooled prevalence of LFTs abnormalities at admission was 46.9% (AST 26.5%, ALT 22.8%, GGT 22.5%, ALP 5.7%, tBIL 8.0%). ALT, AST, tBIL were independent predictors of disease severity (ALT OR 1.54, 95% CI 1.17-2.03; AST OR 3.17, 95% CI 2.10-4.77; tBIL OR 2.32, 95% CI 1.18-4.58) and in-hospital mortality (ALT OR 1.48, 95% CI 1.12-1.96; AST OR 4.39, 95% CI 2.68-7.18; tBIL OR 7.75, 95% CI 2.28-26.40). Heterogeneity among studies was high. The few available data also reported that COVID-19 was associated with increased risk of liver decompensation and mortality in patients with liver cirrhosis.

CONCLUSIONS: LFTs alterations were reported in up to 47% of unselected patients with COVID-19 and were associated with severe disease or in-hospital mortality. In cirrhotic patients, COVID-19 was associated with high risk of liver decompensation or mortality.

Key Words:
SARS-CoV-2, COVID-19, Liver function tests, Severe disease, Mortality, Meta-analysis, Cirrhosis, NAFLD.

Introduction

Liver injury is a common feature of highly pathogenic Coronaviruses-associated disease in humans[1]. Since the very early phases of the last Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) outbreak, several studies from China have found liver function tests (LFTs) to be abnormal in infected patients. These findings were later confirmed by data from Western countries at the time the outbreak had reached pandemic proportions, albeit with a widely variable prevalence across the published studies (3.8[2]-50%[3]). Moreover, the reported impact of liver involvement on clinical outcomes, such as disease severity, intensive care unit (ICU) admission and mortality was contradictory. Despite several systematic reviews with meta-analysis have already investigated the liver involvement of COVID-19[4-11], they mostly pooled data from early Chinese reports without evaluating timepoints of liver biochemistries alterations. Therefore, we aimed to systematically review the prevalence of liver involvement in patients with SARS-CoV-2 infection at their hospital admission, and its correlation with disease severity and clinical outcomes in patients with or without pre-existing chronic liver disease. We also pointed out the pathophysiological links between Coronavirus Disease-2019 (COVID-19) and the liver.

Materials and Methods

This systematic review and meta-analysis was performed according to PRISMA guidelines[12]. We searched both manually and by using an artificial intelligence-based web tool (Risklick.ch, Bern, Switzerland)[13] the following databases: PubMed,

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Medline, PMC, Embase, Web of Science, clinical trial registries, publications from ArXiv, BioRxiv, Elsevier, MedRxiv, WHO sources and other Coronavirus family publications databases for articles published from January, 1st 2020 to August, 3rd 2020. The following search string was used: ((Coronavirus) OR (severe acute respiratory syndrome Coronavirus 2) OR (SARS-CoV-2) OR (novel Coronavirus) OR (nCoV) OR (2019-nCoV) OR (COVID-19)) AND ((liver) OR (cirrhosis) OR (chronic liver disease) OR (features) OR (characteristics) OR (laboratory) OR (liver function tests)). We included all cohort studies of patients infected by SARS-CoV-2 with reported rate of abnormal liver biochemistries (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase [GGT], alkaline phosphatase [ALP], total bilirubin [tBIL]) at the time of admission, and their association with clinical outcomes (disease severity and death). Thus, according to a pre-specified protocol, we excluded studies not clearly reporting the timepoint of liver tests abnormalities, studies at high risk of reporting duplicated cohorts, studies with patients selected by either age or comorbidity criteria, as well as studies reporting cohorts of ICU-admitted-only patients.

Two investigators (FDZ, MDS) independently selected the studies based on eligibility criteria, analyzed their features and findings, and assessed the risk of bias of each study through modified Newcastle-Ottawa scale (mNOS). Any disagreement was solved by consensus with a third expert investigator (FRP). Case series of less than 20 patients, preprints, reviews, editorials, studies related to other Coronaviruses (e.g., SARS or Middle East Respiratory Syndrome – MERS) or to pediatric cohorts, and non-English language papers were excluded (study flow diagram according to PRISMA – Figure 1). Authors were asked to provide relevant missing information by email, otherwise the study was not included in the final analysis.

We performed a pooled estimate of the prevalence of abnormal LFTs (ALT, AST, GGT, ALP, tBIL) according to the laboratory cut-offs reported by each study in patients with RT-PCR-confirmed SARS-CoV-2 infection. We adopted the formula proposed by Wan et al[14] to estimate the mean, using the values of the median and the first and third quartiles, where needed. Subsequently, we performed subgroup analyses on the effect of liver involvement on odds of disease severity and death. The odds ratios (OR) of events occurring in patients with abnormal LFTs at admission were estimated by a random-effects model, using I^2 statistics for heterogeneity assessment. The visual inspection of funnel plot and Egger's test were used to assess publication bias.

Statistical Analysis

The statistical analysis was performed with R Studio 1.3 and Review Manager 5.3, choosing a random-effects model due to high heterogeneity. p-value <0.05 was considered statistically significant.

Results

Characteristics of Included Studies

19,464 records were initially identified, 12,484 were retained after removing duplicates (Figure 1); 12,026 articles were further discarded by title and abstract review, together with 39 non-peer-reviewed pre-prints and 208 non-English papers. Of the remaining 211 papers, 4 clinical trials, 47 reviews and 39 small case series were excluded, as well as 83 articles that did not report information relevant to the analysis. Finally, 38 studies met the eligibility criteria and their main features are summarized in ***Supplementary Table I***. Since it was not possible to assess the extent of the overlap between cohorts enrolled at Tongji[15-17] and Jinyintan[15,18] Hospitals of Wuhan in the same timeframe, we decided to retain the largest cohort[15] in the quantitative analysis, discarding the cohort from Wang et al[17]. Fu et al[16] was discarded regarding AST and ALT analyses, and retained for tBIL analysis, since Yu et al[15] did not provide data about tBIL. The same occurred for Zhou et al[18], discarded from prevalence analysis but retained for mortality meta-analysis. Moreover, Wu et al[19] clearly stated in the main text of the paper that ten patients in their cohort were shared with the cohorts of two other studies included in our analysis[20,21]. We decided to include the study in the final analysis because of the negligible effect on the pooled analysis.

Therefore, we estimated the prevalence of abnormal liver biochemistries at admission on an aggregate cohort of 20724 patients with SARS-CoV-2 infection from 36 studies; raw prevalence estimates from each study are reported in Table I.

The rate of patients with known pre-existing liver disease in the included studies ranges from 0% to 37.6%; the etiology of liver disease was reported in a minority of the studies. Pre-existing viral hepatitis was reported in up to 4.5% of patients by Gu et al[22].

