COVID-19 and liver injury: where do we stand?

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Abstract	The coronavirus SARS-CoV-2 was identified as the cause of COVID-19, a severe acute respiratory syndrome. Several clinical studies refer to liver injury as the most frequent clinical extrapulmonary manifestation. In this review, we summarize the available clinical data concerning liver injury during COVID-19. Although the underlying mechanism of liver impairment is somewhat unclear, transaminases and bilirubin levels are elevated in a substantial proportion of patients. Moreover, more severe alterations in liver enzymes may correlate with a worse clinical course of COVID-19. However, several other cofactors, such as drug-induced liver injury, hyper-inflammatory response to infection, hypoxic hepatitis or preexisting underlying liver disease, cannot be excluded.

Keywords Coronavirus, SARS-CoV-2, COVID-19, liver injury

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Introduction

At the end of 2019, a novel coronavirus (SARS-CoV-2) was identified as the cause of a severe acute respiratory syndrome (coronavirus disease 2019, COVID-19) in Wuhan, a city in the Hubei Province of China. It rapidly spread as an epidemic throughout China, finally resulting in a worldwide pandemic [1]. According to the European Centre for Disease Prevention and Control, up to 02 June 2020 a total of 6,245,352 cases of COVID-19 have been reported, including 376,427 deaths [2].

Pneumonia and respiratory failure appear to be the most frequent serious manifestations of COVID-19, while the spectrum of illness severity ranges from mild (most cases) to critical disease, with an overall case fatality rate of 2.3% [3,4]. However, despite its "respiratory preference", COVID-19 can be recognized as a systemic disease with multiple organ involvement. In this context, recently published data have described abnormal liver function tests, mainly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST),

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as the most common extrapulmonary finding in COVID-19 cases [5,6].

The exact underlying pathophysiology and the clinical implication of COVID-19-associated liver injury have not yet been fully determined, while much research regarding this issue is ongoing. Based on previous experience, the role of coronaviruses in generating liver injury has been documented in patients infected by the SARS-CoV coronavirus, described as an acute respiratory syndrome back in 2003 [7]. While the presence of SARS-CoV-2 has been confirmed in liver tissue, it is unclear whether the liver injury can be caused directly by the coronavirus itself [8-10]. Interestingly, both SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the target cell [8]. However, while it was demonstrated that the ACE2 receptor is expressed in the biliary epithelial liver cells, liver injury in COVID-19 patients is mainly revealed as hepatocyte injury documented by ALT and AST elevation [11]. Thus, an alternative pathophysiology of liver injury may be implicated in these patients [5,12]. One hypothesis is that it may be the result of the characteristic immune-mediated damage and systemic inflammation caused by a hyper-activated response to COVID-19, described in patients with severe clinical manifestations [12,13]. Other possible explanations and alternative mechanisms, such as drug-induced liver damage (DILI) associated with paracetamol, antivirals (remdesivir, lopinavir/ritonavir), antimicrobials (macrolides, quinolones, beta-lactams, chloroquine), or nonsteroidal anti-inflammatory drugs (NSAIDs), and hypoxic hepatitis due to respiratory or cardiac failure in severe cases, cannot be ruled out [10,12].

This review aims to summarize the available data concerning the extent and the role of liver injury as an extrapulmonary manifestation of COVID-19. A literature search in the PubMed database was conducted until 16 April 2020 for studies of

COVID-19. A keyword-base search included the entries "COVID-19" OR "nCOV" OR "novel-coronavirus OR "SARS-CoV-2 AND "liver" OR "transaminases" OR "gastrointestinal". We excluded 2 studies published in Chinese. Finally, we included 22 studies with characteristics of liver injury (liver test abnormalities) in COVID-19 patients.

Clinical studies of liver injury in COVID-19 patients

The first report of liver injury due to COVID-19 was by Chen *et al* [3]. In a total of 99 Chinese patients who had COVID-19, with a mean age of 55.5±13.1 years, the majority of them being male, mild elevations of AST and ALT were recorded in 35% and 28%, respectively. Only one patient experienced a marked elevation of transaminase levels (ALT 7590 U/L and AST 1445 U/L). Moreover, albumin levels were decreased in 98% of the patients, while total bilirubin was increased in 18%. However, 50% of the patients had chronic diseases, with 11% reported as having chronic digestive diseases; it was not clear whether these patients had underlying liver disease. The significance of the aminotransferase elevation was not analyzed further and remained unclear, while there was no comment about the clinical course and the outcome of the patient who presented with acute hepatitis.

