

Incidence, patterns, risk factors, and histopathological findings of liver injury in coronavirus disease 2019 (COVID-19): a scoping review

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) exhibits many extrapulmonary manifestations, including liver injury. This scoping review aimed to provide insight into the incidence, patterns, risk factors, histopathological findings, and relationship with disease severity of COVID-19-associated liver injury. Furthermore, we identified existing gaps in the research on the hepatic manifestations of COVID-19 and highlighted areas for future investigations.

Methods: A scoping review was conducted following the methodological framework suggested by Arksey and O'Malley. Five online databases, along with grey literature, were searched for articles published until 22 May 2020, and we included 62 articles in the review. The research domains, methodological characteristics, and key conclusions were included in the analysis.

Results: Retrospective observational studies comprised more than one-third (41.9%) of the included publications, and 77.8% were conducted on living patients. The incidence of liver injury varied widely across the studies (4.8%-78%), and liver injury was frequently associated with severe COVID-19. We identified the following risk factors for liver injury: male sex, lymphopenia, gastrointestinal involvement, old age, increased neutrophil count,

and the use of hepatotoxic drugs. Histopathological findings indicate that COVID-19 has direct cytopathic effects and causes liver function test derangements secondary to inflammation, hypoxia, and vascular insult.

Conclusions: Liver injury following COVID-19 infection is common and primarily hepatocellular, with a greater elevation of aspartate aminotransferase than of alanine aminotransferase. However, the evidence regarding hepatic failure secondary to COVID-19 is insufficient. Standardised criteria to diagnose liver injury need to be devised. Current use of hepatotoxic drugs necessitates close monitoring of liver function.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has spread to 213 countries and territories, posing a severe threat to public healthcare systems worldwide. As of 29 May 2020, the total number of confirmed cases has surged to 5 701 337, with 357 688 deaths recorded worldwide.¹ Although multiple pharmacological agents are being evaluated, no beneficial, targeted drug or vaccine has been discovered to date, and the number of cases is rising daily. The causative agent of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is believed to be transmitted through respiratory droplets and person-to-person contact. However, evidence of viral RNA in the faeces of COVID-19 patients also suggests the possibility of faecal-oral transmission.^{2,3} The disease typically presents with viral pneumonia-like symptoms of

fever, dry cough, shortness of breath, and fatigue. Nevertheless, gastrointestinal symptoms like diarrhoea, vomiting, and abdominal pain have also been reported.⁴

Although coronavirus mainly targets the respiratory system, it also exhibits many extrapulmonary manifestations. Sepsis, acute cardiac injury, multiple organ failure, and alkalosis are some of the critical complications that have been observed in patients who die of COVID-19.⁵ Several studies have acknowledged the presence of liver injury in patients with COVID-19, mainly indicated by abnormal liver function tests (LFTs).^{6,7} The exact pathophysiology behind the LFT derangements is unknown. It has been suggested that SARS-CoV-2 causes liver injury either via direct viral insult or through an inflammatory cytokine storm.⁸ Other potential mechanisms, such as drug-induced

hepatotoxicity and hypoxic injury, have also been implicated.

Given the rampant nature of SARS-CoV-2 and its repercussions on human health, the research community has responded expeditiously to the new virus, and studies regarding its systemic involvement are continuously being published. We have conducted a scoping review to summarise all articles published regarding hepatic damage in this setting. In this review, we aim to provide evidence of the incidence, patterns, risk factors, and histopathological findings of liver injury in COVID-19 and its association with the severity of disease. Furthermore, we highlight hepatotoxicity in patients with COVID-19 who are treated with antiviral (lopinavir/ritonavir) or antimalarial (hydroxychloroquine) drugs. We identify the existing gaps in current knowledge regarding the topic and provide recommendations for further research. This will help healthcare providers to identify hepatic complications during the pandemic.

Methods

Study design

A scoping review was conducted following the methodological framework of Arksey and O'Malley⁹ by taking the following steps: (a) identification of a definite research objective and search strategy; (b) identification and screening of research articles; (c) selection of research articles according to pre-defined eligibility criteria; (d) extraction and charting of data, and (e) reporting, summarising, and discussing the results.