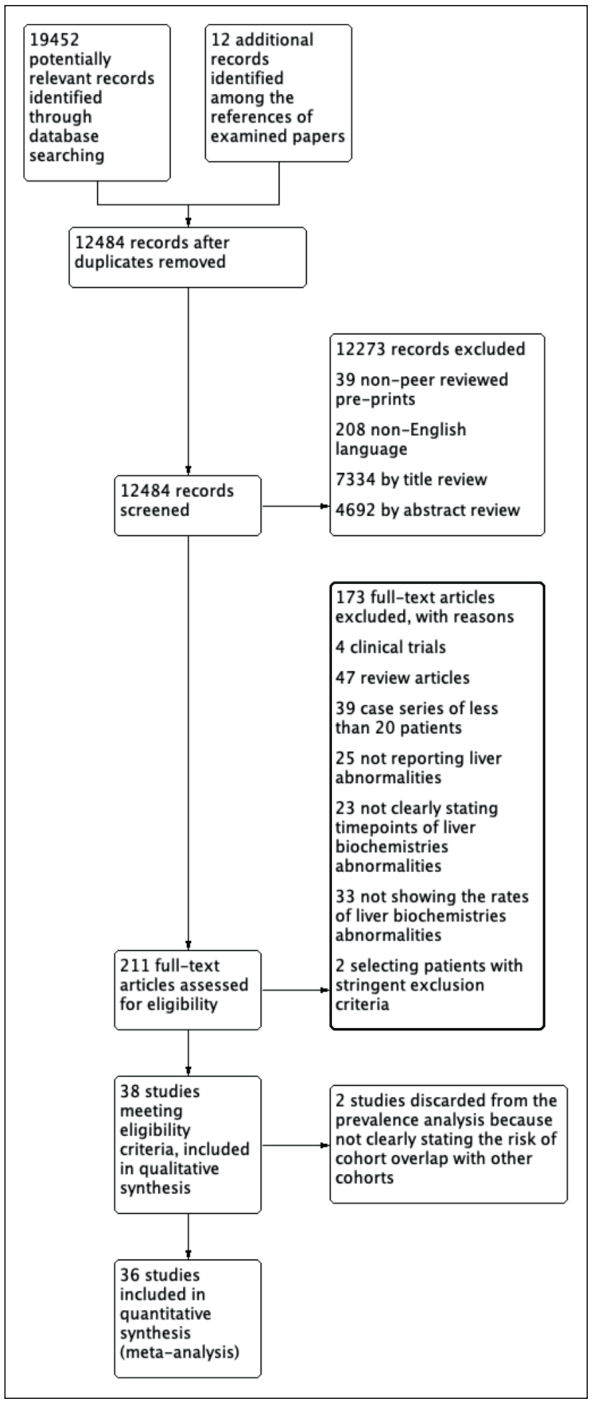

Figure 1. Study flow diagram according to PRISMA.

The quality of the studies meeting eligibility criteria was overall low, beside their retrospective designs, being the median mNOS score 4 (mean 4.7) out of a maximum of 9 ***(Supplementary Table I)***.

Asymmetry in the funnel plot of included studies was confirmed both by visual inspection and by Egger's test (intercept 0.878 p=0.00004; ***Supplementary Figure 1***). Possible sources of asymmetry in our meta-analysis may be attributable to both publication bias and poor methodological quality of the included studies.

Prevalence and Evolution of Lliver Involvement During SARS-CoV-2 Infection

We found a 46.9% prevalence of at least one abnormal LFT at admission (95% CI 37-56.8, across 7 studies[21,23-28], including 2306 patients, Figure 2). ALT was elevated in 22.8% of patients (95% CI 19.0-26.8, across 31 studies[2,3,15,19,21-27,29-48] including 19208 patients, Figure 3A), AST in 26.5% (95% CI 20.3-33.2, across 32 studies[2,3,15,19-27,29,30,33-50] including 18506 patients, Figure 3B), GGT in 22.5% (95% CI 15.8-30, across 8 studies[3,22,23,26,27,29,43,44] including 2231 patients, Figure 3C), ALP in 5.7% (95% CI 2.9-9.4, across 10 studies[3,22,23,26,27,29,40,43,44,46] including 4011 patients, Figure 3D); tBIL in 8.0% (95% CI 5.4-11.0, across 22 studies[2,3,16,19,21-27,29,30,34,36-40,42,43,46] including 8275 patients, Figure 3E). Heterogeneity was >90% for all the analyses.

One of the first analyses performed on a Chinese multicenter retrospective database of 1099 patients showed AST above ULN in 22.2% of patients, rising up to 39.4% in the subgroup with severe COVID-19, whereas ALT was elevated in 21.3% and 28.1% of patients, respectively[30]. Moreover, up to 13.3% of patients with severe disease presented tBIL higher than 17.1 micromol/L (1.0 mg/dl). A recently published systematic review[5] with meta-analysis pooling data from Chinese studies reported an overall prevalence of increased ALT, AST or tBIL of 18%, 21% and 6%, respectively. The highest risk of AST, ALT or tBIL increase was found in patients with severe disease (OR 2.20, 95% CI 1.60-3.02)[5]. However, the analysis focused only on the earliest available studies[17,18,20,30], mainly describing small cohorts.

Subsequent Eastern studies reported a higher prevalence of LFTs abnormalities. In a cross-sectional study including 417 patients from Shenzhen[29], baseline AST or ALT elevation was observed in 46% of patients. Hepatocellular or mixed type liver damage rather than cholestatic type was associated with severe COVID-19 at admission (OR 2.73, 95% CI 1.19-6.30 for hepatocellular type; OR 4.44, 95% CI 1.93-10.23 for mixed type; OR 1.28, 95% CI 0.58-2.82 for cholestatic type). In a large cohort from Hong-Kong the reported rate of ALT or AST elevation was 22.5%; tBIL or ALP were abnormal in 52.1% and 58.5% of patients, respectively[51].

With the progressive expansion of the pandemic throughout the world, further data from West-

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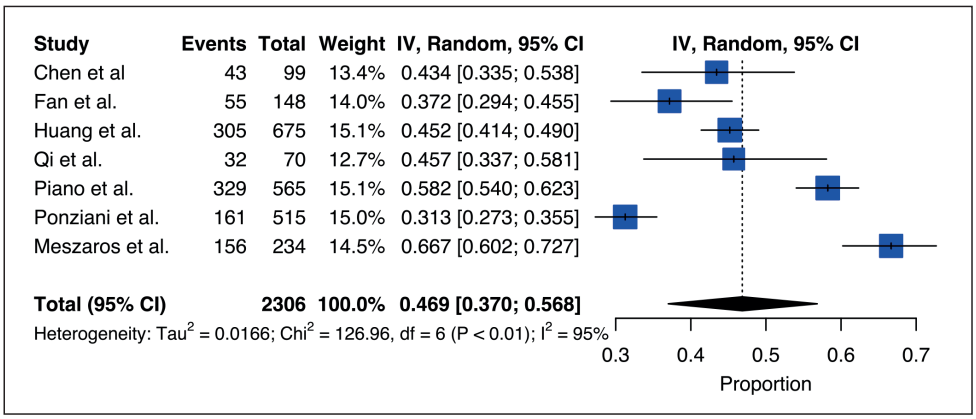

Figure 2. Meta-analysis of prevalence of at least one abnormal liver function test (LFT) at patients' admission.