Another study from China described retrospectively the clinical course of COVID-19 in 62 patients. In this cohort, 16.1% of the patients experienced AST elevation ≥40 U/L [14]. However, the authors mentioned that 11% of the patients had preexisting liver disease. A further study of radiological findings from 81 patients with COVID-19 revealed that more than half of them (53%) also had mildly elevated AST levels [15].

In the first large multicenter study, which included 1099 patients from 522 hospitals in China with laboratory-confirmed COVID-19 (median age 47 years, 42% female, 23.7% having at least one coexisting illness), abnormal liver function tests (AST, ALT and total bilirubin) were recorded in 22.2%, 21.3% and 10.5% of the cases, respectively [16]. No further data were available in this report regarding the impact of the abnormal liver function tests on the patients' general clinical course.

In general, most of the studies from China describe a prevalence of abnormal liver function tests of 20-50%. However, recently published data among 80 imported cases (not Wuhan) of COVID-19 revealed that, compared to cases in Wuhan, liver dysfunction is uncommon (3.75%) [17].

Clinical studies of liver injury in critically ill COVID-19 patients

In a retrospective single-center study of 138 confirmed patients with pneumonia due to COVID-19, the median AST and ALT levels were reported to be significantly higher in patients who had been treated in the intensive care unit (ICU), rather than in non-ICU beds: 52 (range: 30-70) U/L vs. 29 (21-38) U/L, P<0.001; and 35 (19-57) U/L vs. 23 (15-36) U/L,

P=0.007, respectively. However, in this cohort, the percentage of patients with AST/ALT elevation was not provided [8].

Similarly, in a recently published cohort of 41 patients with laboratory-confirmed COVID-19, 37% of the patients presented AST elevation, while the median levels of ALT and total bilirubin were 32 (21-50) U/L and 0.68 (0.56-0.81) mg/dL, respectively [18]. In accordance with previous reports, the authors also revealed that ICU patients experienced slightly higher levels of AST, ALT and total bilirubin than non-ICU patients.

Cai *et al* reported that 8.7% of 298 patients infected by COVID-19 presented abnormal AST and ALT levels [19]. Cholestatic enzymes, such as γ-glutamyl transferase/alkaline phosphatase (GGT/ALP), were also slightly elevated in a few patients (3.1% and 3.0%). The incidence of liver injury in severe patients (36.2%) was markedly higher than that in mild patients (9.6%).

A retrospective study of the clinical characteristics of 128 laboratory-confirmed COVID-19 cases did not harmonize with previous findings, since AST/ALT levels did not differ significantly between severe and non-severe cases: (28.89±31.83 U/L vs. 43.87±47.8 U/L, P>0.05; and 27.98±25.8 U/L vs. 44.13±36.26 U/L, P>0.05, respectively [20].

In a single-center study that included 52 critically ill adult patients with COVID-19 pneumonia admitted to the ICU, liver dysfunction was recorded in 15 (29%) of them [21]. Finally, 32 (61.5%) patients died, but no difference was recorded in the incidence of liver dysfunction between survivors (30%) and non-survivors (28%). However, in this paper, the term "liver dysfunction" is not clearly defined by the authors. Thus, the proportion of patients with abnormal AST, ALT, total bilirubin and prothrombin time (PT) status is not mentioned.

The evaluation of possible prognostic factors for the presence of refractory COVID-19 was assessed in a very recent retrospective study that included a total of 155 patients. Eighty-five patients were classified as "refractory", defined as not reaching obvious clinical and radiological remission within 10 days after hospitalization [22]. Only AST levels were significantly higher in refractory cases: 37 (25-65) vs. 32 (23-38), P=0.004. However, multivariate analysis revealed that only male sex (P=0.047; odds ratio [OR] 2.206, 95% confidence interval [CI] 1.012-4.809) and anorexia on admission (P=0.030; OR 3.921, 95%CI 1.144-13.443) were risk factors for disease refractoriness.

To identify risk factors for death in patients with COVID-19, a retrospective cohort study included 191 patients (54 non-survivors and 137 survivors) [23]. ALT levels were statistically significantly different between non-survivors and survivors: 40 (24-51) vs. 27 (15-40), P=0.005. However, multivariate analysis revealed that in-hospital mortality was associated only with older age (OR 1.1, 95%CI 1.03-1.17, per year increase; P=0.0043), with a higher sequential organ failure assessment (SOFA) score (OR 5.65, 95%CI 2.61-12.23; P<0.0001), and with a d-dimer test above 1 μg/mL (OR 18.42, 95%CI 2.64-128.55; P=0.0033) on admission.