Literature search strategies

The reviewed literature was identified by searching five online databases (PubMed, Google Scholar, Scopus, Wiley, and ScienceDirect) without any language restriction from 1 January 2020 to 22 May 2020. Grey literature was also searched in medRxiv and bioRxiv. Moreover, the reference lists of all identified articles were searched for additional sources. A variety of keywords were employed, according to the following search string: "liver injury" OR "hepatic damage" OR "liver functional abnormality" OR "cirrhosis" OR "decompensated liver disease" OR "acute liver failure" OR "chronic liver failure" OR "acute on chronic liver failure" AND "COVID-19" OR "SARS-CoV-2" OR "coronavirus disease". The full electronic search strategy is provided in the online supplementary Appendix.

Identification, screening, and selection of relevant studies

We aimed to summarise all of the scientific literature demonstrating liver dysfunction in COVID-19 and to identify the gaps in knowledge regarding hepatic

2019冠狀病毒病 (COVID-19) 造成肝損傷的發生率、模式、危險因素和組織病理學發現：範圍性綜述

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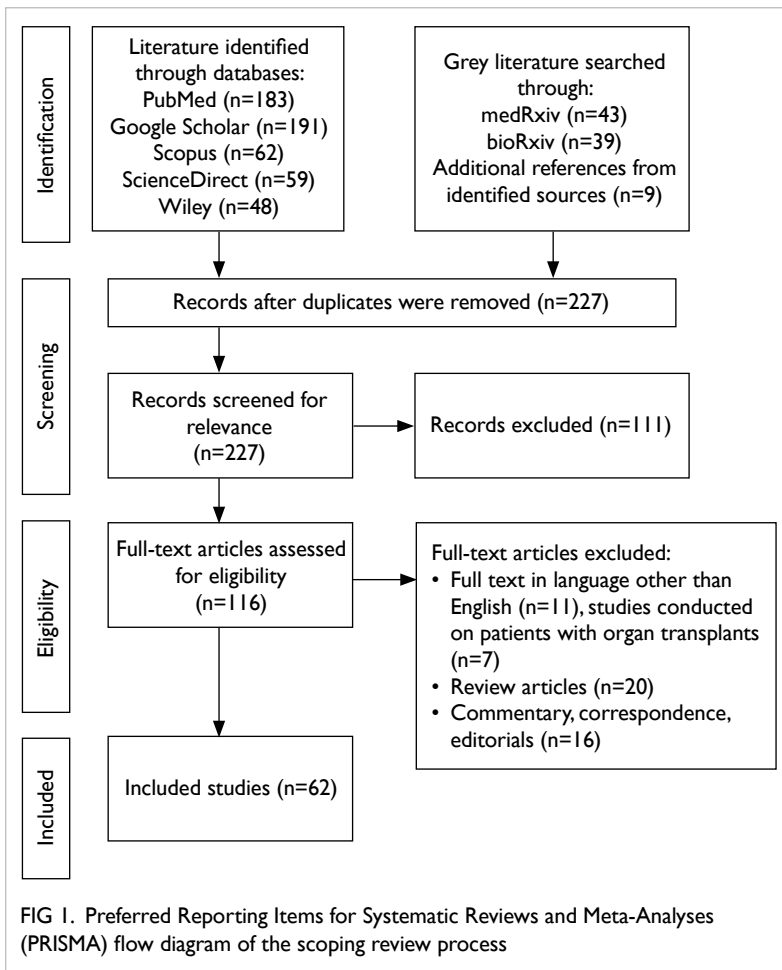
背景：2019冠狀病毒病 (COVID-19) 具有許多肺外表現，當中包括肝損傷。本範圍性綜述旨在探入了解與COVID-19相關肝損傷的發生率、模式、危險因素、組織病理學發現，以及與疾病重度關係。此外，我們在文獻中找出COVID-19肝表現和需要進一步研究領域的存在差距。