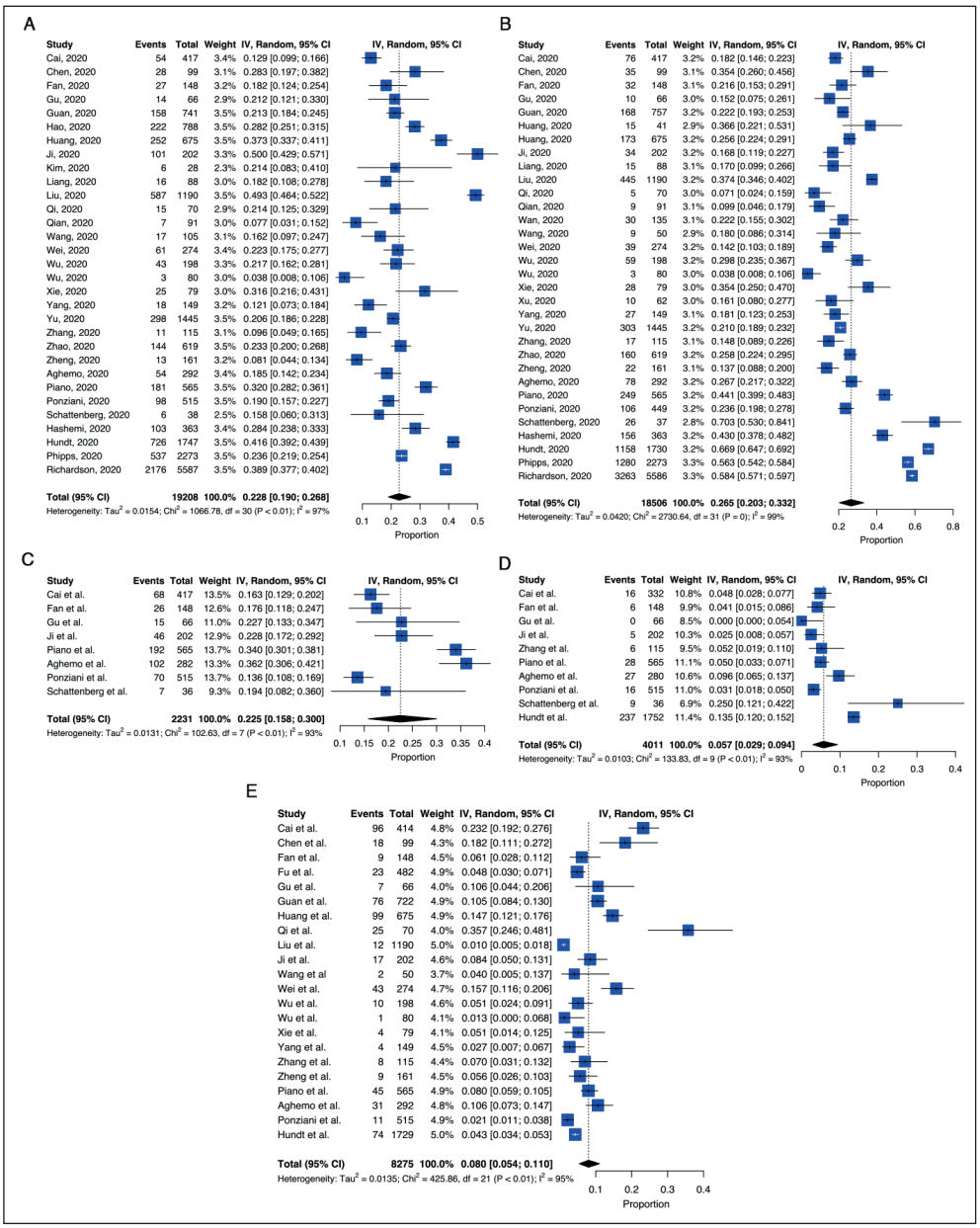

Figure 3. Meta-analysis of prevalence of alanine aminotransferase (ALT; **A**), aspartate aminotransferase (AST; **B**), gamma glutamyl transferase (GGT; **C**), alkaline phosphatase (ALP; **D**) or total bilirubin (tBIL; **E**) elevation at patients' admission.

Table I. Raw prevalence of abnormal liver function tests (LFTs) at admission in SARS-CoV-2 positive patients, as extracted from the included papers.