Apart from Chinese studies, data from the first patients with COVID-19 admitted to 2 hospitals in New York City were published very recently [24]. This retrospective case

series included 393 patients, of whom 130 (33%) developed respiratory failure leading to invasive mechanical ventilation. Liver cirrhosis was recorded in 6/393 (1.5%) of the patients. Regarding laboratory findings, AST and AST elevation (>40 U/L) were present in 46.5% and 32% of the patients respectively, while total bilirubin elevation (>1 mg/dL) was documented in 9.1%. The patients who required mechanical ventilation were more likely to have elevated liver function tests than patients with no invasive mechanical ventilation (AST 63% vs. 38%, ALT 37.5% vs. 29.1%, total bilirubin 14.1% vs. 6.5%). Eventually, 40 (10.2%) patients died, but no death was due to liver failure (obviously not even cirrhotic patients).

Clinical studies dealing with general gastrointestinal (GI) symptoms and especially with COVID-19-induced liver injury

Recently, Luo *et al* evaluated a large cohort of 1141 patients with COVID-19, focusing on the GI symptoms, finally recorded in 183 (16%) patients. As previously described, a mild increase in serum aminotransferases was noted: AST 65.8±12.7 U/L and ALT 66.4±13.2 U/L [25].

Very recently, researchers from the Shanghai Public Health Clinical Center included in a retrospective study (still in press) 148 confirmed COVID-19 cases from January 20 to January 31, 2020 [26]. The aim of this study was to characterize COVID-19-related liver damage. Their analysis revealed that the 50.7% of patients who presented with abnormal liver functions at admission were more likely to be male (62.67% vs. 38.36%, P=0.005) and had a higher fever (44% vs. 27.4%, P=0.035). Moreover, the utilization rate of lopinavir/ritonavir after admission was significantly higher in patients with emerging liver injury than in patients with normal liver tests. However, the only significant impact of the presence of liver injury was a relatively prolonged length of hospital stay.

In the same context, the first published study is a retrospective study of 79 non-ICU hospitalized patients with COVID-19 at the Jinyintan Hospital from February 2 to February 23, 2020, comparing their clinical characteristics in relation to liver injury [6]. In order to evaluate the role of SARS-CoV-2 in liver injury, the authors did not include patients with viral hepatitis, alcoholic liver disease, liver malignancy or other known chronic liver disease. Although ALT and AST levels were elevated in 31.6% and 35.4% of the cases, respectively, their median values were <3× the upper limit of normal (ULN) at baseline. Moreover, the median value of bilirubin was 0.74 (0.47-0.9) mg/dL, with normal ALP and GGT. Trying to assess some correlations, logistic regression analyses in this study revealed that the extent of pulmonary lesions on computed tomography was a predictor of liver function damage (OR 5.265, 95%CI 1.025-1.371, P=0.022).

Another retrospective study enrolled a large number of patients (N=651), of whom 74 (11.4%) presented with GI symptoms [27]. Liver dysfunction was more common in the group of GI patients than in the non-GI patients: 13/74 (17.57%) vs. 51/577 (8.84%), respectively, P=0.035. Interestingly, only AST levels were statistically significantly higher in GI patients than in non-GI patients: 29.35 (20.87-38.62) vs. 24.4 (19.0-32.0), respectively, P=0.02. However, multivariate analysis of risk factors for the severe/critical patients with COVID-19 with GI symptoms did not indicate AST/ALT as a significant variable.

In accordance with these results, Pan *et al* recently evaluated the clinical characteristics of COVID-19 patients with GI symptoms [28]. Among 204 patients (age 52.9±16 years, 107 men), about half of them (103 patients; 50.5%) reported a GI symptom, while AST/ALT elevations were recorded in less than 15% of the patients. Some indexes of liver function, namely AST, ALT and PT, were significantly higher in GI patients than in non-GI patients (35.12±26.58 vs. 27.48±23.98, P=0.032; 42.24±43.83 vs. 29.53±23.58, P=0.011; 13.13±1.88 vs. 12.53±1.89, P=0.024, respectively). Although digestive symptoms became more pronounced in accordance with COVID-19 severity, there was no significant difference in discharge time, days of intensive care or mortality between GI and non-GI patients.