方法：根據Arksey和O'Malley建議的方法框架進行範圍性審查。搜索了五個在線數據庫以及灰色文獻，以查找直到2020年5月22日為止發表的文章。共納入62篇文章，分析它們的研究領域、方法學特徵和主要結論。

結果：62篇文章中，超過三分之一為回顧性觀察研究 (41.9%)，有關倖存患者的研究佔77.8%。這些研究當中，肝損傷的發生率存在很大差異 (4.8%-78%)，並且肝損傷通常與嚴重COVID-19相關。研究也確定以下肝損傷的危險因素，包括男性、淋巴細胞、胃腸道受累、老年、中性粒細胞數目增加以及使用肝毒性藥物。組織病理學發現顯示COVID-19會直接影響細胞病變，引起繼發於炎症、缺氧和血管損傷的紊亂。

結論：COVID-19常造成肝損傷，主要是肝細胞，與丙氨酸轉氨酶相比，天冬氨酸轉氨酶的上升幅度更大。不過，有關COVID-19繼發肝衰竭的證據不足。應當制定診斷肝損傷的標準化標準。使用肝毒性藥物時必須對肝功能進行密切監測。

damage in SARS-CoV-2 infection for further research. Three researchers (TBA, SK, and MSS) independently searched through the literature, and all sets of literature were then compared. Disagreements on the inclusion or exclusion of literature were resolved through discussion or, if necessary, by including a fourth researcher (HH) to make the final decision. Articles were screened according to pre-defined eligibility criteria. The inclusion criteria were as follows: (1) study design: retrospective observational study, retrospective cohort study, retrospective descriptive study, prospective observational study, prospective case-cohort, cross-sectional, case report, case series, or meta-analysis; (2) language: studies published in English only; (3) publication status: preprints and published articles; (4) dates considered: studies published from 1 January 2020 to 22 May 2020; and (5) all relevant papers describing functional abnormalities of the liver in COVID-19. The exclusion criteria were as follows: (1) language: articles published in any language other than English; (2) study design: review article, editorial, letter to the editor, correspondence, or commentary; and (3) studies conducted on patients who had undergone organ transplants. Duplicate articles were excluded. Ultimately, 62 articles were included in this review conducted in accordance with the Preferred



Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (Fig 1).¹⁰

Data extraction and charting from included studies

After article selection, data were extracted and recorded on a pre-designed datasheet. The extracted data included the article's title, study design, study setting, study population, sample size, research domain, and key conclusions.

Summarising the studies

The articles that assessed liver injury in patients with COVID-19 belong to two categories: (a) studies that employed pre-defined clinical criteria for liver injury in COVID-19, and (b) studies that did not employ any pre-defined criteria and only reported LFT derangements in COVID-19. Based on the primary research objectives, each article was classified into one of the following main research domains: incidence of liver injury, patterns of liver injury, and risk factors for liver injury in COVID-19, associations of liver injury or underlying liver disease (eg, chronic liver disease) with the severity of COVID-19, drug-induced liver injury in COVID-19, and histopathological findings of

liver injury in COVID-19. The methodological characteristics (study design, study setting, type of population, and sample size) of all studies were also analysed.

Results and discussion

Characteristics of studies

A total of 62 articles were included in this scoping review, among which 10 were preprints, and 52 were published in peer-reviewed journals, including *The Lancet* and *Journal of the American Medical Association*. About 23 studies (16 retrospective observational, 2 retrospective cohort, 1 retrospective descriptive, 1 prospective observational, 1 prospective case-cohort, 1 cross-sectional, and 1 meta-analysis) documented the incidence of liver injury in COVID-19.¹¹⁻³³ Around half of the eligible studies (n=29, 46.8%) showed an association between the severity of COVID-19 and the degree of liver injury.^{11-17,19-23,28,29,34-48}

Out of the 27 studies assessing liver injury in COVID-19, 44.4% (n=12) had pre-defined clinical criteria for liver injury, whereas 55.6% (n=15) did not have any specific pre-defined criteria. The details of these studies are given below. The studies predominantly depicted significant elevation of aspartate aminotransferase (AST) than of alanine aminotransferase (ALT) in case of liver injury, which was found to be proportional to the severity of COVID-19.