Study	Patients (n)	Country (n)	M (%)	Mean age (y)	Any abnormal LFT (n)	Available LFTs n)	Abnormal LFTs (%)	Abnormal AST (n)	Available AST (n)	Abnormal AST (%)	Abnormal ALT (n)	Available ALT (n)	Abnormal ALT (%)	Abnormal GGT (n)	Available GGT (n)	Abnormal GGT (%)	Abnormal ALP (n)	Available ALP (n)	Abnormal ALP (%)	Abnormal tBIL (n)	Available tBIL (n)	Abnormal tBIL (%)
Cai et al[29]	417	China	47.5	47	–	–	–	76	417	18.2	54	417	12.9	68	417	16.3	16	332	4.8	96	414	23.2
Chen et al[21]	99	China	68	55.5	43	99	43.4	35	99	35.4	28	99	28.3	–	–	–	–	–	–	18	99	18.2
Fan et al[23]	148	China	49.3	50	55	148	37.2	32	148	21.6	27	148	18.2	26	148	17.6	6	148	4.1	9	148	6.1
Fu et al[16]	482	China	50.4	54.3	–	–	–	†	†	†	†	†	†	–	–	–	–	–	–	23	482	4.8
Gu et al[22]	66	China	52.8	43	–	–	–	10	66	15.2	14	66	21.2	15	66	22.7	0	66	0	7	66	10.6
Guan et al[30]	1099	China	58.1	46.7	–	–	–	168	757	22.2	158	741	21.3	–	–	–	–	–	–	76	722	10.5
Hao et al[31]	788	China	51.6	42.3	–	–	–	–	–	–	222	788	28.2	–	–	–	–	–	–	–	–	–
Huang et al[20]	41	China	73	49.3	–	–	–	15	41	36.6	–	–	–	–	–	–	–	–	–	–	–	–
Huang et al[24]	675	China	46.4	53.5	305	675	45.2	173	675	25.6	252	675	37.3	–	–	–	–	–	–	99	675	14.7
Ji et al[3]	202	China	55.9	44.5	–	–	–	34	202	16.8	101	202	50.0	46	202	22.8	5	202	2.5	17	202	8.4
Kim et al[32]	28	S. Korea	53.6	42.6	–	–	–	6	28	21.4	–	–	–	–	–	–	–	–	–	–	–	–
Liang et al[33]	88	China	58	42.7	–	–	–	16	88	18.2	15	88	17.0	–	–	–	–	–	–	–	–	–
Liu et al[34]	1190	China	53.4	57	–	–	–	445	1190	37.4	587	1190	49.3	–	–	–	–	–	–	12	1190	9.4
Qi et al[25]	70	China	55.7	38.3	32	70	45.7	5	70	7.1	15	70	21.4	–	–	–	–	–	–	25	70	35.7
Qian et al[35]	91	China	40.7	47.8	–	–	–	7	91	7.7	9	91	9.9	–	–	–	–	–	–	–	–	–
Wan et al[49]	135	China	53.3	46	–	–	–	–	–	–	30	135	22.2	–	–	–	–	–	–	–	–	–
Wang et al[36]	105	China	53.3	46.1	–	–	–	9	50	18.0	17	105	16.2	–	–	–	–	–	–	2	50	4.0
Wei et al[37]	276	China	56.2	50	–	–	–	39	274	14.2	61	274	22.3	–	–	–	–	–	–	43	274	15.7
Wu et al[19]	201	China	63.7	51.3	–	–	–	59	198	29.8	43	198	21.7	–	–	–	–	–	–	10	198	5.1
Wu et al[2]	80	China	48.8	46.1	–	–	–	3	80	3.8	3	80	3.8	–	–	–	–	–	–	1	80	1.3
Xie et al[38]	79	China	55.7	58	–	–	–	28	79	35.4	25	79	31.6	–	–	–	–	–	–	4	79	5.1
Xu et al[50]	62	China	56	41.7	–	–	–	10	62	16.1	–	–	–	–	–	–	–	–	–	–	–	–
Yang et al[39]	149	China	54.4	45.1	–	–	–	27	149	18.1	18	149	12.1	–	–	–	–	–	–	4	149	2.7
Yu et al1[5]	1445	China	50.4	62.3	–	–	–	303	1445	21.0	298	1445	20.6	–	–	–	–	–	–	–	–	–
Zhang et al[40]	115	China	42.6	49.5	–	–	–	17	115	14.8	11	115	9.6	–	–	–	6	115	5.2	8	115	7.0
Zhao et al[41]	619	China	49.9	58.2	–	–	–	144	619	23.3	160	619	25.8	–	–	–	–	–	–	–	–	–
Zheng et al[42]	161	China	49.7	45.0	–	–	–	13	161	8.1	22	161	13.7	–	–	–	–	–	–	9	161	5.6
Aghemo et al[43]	292	Italy	68.2	65	–	–	–	78	292	26.7	54	292	18.5	102	282	36.2	27	280	9.6	31	292	10.6
Meszaros et al[28]	234	France	63.7	67	156	234	66.7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Piano et al[26]	565	Italy	63	66	329	565	58.2	249	565	44.0	181	565	32.0	192	565	34.0	28	565	5.0	45	565	8.0
Ponziani et al[27]	515	Italy	62.7	65	161	515	31.3	106	449	23.6	98	515	19.0	70	515	13.6	16	515	3.1	11	515	2.1
Schattenberg et al[44]	44	Germany	68.2	68	–	–	–	26	37	70.3	6	38	15.8	7	36	19.4	9	36	25.0	–	–	–
Hashemi et al[45]	363	USA	55.4	63.4	–	–	–	156	363	43.0	103	363	28.4	–	–	–	–	–	–	–	–	–
Hundt et al[46]	1827	USA	53	64.6	–	–	–	1158	1730	66.9	726	1747	41.6	–	–	–	237	1752	13.5	74	1729	4.3
Phipps et al[47]	2273	USA	57	64.3	–	–	–	1280	2273	56.3	537	2273	23.6	–	–	–	–	–	–	–	–	–
Richardson et al[48]	5700	USA	60.3	63.3	–	–	–	3263	5586	58.4	2176	5587	38.9	–	–	–	–	–	–	–	–	–
Pooled	**20724**		**56.1**	**58.9**	**1081**	**2306**	**46.9**	**6001**	**19208**	**31.2**	**8040**	**18506**	**43.4**	**526**	**2231**	**23.6**	**350**	**4011**	**8.7**	**724**	**8275**	**8.8**

† Not imputed due to relevant risk of cohort overlap.
Aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma glutamyl transferase (GGT); alkaline phosphatase (ALP); total bilirubin (tBIL); United States of America (USA).

ern studies reported similar figures. In a small cross-sectional study from Boston, United States of America (USA), Bloom et al[52] observed that at least one LFT among AST, ALT, ALP or tBIL was abnormal in 69% of patients at hospital admission.

Retrospective data from 5700 COVID-19 patients from the New York City area showed a prevalence of 39% and 58.4% of ALT or AST elevation at the admission[48]. In another large retrospective study of 2273 SARS-CoV-2 positive and 1108 SARS-CoV-2 negative patients followed-up for up to 5 weeks[47], patients who tested positive had higher median ALT peak values than those who tested negative, both at and during hospitalization.

In a retrospective multicenter Italian study, Piano et al[26] reported a 58% prevalence of abnormal LFTs at the admission. In our single-center study, including 515 patients without severe chronic liver disease, we reported slightly lower rates, with 31.3% occurrence of abnormal baseline LFTs and elevated AST, ALT, GGT in 20.4%, 19%, 13.6% of patients, respectively[27]. This was comparable with data by Aghemo et al[43] and Vespo et al[53], reporting AST, ALT or GGT elevation in 18.5%, 26.7% and 36.2% of patients.

Overall, the analyzed studies show that severe liver injury (e.g., ALT or AST >3xULN or GGT, ALP or tBIL >2xULN) or acute hepatitis are a rare event[26,27,29,40,51,54-56].

The few papers reporting the evolution of LFTs abnormalities during hospitalization showed a worsening trend, associated with the use of tocilizumab, acetaminophen, piperacillin/tazobactam and lopinavir/ritonavir[26,29] progressively improving and returning to baseline during follow-up[24,27,57].

Thus, the prevalence of LFTs abnormalities varied widely in the published cohorts from China and Western countries, ranging from 31.3 to 66.7%, with an even greater variation when considering the single LFT was considered (AST 3.8-70.3%, ALT 3.8-50%, GGT 13.6-34%, ALP 2.5-25%, tBIL 1.3-23.2%; Table I). Such a high variability can be explained by methodological issues. Indeed, the timing of LFTs determination was often not specified, leading to the possible inclusion of values registered during hospitalization with the consequent influence of multiple factors (e.g., drugs, bacterial infections, mechanical ventilation). Cai et al[29] reported the use of lopinavir/ritonavir antiviral treatment to be related to a higher risk of liver injury (OR 4.44, 95% CI 1.50-13.17). A pharmacological link between medications and liver involvement during COVID-19 has also been confirmed by a retrospective analysis of 5771 patients enrolled in ten Chinese hospitals[57]. Nearly 70.5% of patients in this cohort were receiving antivirals, and 79% of them were on Chinese traditional medications at the time of LFTs determination. In this study, the use of antibiotics, antifungals, corticosteroids, and antiviral drugs was associated with LFTs elevation.