Cai *et al* recently evaluated the clinical characteristics of 417 laboratory-confirmed COVID-19 patients with abnormal liver tests [29]. Liver test abnormality was defined by the elevation of ALT >40 U/L, AST >40 U/L, ALT and total bilirubin >1 mg/dL, while patients with ALT and/or AST >3x ULN were classified as having hepatocyte-type liver injury. The authors compared liver function tests on admission and during hospitalization concerning COVID-19 severity. On admission, 170 (41%) patients had abnormal liver test results, while 33 (5%) had signs of hepatocyte-type liver injury. The presence of abnormal liver tests became more pronounced during hospitalization within 2 weeks, while 26.7% of the patients progressed to severe pneumonia. Moreover, patients with hepatocyte-type injury or mixed-type injury (the combination of both ALT/AST >3× ULN and GGT/ALP >2× ULN) at admission had higher odds of progressing to severe pneumonia (OR 2.73, 95%CI 1.19-6.3, and OR 4.44, 95%CI 1.93-10.23, respectively). However, during hospitalization, the use of lopinavir/ritonavir was correlated with liver injury (OR 4.44 to 5.03, both P<0.01), indicating a possible DILI as cofactor. Moreover, a liver biopsy from one patient who died showed that liver function impairment during hospitalization could be partly due to the drugs used for treatment, or due to sepsis and shock. The authors concluded that patients with abnormal liver tests had higher risks of progressing to severe disease, but the detrimental effects on the liver were mainly related to certain medications used during hospitalization.

Preliminary results from a multicenter cohort with 70 patients (67 non-severe disease) with COVID-19 indicated liver injury (ALT, AST or bilirubin above normal value) on admission in 45.71% of them [30]. The hospitalization days were not statistically significantly different between patients with or without liver injury: 16 (12-20) vs. 15 (10-22.5), P=0.81. Since the study population did not receive any medication before admission, the liver injury in these patients was probably caused by a coronavirus-mediated mechanism.

Table 1 Characteristics of liver injury (liver test abnormalities) from various COVID-19 studies

Patients (N)	Preexisting liver disease, (%)	AST elevation, (%)	AST levels, U/L	ALT elevation, (%)	ALT levels, U/L	Total bilirubin elevation, (%)	Total bilirubin levels, mg/dL	PT prolongation, (%)	PT, sec	Liver failure, n (%)	Reference
99	-	35	34 (26-48)	28	39 (22-53)	18	0.88±0.43	5	11.3±1.9	0	Chen 2020 [3]
79	excluded	35.4	30 (23-50)	31.6	34 (18-67)	5.1	0.8 (0.51-1.03)	-	-	0	Xie 2020 [6]
138	2.9	-	31 (24-51)	-	24 (16-40)	-	0.57 (0.49-0.82)	58	13 (12.3-13.7)	0	Wang 2020 [8]
36	-	58.06	43 (30-51)	13.33	26 (18-38)	12.9	0.66 (0.44-1.12)	-	-	0	Huang 2020 [13]
62	11	16.1	26 (20-32)	-	22 (14-34)	-	-	-	-	0	Xu 2020 [14]
81	9	53	-	-	46.2±29.5	-	0.7±0.21	-	10.7±0.9	0	Shi 2020 [15]
1099	2.3	22.2	-	21.3	-	10.5	-	-	-	0	Guan 2020 [16]
80	1.25	3.75	30 (19-39)	3.75	24 (12-38)	1.25	0.39 (0.32-0.7)	0	0.8 (9.3-13.2)	0	Wu 2020 [17]
41	2	37	34 (26-48)	-	32 (21-50)	-	0.68 (0.56-0.81)	-	11.1 (10.1-12.4)	0	Huang 2020 [18]
298	2.7	8.7	48 (30-65)	8.7	48 (24.5-59.5)	3.1	0.82 (0.58-1.29)	-	-	0	Cai 2020 [19]
128	-	-	30.63±18.85	-	31.35±20.36	-	-	-	-	0	Cao 2020 [20]
52	-	-	-	-	-	-	-	-	-	-	Yang 2020 [21]*
85	4.5	-	32 (24-48)	-	23 (16-38)	-	-	-	-	-	Mo 2020 [22]
191	-	-	-	31	30 (17-46)	-	-	6	-	0	Zhou 2020 [23]
393	1.5	46.5	-	32	-	9.1	-	-	-	0	Goyal 2020 [24]
183	-	-	65.8±12.7	-	66.4±13.2	-	-	-	-	-	Luo 2020 [25]
148	-	21.6	(37-107)	18.2	(41-115)	6.1	(1.23-2.73)	-	-	0	Fan 2020 [26]
74	10.81	-	29.35 (20.87-38.62)	-	25.0 (15.75-38.47)	-	-	-	-	-	Jin 2020 [27]
204	0.98	10.78	31.36±25.55	13.23	35.98±35.82	-	0.8±0.6	-	12.83±1.91	0	Pan 2020 [28]
417	5.04	18.22	26.5 (21-35)	12.9	21 (15-31)	23.74	0.64 (0.49-0.95)	-	-	2 (0.5)	Cai 2020 [29]
70	-	7.14	(42.9-61)	21.43	(42-72.7)	35.71	(1.05-8.65)	-	-	0	Qi 2020 [30]
82	2.4	61.1	72 (30-71)	30.6	26 (18.5-47.5)	30.6	0.8 (0.58-1.34)	-	13.2 (12.3-14.3)	1 (1.2)	Zhang 2020 [31]