Fewer studies (n=6) mentioned any histopathological findings of liver injury in patients with COVID-19, but the most common findings mentioned were mild sinusoidal dilatation, microvesicular steatosis, and minimal lymphocytic infiltration.^{36,49-53} Eight studies assessed the impact of drugs on potential liver damage. Half of those studies (n=4, 50%) concluded that the use of lopinavir/ritonavir increases the odds of liver injury. Other drugs described as having the potential to cause hepatotoxicity in COVID-19 included hydroxychloroquine (n=1, 12.5%), tocilizumab (n=2, 25%), and remdesivir (n=1, 12.5%).^{12,18,54-59}

The methodological characteristics of the finalised studies were also analysed. The largest number of the studies were retrospective observational studies (n=26, 41.9%), followed by meta-analyses (n=10, 16.1%), case reports (n=9, 14.5%), case series (n=7, 11.3%), prospective observational studies (n=3, 4.8%), and others (Table 1). All studies except for meta-analyses, case reports, and series included a targeted population. Among the 36 articles with a targeted population, more than three-quarters (n=28, 77.8%) were conducted only on living patients with COVID-19, whereas the remainder (n=8, 22.2%) included patients who died. Of the finalised studies, 38.9% (n=14) had sample sizes of 5 to 60. The included

studies' methodological characteristics are given in Table 1.

Incidence of liver injury in patients with COVID-19

Several observational studies documenting the clinical characteristics of patients with COVID-19 have reported liver injury.¹¹⁻³³ They have mentioned liver enzyme elevation without commenting on the clinical signs of hepatic dysfunction, which include hepatomegaly, ascites, and jaundice.^{11-30,32} The incidence of liver injury has varied widely across studies, from 4.8% to a striking 78%.¹¹⁻³³ However, the term 'liver injury' has not been defined uniformly. The definitions used in various studies have ranged from slight transaminasaemia to enzyme elevation more than 3 times higher than the upper limit of normal (Table 2^{11,12,16-18,20,22-24,31-33}). Additionally, several studies did not establish any clinical or laboratory criteria to define liver injury (Table 3^{13-15,19,21,25-29,34,35,37,46,60}). Many studies failed to mention the date on which LFTs were performed, thus creating non-uniformity in their reported values. Case reports have identified the presence of liver injury across the entire age spectrum, ranging from 55 days to 65 years.^{50,57,58,61,62}

Pathogenesis of liver dysfunction in COVID-19

The pathogenesis of liver involvement in COVID-19 infection is assumed to be multifactorial. However, none of the available hypotheses provide a complete explanation, and further investigation is required not only to understand the mechanism but also to formulate appropriate management plans. Figure 2 illustrates the possible mechanisms of hepatic dysfunction in COVID-19.

Direct viral invasion

The proposed receptor for the virus, angiotensin-converting enzyme 2 receptor (ACE2R), has been found only sparsely in hepatocytes. Chai et al⁶³ demonstrated ACE2 expression in 2.6% of hepatocytes, whereas up to 59.7% of cholangiocytes expressed ACE2R. Seow et al⁶⁴ also revealed the presence of ACE2 in liver progenitor cells, especially those destined to become cholangiocytes. These findings imply direct invasion of cholangiocytes and progenitor cells, thus resulting in necrosis and impaired regeneration of cholangiocytes. The tight junctions between cholangiocytes also seem to be altered during COVID-19 infection, which may be responsible for the observed cholestasis in patients.⁶⁵ Significant necrosis of and rapid viral replication within cholangiocytes has also been observed by Zhao et al⁶⁵ in a human liver ductal organoid model.

However, Zhou et al⁶⁶ argued against this proposed mechanism by highlighting that ACE2Rs

on cholangiocytes are confined to the apical surface, from where viral invasion is unlikely. Furthermore, the hepatic pattern of LFT elevation fails to explain this possible ductal pathology. Hepatocytes also express the protein furin, which may play a role in liver damage upon entry of the virus into the cells.