Management of missing data also represents a major pitfall, considering the retrospective design of the reported studies. Missing AST values can reach percentages up to 53.8% in some studies[51]. Excluding from the analysis patients with missing values or those with less than two determinations during follow-up may have excluded those with mild disease, better outcomes or earlier discharge.

Furthermore, underlying pre-existing liver diseases might have been under or misreported. Chen et al[58] described hepatitis B surface antigen (HBsAg) to be detected in 4% of their cohort of patients with COVID-19, while the recently estimated prevalence of hepatitis B virus (HBV) infection in the Chinese general population is as high as 6.89%[59]. Shi et al[60] reported 9% of patients in their cohort to be affected by "hepatitis or liver cirrhosis", without any further specification. In studies from USA, only a small proportion of patients with COVID-19 was diagnosed with chronic liver disease (6.7% Bloom et al[52]; 0.2% Richardson et al[48]) or cirrhosis (1.7% Bloom et al[52]; 0.4% Richardson et al[48]), despite a prevalence of obesity as high as 45%, likely underestimating the prevalence of nonalcoholic fatty liver disease (NAFLD)[48,52].

Liver Involvement and Clinical Outcomes

Although severe COVID-19 has been associated with abnormal LFTs in both Chinese and Western studies[3,5,15,17,20,22-28,31,34,37-40,43-46,48,50,52,57,58,61] the correlation with clinical outcomes is matter of debate.

Aghemo et al[43] identified ALP elevation as an independent predictor of poor outcome. Consistent with this finding, our group reported ALP peak values to be a risk factor for hospital mortality (OR 1.007, 95% CI 1.002-1.01, p=0.005)[27]. On the other hand, baseline abnormal LFTs were predictive of ICU admission (OR 2.19, 95% CI 1.24-3.89, p=0.007) but not of mortality, which was instead affected by age, comorbidities, occurrence of acute respiratory distress syndrome (ARDS) and inflammatory status.

Lei et al[57] reported a significantly increased risk of all-cause mortality for patients with AST ranging from 40 to 120 U/L and >120 U/L (OR 4.81 and 14.87, respectively).

In a Spanish cohort of 160 patients with COVID-19, FIB-4 [a score combining age, AST, ALT and platelets (PLTs)] was positively correlat-

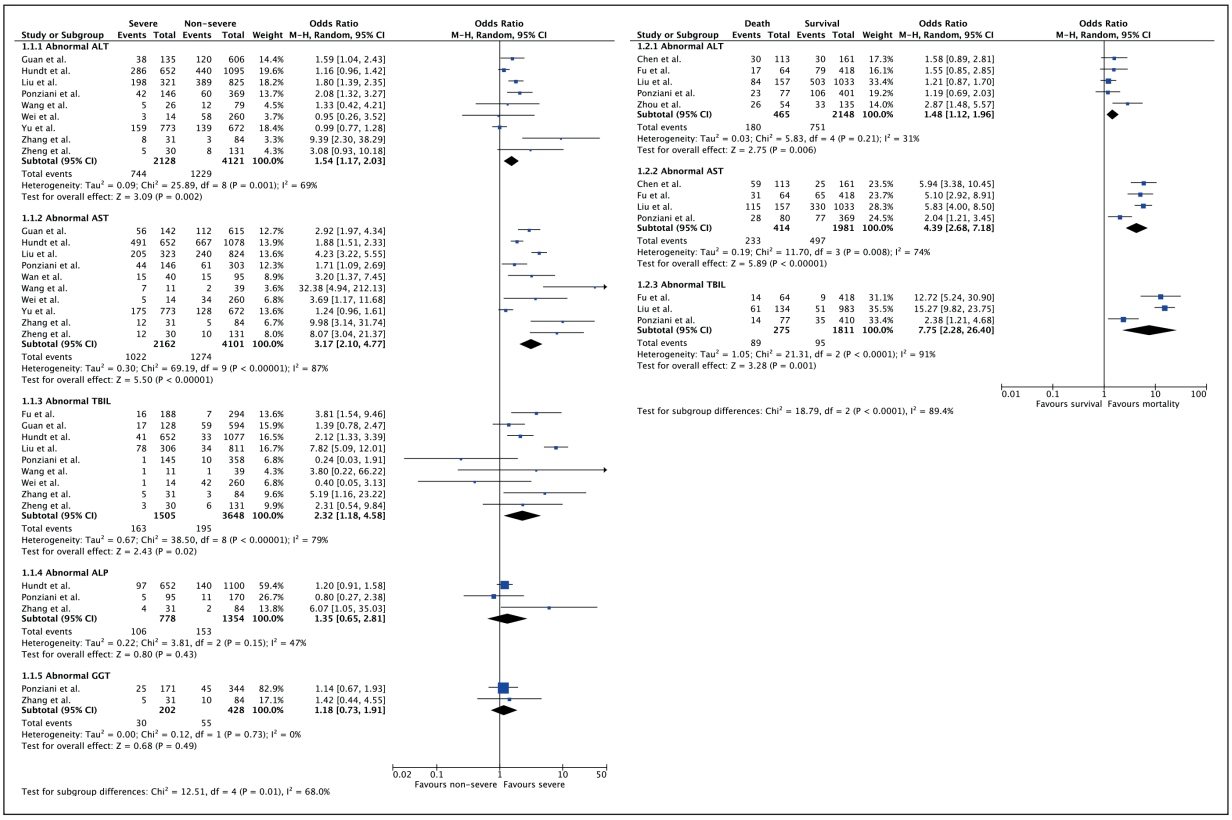

Figure 4. Meta-analysis of the association of abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) or total bilirubin (tBIL) elevation at patients' admission with the odds of severe COVID-19 (**A**) or mortality (**B**).

ed with the need for mechanic ventilation[62]. Since the Authors did not find significant differences between PLTs count at baseline between patients requiring or not mechanical ventilation, and only middle-aged subjects were included, it seems reasonable that AST and ALT elevation were the only determinants of FIB-4 values, being associated with poor outcomes.

Other studies assessing the predictive value of liver involvement on composite outcomes revealed a clear association with ICU admission/death (OR 4.00, 95% CI 2.15-7.44)[26] or ICU admission/mechanical ventilation/death (OR 7.92, 95% CI 4.14-15.14)[51]. Conversely, in a population of patients from USA[47], the multivariable analysis revealed a weak association of peak ALT with the composite outcome of death or discharge to hospice (OR 1.22, 95% CI 1.10-1.35).