Categorical data are presented as percentages and continuous data as medians with interquartile range (IQR) or mean±SD, depending on the original study

*Liver dysfunction was assessed as 29%

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time

Data concerning liver injury in deceased cases of COVID-19

These data are supported by 2 studies so far. The first was performed by Zhang *et al*, who presented an interesting study that evaluated the clinical characteristics of 82 death cases with COVID-19 [31]. Respiratory failure was the leading cause of death (69.5%), followed by sepsis syndrome/multiple organ dysfunction syndrome (28.0%), while liver injury was recorded in 78% of the patients. One patient died from liver failure, while the authors observed a significant association between AST, ALT levels and time from initial symptom to death. The other study with 36 non-survivors due to confirmed COVID-19 revealed elevation of ALT and AST in 13.33% and 58.06% of the patients, respectively [13].

Concluding remarks

In this review, we have summarized the recent reports of COVID-19-related liver injury, data that are obviously changing rapidly day by day. Although the pathophysiology behind liver injury in COVID-19 remains unresolved, several theories have been proposed, but a multifactorial mechanism seems most likely. Undoubtedly, the available clinical data so far show that the incidence of liver impairment in COVID-19 ranged from 6-61%, mainly indicated by abnormal ALT/AST levels (Table 1). However, most of the cases experienced a mild AST/ALT elevation (usually <3× ULN), accompanied by slightly elevated bilirubin levels. Since ACE2 receptors are expressed especially in the bile ducts, one may suppose that patients should have some degree of cholestasis or jaundice. However, this seems not to be the case in everyday practice and, remarkably, even ICU patients did not present with elevated ALP/GGT.

Although the rate of developing liver injury was higher in patients with severe clinical manifestations of COVID-19 than in mild patients, these differences were statistically non-significant in all studies. Moreover, the role of liver dysfunction as a potent predictor of severe COVID-19 manifestation or death was not documented by all selected studies [23,24]. However, in a recently published study, patients with abnormal liver tests had a higher risk of progressing to severe disease [29]. Moreover, in a death case study, one patient died from liver failure and a significant association was revealed between AST and ALT levels and time from initial symptom to death [31].

The possibility of DILI during hospitalization, and other cofactors, such as hypoxic hepatitis, as causes of liver dysfunction, or rhabdomyolysis as a cause of elevated liver enzymes cannot be easily ruled out in clinical practice [29,32]. There are only limited available data linking underlying liver diseases with the course of SARS-CoV-2 infection (pre-existing liver disease ranged from 2-11% in the available data). The European Association for the Study of the Liver and the European Society of Clinical Microbiology and Infectious Diseases have issued a position paper, providing recommendations for clinicians who care for patients with chronic liver diseases during the current COVID-19 pandemic [33]. This position paper promotes telemedicine in the outpatient setting and suggests avoiding nosocomial dissemination. Additionally, the paper provides recommendations to prevent acetaminophen overdosing, to prevent administration of any NSAID, to continue treatment for cirrhosis-associated complications, to avoid reducing immunosuppressive therapy in patients with autoimmune liver diseases, to include testing for SARS-CoV-2 in patients with acute decompensation or acute on chronic liver failure, and to consider early admission according to the presence of additional risk factors.

In conclusion, the experience so far of clinicians and researchers worldwide suggests that attention should be paid to liver function in all patients infected by COVID-19, but slight/moderate abnormalities are likely to be of small importance. However, during the course of the disease, one of the important issues which should be taken into consideration is the use of drugs that may induce DILI in these patients (especially when study protocols are scheduled). Finally, increased surveillance with careful monitoring of serum hepatic enzymes is imperative, especially in hospitalized patients or those with liver comorbidities.

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