Hypoxia

Decreased oxygen saturation has been a feature of COVID-19 pneumonia, and this may result in hypoxic injury to multiple organs, including the liver.⁶⁷

High positive end expiratory pressure

High values of positive end expiratory pressure used during mechanical ventilation in severe patients may result in hepatic congestion by increasing the pressure on the right atrium and thereby impeding venous return. However, the presence of comparable liver functional abnormalities in patients without ventilation renders that assumption inconclusive.⁶⁸

Systemic inflammation and cytokine storm

An inflammatory response to the virus may lead to persistent leukocytic activation and the release of many mediators responsible for cellular injury. The involvement of a cytokine storm in liver damage has been supported by patients' elevated levels of interleukins 2, 6, and 10, interferon-gamma, serum ferritin, and C-reactive protein.¹⁷

TABLE 1. Methodological characteristics of studies

Methodological characteristics of studies	Categories	No. (%)
Study design	Prospective case-cohort	1 (1.6%)
	Retrospective descriptive	2 (3.2%)
	Case series	7 (11.3%)
	Case report	9 (14.5%)
	Meta-analysis	10 (16.1%)
	Retrospective observational	26 (41.9%)
	Cross-sectional	1 (1.6%)
	Prospective observational	3 (4.8%)
	Retrospective cohort	3 (4.8%)
Type of study population (excluding meta-analyses and case reports/series)	Total studies with a targeted population	36
	Patients (alive)	28 (77.8%)
	Patients (deceased)	8 (22.2%)
Sample size (excluding meta-analyses and case reports/series)	5-60	14 (38.9%)
	61-150	10 (27.8%)
	151-300	4 (11.1%)
	301-500	5 (13.9%)
	>500	3 (8.3%)

TABLE 2. Summary of COVID-19 studies with pre-defined criteria for liver injury/hepatic dysfunction

Author	Study type	Study location	Sample size	Clinical criteria for liver injury/hepatic dysfunction	Incidence of liver injury/hepatic dysfunction, % (n)	Liver function tests (median [IQR] or mean [SD])	Risk factors of liver injury/hepatic dysfunction	Study notes
Cai et al ¹²	Cross-sectional study	Shenzhen, China	417	ALT and/or AST 3 times ULN; ALP, GGT and/or TBIL 2 times ULN	21.5% (90)	ALT = 21 (15-31)* AST = 26.5 (21-35)* TBIL = 10.9 (8.3-16.3)*	Use of lopinavir/ritonavir	Patients with liver injury (ALT = 47 [38-65.2]* U/L; AST = 47.2 [30.9-63.8]* U/L) were at increased risk of severe disease Liver injury was mainly caused by medications used during hospitalisation
Cai et al ¹⁶	Retrospective observational	Shenzhen, China	298	ALT and/or AST 3 times ULN; GGT and/or TBIL 2 times ULN	14.8% (44)	ALT = 21 (15-30.7)* AST = 27.3 (22-36.3)* TBIL = 10.9 (8.2-15.9)*	Use of drugs such as lopinavir and ritonavir	Liver injury was mainly observed in severe patients (ALT = 42 [28-78]* U/L; AST = 38 [23-65.5]* U/L) and is likely to be an outcome of drugs used to treat the infection
Fan et al ¹⁸	Retrospective observational	Shanghai, China	148	Liver function tests above ULN	37.2% (55)	-	Male sex, elevated CRP/PCT, use of lopinavir/ritonavir	COVID-19-related liver injury may be relatively mild Liver injury may be related to the use of lopinavir/ritonavir
Lei et al ²²	Retrospective cohort	Hubei, China	5771	ALT 3 times ULN	6.2% (357)	ALT = 24.0 (15.1-39.0)* AST = 24.0 (17.0-35.0)* TBIL = 10.4 (7.9-14.1)* ALP = 64.0 (51.0-83.0)*	Male sex, systemic corticosteroids, increased neutrophil count, decreased lymphocyte count, and fever	Patients with severe disease had higher AST levels (31.0 [21.0-46.0]* U/L) compared with those who had non-severe disease (22.0 [17.0-31.0]* U/L). Elevated AST was associated with high mortality risk
Hajifathalian et al ²³	Retrospective observational	New York, United States	1059	Elevated ALT, AST, ALP, or TBIL	62% (657)	ALT = 49.5 (64.9)† AST = 59.5 (78.5)† TBIL = 11.97 (10.26)† ALP = 88.1 (74.1)†	Old age	In-patients had a statistically significant increase in AST compared with out-patients (62.1 [82.1]† vs 46.4 [56.2]† U/L) Liver injury at presentation was an independent predictor of poor clinical outcomes (ICU admission or death)
Jin et al ²⁴	Retrospective observational	Zhejiang, China	651	AST <40 U/L ALT <50 U/L	9.8% (64)	-	GI symptoms	Incidence of liver injury in patients with GI symptoms was higher than that in those without GI symptoms (17.57% vs 8.84%). AST was significantly higher in patients with GI symptoms
Xie et al ¹⁷	Retrospective observational	Wuhan, China	79	Elevated AST, ALT, or TBIL	36.7% (29)	ALT = 34 (18-67)* AST = 30 (23-50)* TBIL = 13.6 (8.8-17.6)*	Male sex, increased WBC and neutrophil count, elevated CRP, lung lesions on CT	Severe lung lesions on CT may be related to higher incidence of liver injury. In patients with liver injury, GGT and ALP levels were also elevated compared with those in patients without liver injury
Wang et al ¹¹	Retrospective observational	Beijing and Anhui, China	156	ALT or AST <40 U/L for >7 days	41% (64)	-	-	Liver enzyme abnormality was associated with severe disease, higher A-aDO ₂ and GGT, and lower albumin and lymphocytes