Some limitations should be taken into account, as they affect virtually all the cited studies. The use of composite outcomes limits the interpretation of the results; firstly, because it is not possible to understand the relative weight of specific factors on each outcome; secondly, because mortality was mainly combined with ICU admission, the latter usually biased by other factors such as age, comorbidities, and even ICU beds availability. This reason has been particularly true during the COVID-19 outbreak, as the proportions of the pandemic has overwhelmed the capacity of the health systems of ensuring universal access to intensive care[63]. Furthermore, we do believe that several studies might have over-emphasized the role of peak liver biochemistries values as predictors of clinical outcomes, as peak values might be influenced by a number of confounding factors (e.g., antiviral therapy, systemic inflammatory response) and should be cautiously interpreted in the absence of a time relationship with clinical worsening. As recently published[27], we noted the tendency of liver tests to reach their peak mainly after admission to ICU.

The meta-analysis of the studies meeting eligibility criteria and showing useful information for comparison between LFTs and clinical outcomes highlighted that either abnormal ALT (OR 1.54, 95% CI 1.17-2.03; I^2=69%; 6249 patients from 9 studies[15,27,30,34,36,37,40,42,46]), AST (OR 3.17, 95% CI 2.10-4.77; I^2=87%; 6263 patients from 10 stud-

ies[15,27,30,34,36,37,40,42,46,49]) or tBIL (OR 2.32, 95% CI 1.18-4.58; I^2=79%; 5153 patients from 9 studies[16,27,30,34,36,37,40,42,46]) were associated with severe COVID-19, according to the definition adopted in each study, whereas abnormal ALP or GTT were not (OR 1.35, 95% CI 0.65-2.81; I^2=47%; 2132 patients from 3 studies[27,40,46] for ALP; OR 1.18, 95% CI 0.73-1.91; I^2=n/a; 630 patients from 2 studies[27,40] for GGT) (Figure 4A).

Conversely, either abnormal ALT (OR 1.48, 95% CI 1.12-1.96; I^2=31%; 2613 patients from 5 studies[16,18,27,34,58]), AST (OR 4.39, 95% CI 2.68-7.18; I^2=74%; 2395 patients from 4 studies[16,27,34,58]), or tBIL (OR 7.75, 95% CI 2.28-26.40; I^2=91%; 2086 patients from 3 studies[16,27,34]) were associated with increased odds of mortality (Figure 4B).

The heterogeneity across our comparisons was generally high (except for ALP/disease severity and ALT/mortality), being mainly ascribed to either the different definitions of severe COVID-19 given in the single studies and the different cut-offs for abnormal tests across them. In addition, it should be noted that it was rarely reported whether a worse disease phenotype was already present at the time of hospital admission or, rather, if patients worsened during hospitalization, so this should prompt cautious interpretation of the results. The short duration of patients' follow-up can also have led to the underestimation of the odds of mortality.

Notably, most of the studies included in our meta-analysis enrolled cohorts of hospitalized patients, presenting with a symptomatic disease. Hence, our results should not be generalized to the whole population of patients with SARS-CoV-2 infection and need to be validated by prospective cohort studies.

COVID-19 and Pre-Existing Liver Disease

General studies on patients with COVID-19 reported scattered and non-specific information on patients with pre-existing chronic liver disease. Due to the small number of available studies, eight reporting on patients with chronic liver disease, six on patients with liver cirrhosis, and 4 on patients with NAFLD, no meta-analysis was performed, and we decided to simply describe the outcomes of COVID-19 in these subgroups of patients.

Chronic Liver Disease and Cirrhosis

Grasselli et al[64] did not found any association between pre-existing liver disease and mortality in a large cohort of critically ill Italian patients. Conversely, a large prospective study on hospitalized patients with COVID-19 from the United Kingdom highlighted a high risk of mortality in patients with chronic liver disease (HR for pre-existing moderate/severe liver disease 1.51, 95% CI 1.21-1.88, $p<0.001$)[65], as confirmed by the OpenSAFELY platform database (age-sex adjusted HR 2.39, 95% CI 2.06-2.77), which includes more than 17 million patients registered in the English National Health System (NHS)[66].

A retrospective study[67] across 34 centers in the USA, based on electronic medical records and having the specific endpoint of assessing the outcome of patients with COVID-19 and pre-existing liver disease, revealed a significantly higher risk of 30-day mortality (RR 2.8, 95% CI 1.9-4.0, $p<0.001$), even higher in the subgroup of patients with liver cirrhosis (RR 4.6, 95% CI 2.6-8.3, $p<0.001$). Another study on 363 hospitalized patients from the USA[45] described the presence of known chronic liver disease in 19% patients with COVID-19, mainly related to NAFLD (15.5%), 9 of them with liver cirrhosis. Beside the significantly higher rate and magnitude of baseline LFTs alteration observed in this subgroup of patients, the multivariate analysis revealed that it was a risk factor for mechanical ventilation and ICU admission, but not for death.

Chinese studies reported that pre-existing chronic HBV infection was associated with LFTs elevation in up to 27.6% patients with SARS-CoV-2 infection[68,69], with 13.3% rate of liver injury during hospitalization, progressing to acute on chronic liver failure (ACLF) in 4 cases[70]. Surprisingly, the only two patients with known liver cirrhosis in that cohort did not develop liver injury.

The most relevant data on the clinical course of COVID-19 in patients with liver cirrhosis come from two international joint registries: the "SECURE-Cirrhosis" for Americas, China, Japan and Korea; and the "COVID-Hep" for the rest of the world[71,72].

In the preliminary report on the outcomes of the first 152 submissions[73], the mortality rate of patients with cirrhosis was 39.8%, far exceeding that reported in unselected populations, hospitalized patients with cirrhosis in the era preceding COVID-19, and in patients with cirrhosis admitted with influenza[73]. In the multivariate analysis, Child-Turcotte-Pugh (CTP) score positively predicted mortality of patients with liver cirrhosis and COVID-19 (CTP-B OR 4.90, 95% CI 1.16-20.61; CTP-C OR 28.07, 95% CI 4.42-178.46). Hepatic decompensation occurred in 36.9% of patients and was strongly associated with the risk

of death. As of August 25th 2020, the combined registry included a total cohort of 1102 patients, 424 of whom are reported with non-cirrhotic chronic liver disease, 508 with cirrhosis, and 170 liver transplant recipients.

A retrospective multicenter comparative analysis[74] between a group of 50 Italian cirrhotic patients with COVID-19 and a historical control group of cirrhotic patients hospitalized for liver decompensation due to bacterial infections underscored a significant worsening of CTP and model for end-stage liver disease (MELD) scores at the admission compared to the last available visit. Overall, 46% of patients experienced liver decompensation during hospitalization, whereas ACLF occurred in 45% of them. The 30-day cumulative probability of overall mortality was 34%, mainly related to respiratory failure; independent predictors of mortality in the multivariate analysis were MELD score, Chronic Liver Failure Consortium (CLIF-C) ACLF score and moderate/severe respiratory failure.