Abbreviations: A-aDO₂ = alveolar-arterial oxygen tension difference; ALP = alkaline phosphatase (U/L); ALT = alanine aminotransferase (U/L); AST = aspartate aminotransferase (U/L); COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; GGT = gamma-glutamyl transferase (U/L); GI = gastrointestinal; ICU = intensive care unit; IQR = interquartile range; PCT = procalcitonin; SD = standard deviation; TBIL = total bilirubin (μmol/L); ULN = upper limit of normal; WBC = white blood cell

* Data are shown as median and IQR (in parentheses)

† Data are shown as mean and SD (in parentheses)

TABLE 2. (cont'd)

Author	Study type	Study location	Sample size	Clinical criteria for liver injury/hepatic dysfunction	Incidence of liver injury/hepatic dysfunction, % (n)	Liver function tests (median [IQR] or mean [SD])	Risk factors of liver injury/hepatic dysfunction	Study notes
Bloom et al ²⁰	Prospective observational	Massachusetts, United States	60	Grade 0: AST <40 U/L or ALT <55 U/L (male); AST <32 U/L or ALT <33 U/L (female) Grade 1: AST = 41-120 U/L or ALT = 34-99 U/L (male); AST = 33-96 U/L or ALT = 34-99 U/L (female) Grade 2: AST = 121-200 U/L or ALT = 166-275 U/L (male); AST = 97-160 U/L or ALT = 100-165 U/L (female) Grade 3-4: AST >201 U/L or ALT >276 U/L (male); AST >161 U/L or ALT >166 U/L (female)	Grade 0: 7% (4) Grade 1: 54% (32) Grade 2: 22% (13) Grade 3-4: 17% (10)	ALT = 39 (24)† AST = 55 (37)† TBIL = 0.9 (2.2)†	Severe disease	AST in patients requiring intubation was significantly higher compared with the level in those without intubation (364 [572] vs 77 [54])†
Chen et al ⁵¹	Retrospective observational	Wuhan, China	21	Jaundice with TBIL of ≥ 3 mg/dL and ALT 5 times ULN and/or ALP 2 times ULN	4.8% (1)	ALT = 26 (16-42)* AST = 27 (21-47)* TBIL = 8.8 (6.8-10.3)*	-	ALT and AST were significantly higher in severe cases (ALT = 42 [32.5-50]* U/L; AST = 47 [28-74.5]* U/L) than moderate cases
Qi et al ³²	Multicentre cohort	China	70	ALT <40 U/L, AST <40 U/L, TBIL <17.1 μ mol/L	45.7% (32)	-	Longer time from onset of illness to admission	-
Zheng et al ³³	Retrospective observational	Hangzhou, China	34	ALT 2 times ULN or conjugated bilirubin or combined increase in AST, ALP, and TBIL provided that one of them was >2 times ULN	41.2% (14)	ALT = 20 (20-30)* TBIL = 12 (7.6-18.6)*	Receiving invasive mechanical ventilation	-