A multicenter North American retrospective study[75] included 37 cirrhotic patients hospitalized for COVID-19, matched in a 1:2-1:5 fashion by age and gender with non-cirrhotic patients with COVID-19 and cirrhotic patients without COVID-19. The Authors found a higher death/hospice rate in the cirrhosis-COVID-19 group compared with the COVID-19-alone group (30% *vs.* 13%, p=0.03), confirming that underlying cirrhosis plays a detrimental role on clinical outcome. Conversely, mortality risk was similar in cirrhotic patients with or without COVID-19 (19% *vs.* 30%, p=0.16), although the two groups were not matched by the stage of liver disease. On multivariable analysis, a higher Charlson Comorbidity Index was associated with greater risk of mortality (OR 1.23, 1.11-1.37, p<0.00001). On the other hand, a small Chinese study of 21 patients with cirrhosis and COVID-19 displayed a mortality rate of 23.8%, failing to demonstrate any clear prognostic association, perhaps due to the small sample size[76].

NAFLD

NAFLD has been advocated as a risk factor for severe COVID-19.

Ji et al[3] performed a retrospective study on 202 consecutive Chinese patients admitted with COVID-19, 33% of whom with known NAFLD as assessed by non-invasive methods (hepatic steatosis index and/or abdominal ultrasound examination). Abnormal LFTs were reported in 50% of patients at the admission, 33% showing persistent abnormalities throughout the entire hospitalization. Patients with NAFLD had higher risk of disease progression (44.7% *vs.* 6.6%, p<0.0001) and of developing abnormal LFTs from admission to discharge (70% *vs.* 11.1%, p<0.0001).

Targher et al[77] also confirmed a higher risk of severe COVID-19 in the subgroup of patients with NAFLD assessed by computed tomography (CT) scan and with intermediate/high risk of fibrosis *vs.* patients without NAFLD (OR 2.95, 95% CI 1-37-6.34, p<0.005), suggesting a role for liver fibrosis in the pathogenesis of severe COVID-19 and its underlying cytokine storm.

Zhou et al[78] further described the association of NAFLD with COVID-19 severity, but only in patients younger than 60 years.

Although the association between NAFLD, increased inflammation and COVID-19 severity can be intriguing, the arbitrary definition of disease progression and the bias of selecting a subgroup of patients with NAFLD status, mainly assessed by indirect methods, from a larger cohort may have affected the results[79].

Indeed, data from the UK Biobank (UKBB) cohort suggested that genetic predisposition to hepatic fat accumulation did not increase the probability of the evolution towards severe COVID-19, thus denying the causal role of NAFLD in this condition[80].

Overall, in patients with NAFLD without cirrhosis, comorbidities related to metabolic dysfunction, such as hypertension, obesity, heart disease and diabetes probably exert an unfavorable prognostic role rather than the liver condition *"per se"*, as reported in the general population of COVID-19 patients[81]. In this light, patients affected by NAFLD and COVID-19 present a greater fragility and an increased risk of developing a severe disease, hence they require close clinical monitoring. On the other hand, concerns have been raised about the possible role of cytokines released during COVID-19 in expediting NAFLD progression, thus encouraging NAFLD status assessment during COVID-19[82].

Histopathological Findings in Liver Tissue of Patients With COVID-19

Available data on liver histology have raised several concerns about the underlying mechanism related to hepatic involvement in SARS-CoV-2 infection.

An early report from China described moderate microvesicular steatosis and mild lobular and portal activity as the main pathological features found in liver biopsy specimens of a 50-year-old

man dead for COVID19, suggesting either a direct damage of SARS-CoV-2 or drug-induced liver injury as the underlying mechanism[83].

Mild sinusoidal dilation, unspecific inflammation (lobular, periportal or sinusoidal lymphocytes, neutrophils, plasma cells), steatosis, shock necrosis, apoptotic hepatocytes have been observed in post-mortem liver biopsies[29,40,84-86]. The largest available series including 80 consecutive autopsies described shock-related changes in half of cases and features of hypoxic hepatitis features (e.g., centrilobular necrosis)[87]. Of note, in a small case series from New York[88], numerous platelet-fibrin microthrombi were identified in hepatic sinusoids in samples from six out of seven deceased patients, with ischemic type hepatic necrosis in two of them.

As regards the hypothesis of a direct viral cytopathic effect, Wang et al[84] observed on electron microscopy the presence of numerous particles in the cytoplasm of hepatocytes, interpreted as Coronavirus particles. However, PCR for viral genome on liver samples was not performed, therefore not allowing to exclude a possible alternative origin (e.g., intrahepatic cholesterol crystals, lamellations, "crown-like" structures seen in patients with NAFLD, multi-vesicular bodies, exosomes)[89,90]. Other Authors demonstrated the presence of SARS-CoV-2 genome by RT-PCR assay in only one out of four post-mortem liver samples[91], whereas in a recent study low levels of viral RNA were detected by RT-PCR in brain, heart, testicle and kidney, but liver samples were not analyzed[86].

Rationale for Liver Involvement During SARS-CoV-2 Infection

Similar to SARS-CoV, SARS-CoV-2 cell entry is dependent on the interaction between viral spike protein and angiotensin-converting enzyme 2 (ACE2) expressed on the surface of target cells[92]. The combined action of the transmembrane protease serine 2 (TMPRSS2), an androgen-induced[93] trans-membrane serine protease that primes the spike protein ultimately facilitating cell entry, is required for viral infection in *in vitro* models; TMPRSS2 inhibitors, such as camostat mesylate, can block SARS-CoV-2 infection of lung cells *in vitro*[94].

Several studies aimed to determine the expression levels of ACE2 and TMPRSS2 in organ samples, including liver and small intestine. No immunohistochemical staining for ACE2 was observed in Kupffer cells, hepatocytes, or endothelium of sinusoids, while luminal staining in bile ducts was occasionally detected[95]. Notably, ACE2 is abundantly expressed by enterocytes in the small intestine with a brush border pattern, but not in the colon. More recent reports[96,97] involving scRNA-seq datasets of human tissues refined those data, describing low levels of ACE2 mRNA expression in a small rate of cholangiocytes, but not in other cell types from adult livers. Liver cells did not co-express ACE2 and TMPRSS2, apparently denying the hypothesis of a direct liver tropism of SARS-CoV-2. Conversely, colonic and ileal enterocytes showed increased levels of both ACE2 and TMPRSS2, with a relevant grade of co-expression[96]. On the other hand, transcriptomic analysis of SARS-CoV-2 infection in a model of liver ductal organoids demonstrated cholangiocytes co-expression of ACE2 and TMPRSS2 and organoids susceptibility to SARS-CoV-2 infection, resulting in cell apoptosis, impairment of epithelial barrier dysfunction and bile acids transportation[98]. Such a heterogeneity in ACE2 and TMPRSS2 expression levels in the liver reported by different studies[99-101] remained unsolved also after the interrogation of three recently published liver cell atlases. Indeed, the rate of cells co-expressing ACE2 and TMPRSS2 in healthy livers ranged from none to 2.52% for cholangiocytes and from none to 0.04% for hepatocytes[102]. Interestingly, RNA sequencing of cells from cirrhotic livers revealed an opposite condition, with a higher rate of ACE2 and TMPRSS2 co-expression in hepatocytes (0.26% *vs.* none) and a lower one in cholangiocytes (0.05% *vs.* 0.45%) as compared to healthy livers[99,102].

Beside the uncertain hypothesis of a direct viral cytopathic effect on liver cells, other indirect mechanisms may explain liver involvement during SARS-CoV-2 infection.

Hypoxic hepatitis features, as already discussed, has been reported in post-mortem liver biopsies of patients dead after COVID-19[87]. Generally speaking, hypoxic hepatitis occurs in 2.5% of patients admitted in ICU, and its prevalence is as high as 40% in patients with increased serum aminotransferase prior to ICU admission, with a poor prognosis (59% in-hospital mortality)[103,104]. The pathophysiology of hypoxic hepatitis involves most frequently venous congestion in right-sided heart failure, as well as an inability of hepatocytes to utilize oxygen in septic shock and inflammation-mediated diseases. When both the mechanisms are coupled, their combined effects make liver hypoxic damage more likely[103], as may

occur in critically ill patients with COVID-19 and comorbid conditions.

Enhanced immune response leading to cytokine storm has been implicated in the pathogenesis of the clinical manifestations of severe COVID-19 (e.g., fever, respiratory and multi-organ failure)[105-107]. Nevertheless, decreased counts of natural killer (NK) and CD8+ T cells have been reported, especially in patients with severe disease, as well as the increased expression of NKG2A, an inhibitory receptor known to reduce the ability of NK cells of producing CD107a, interferon (IFN)-gamma, interleukin (IL)-2, granzyme B, and tumor necrosis factor alpha (TNF-alpha), leading to their functional exhaustion[108]. The observed depletion of circulating CD8+T-cells may reflect their trapping in the liver, which is thought to be the main determinant of liver damage in viral infections as observed during influenza, measles and SARS[109].

Early reports from China recognized a hyperexpression of pro-inflammatory cytokines, such as IL-6, IL-1beta, IL-2, IL-8, IL-17, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), C-X-C motif chemokine ligand 10 (CXCL10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1alpha (MIP-1a), and TNF-alpha in most patients with severe COVID-19, consistent with inflammasome activation[110], with a net negative prognostic value[20,111-113]. Diao et al[114] reported TNF-alpha, IL-6 and IL-10 levels to be elevated in infected rather than in non-infected patients, and even more elevated in those requiring ICU admission. Interestingly, they found a negative correlation between cytokines serum levels and lymphocyte count, and an increase in exhausted T-cells in infected patients, especially those requiring ICU admission. These findings are consistent with a cytokine storm syndrome, sharing many clinical and pathological similarities with other syndromes associated with excessive cytokine release (e.g., therapeutic infusions of monoclonal antibodies, secondary hemophagocytic lymphohistiocytosis (HLH), and therapy with chimeric antigen receptor T-cells (CAR-T cell), in which a mild and transient liver involvement is frequently observed[115-117]. We recently demonstrated a correlation between LFTs abnormalities and IL-6 serum levels in patients with COVID-19, further confirming these data[118].

As already discussed, the occurrence of drug induced liver injury (DILI) has been hypothesized as a mechanism of liver involvement during SARS-CoV-2 infection. Indeed, the large use of off-label antiviral drugs, such as lopinavir, darunavir or ritonavir, even in associated schemes, can contribute to liver injury, and drug hepatotoxicity may be induced more easily in individuals with baseline ALT elevation[119]. However, pathological findings strongly consistent with this hypothesis are scarce[83].

Intriguingly, alterations of the gut microbiome may also contribute to hepatic damage[120]. They can be caused by viral infection of enterocytes, which impairs the intestinal uptake of tryptophan, hence the production of antimicrobial peptides, mainly through the downregulation of ACE2 after viral entry[121-123]. Assante et al[124] hypothesized that the perturbation of the gut-liver axis can increase the risk of developing severe COVID-19 in patients with NAFLD, due to the dysregulation of gut epithelial barrier, the translocation of PAMPS and their effect on toll-like receptors (TLRs) in the liver[125], moreover the gut micriobiota has been supposed to be a possible candidate for adjuvant therapies during SARS-CoV-2 infection[126,127].

Finally, AST and ALT are released in case of muscle injury. Creatine phosphokinase (CPK) serum levels can increase during viral infections, as also reported for SARS-CoV-2[128]. A contribution of cardiac injury or severe rhabdomyolysis to transaminases serum levels can be hypothesized, although clinically relevant events of this type have been reported only occasionally in patients with COVID-19[128]. In particular, in our study only a minority of patients presented with muscles pain (2.1%), and although those with abnormal LFTs showed high CPK serum levels (154 *vs.* 102 IU/L), the concomitant increase in GGT supports a primary liver involvement during SARS-CoV-2 infection[27].

Conclusions

COVID-19 is frequently associated with alterations of LFTs, with a prevalence that is just under 50%. Our meta-analysis suggests that abnormal LFTs are a hallmark of COVID-19 in hospitalized patients since its very early phases, being often already present at hospital admission. LFTs abnormalities at admission are associated to disease severity and in-hospital death. This association may seem evident for elevated bilirubin, as a marker of liver failure, also included in clinical tools for evaluation of critically ill

patients (e.g., SOFA score). On the other hand, abnormal ALT and, to a greater extent abnormal AST at admission are associated with increased odds of death in hospitalized COVID-19 patients. The innovative information carried by our study is represented by the association between clinical outcomes and admission LFT abnormalities in studies from worldwide, since the meta-analyses published so far did not pay attention to the time-point LFTs were observed. In our opinion, this is a major pitfall, as LFTs might be influenced by multiple other confounders during the course of COVID-19 (e.g., DILI, mechanical ventilation). This highlights that the prognostic power of LFTs at the admission derives from their role as surrogate markers of systemic inflammatory status, hypoxia, and need for multidrug therapy, whereas a direct cytopathic effect of SARS-CoV2 seems unlikely.

One important limitation of our meta-analysis is the unknown effect of pre-existing liver disease on admission LFT abnormalities, due to the lack of sufficient information about the severity of pre-existing liver disease in the examined cohorts. We advise for prospective cohort studies with an *ad-hoc* design to clarify this issue.

From a clinical point of view, based on available literature, we advise to frequently test hospitalized patients with COVID-19 for liver biochemistries, which can be an easy-to-use additional tool for monitoring patients and for the early stratification of prognosis. Furthermore, prospective cohort studies are urgently needed to validate these findings.

The prognosis of patients with pre-existing chronic liver disease, specifically cirrhosis, is unfavorable, with a high rate of morbidity and mortality. Thus, a strict adoption of the pre-emptive measures recommended by International Societies is mandatory for this population of patients.

Conflict of Interests

The authors declare that they have no conflicts of interests.

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