Endothelial dysfunction

Liver dysfunction may occur secondary to vascular pathology, resulting in endotheliitis, coagulopathy, thrombus formation, and ischaemic parenchymal necrosis. Angiotensin-converting enzyme 2 receptors are expressed on the endothelium, making it susceptible to viral invasion, which leads to the recruitment of inflammatory cells and elaboration of inflammatory cytokines. The immune response may also exacerbate the damage.⁶⁹

Drug-induced hepatotoxicity

A number of drugs currently in use have hepatotoxic potential, which might be further exaggerated in the setting of chronic liver disease (CLD).^{12,56,58} The mechanisms for individual drugs are not clearly defined.

Patterns of liver injury in COVID-19

The patterns of liver injury in COVID-19 patients include both reversible dysfunction and irreversible injury as a component of multiorgan failure in terminally ill patients.^{40,57-59,61,62} However, hepatic dysfunction in COVID-19 cases is usually mild, and

deranged LFTs tend to recover within a few days after discharge.⁴⁸ Predominant elevation of ALT and AST indicates hepatocellular injury.¹² The abnormalities in AST have been more severe compared with those of ALT.^{20,22,23,34,37,44,45} This finding is intriguing, as ALT, being more liver-specific, is the enzyme that is generally expected to be significantly elevated in case of hepatocellular injury. However, a few studies have hypothesised that AST elevation could be secondary to viral-mediated direct liver damage.^{20,21} The mechanism behind predominant AST elevation in the presence of viral aetiology remains unclear.

Elevation of the ductal enzymes gamma-glutamyl transferase and alkaline phosphatase (ALP) has been reported in some studies.^{22,23,70} Elevated ALP was also reported alongside elevated AST and ALT in a case of acute hepatitis following COVID-19 infection.⁶¹ Cardoso et al⁷¹ studied the temporal patterns of liver enzyme levels in critically ill patients and observed that a cholestatic pattern emerged later in the course of illness. Most studies have not mentioned the presence of any liver enzyme abnormalities at the time of liver injury. Hence, the extent of liver damage and the pattern of injury could not be accurately assessed.

TABLE 3. Summary of studies without pre-defined criteria for liver injury/hepatic dysfunction in COVID-19

Author	Study type	Study location	Sample size	Incidence of liver injury/hepatic dysfunction, % (n)	Liver function tests (median [IQR]/mean [SD])	Risk factors of liver injury/hepatic dysfunction	Study notes
Cholankeril et al ²¹	Retrospective observational	California, United States	116	40% (26 of 65)	ALT = 32 (22-48)* AST = 35 (22-58)* TBIL = 6.84 (5.13-11.97)*	-	Severity of COVID-19 was correlated with elevated AST
Wan et al ³⁴	Case series	Chongqing, China	135	-	ALT = 26 (12.9-33.15)* AST = 33.4 (27.8-43.7)* TBIL = 8.6 (5.9-13.7)*	-	Patients with severe disease had higher AST levels (33.6 [25.7-44.2]* U/L) than patients with non-severe disease (22.4 [16.9-30.5]* U/L)
Zhang et al ²⁹	Retrospective observational	Wuhan, China	82	78% (64)	ALT = 30.5 (22.0-102.5)* AST = 74.5 (35.5-184.0)*	-	There was a significant correlation between AST, ALT, and time from initial symptom to death
Ding et al ¹³	Retrospective descriptive	Wuhan, China	5	60% (3)	ALT = 18 (7-63)* AST = 22 (15-56)* TBIL = 5.3 (4.3-8)*	-	Liver injury was more commonly seen in patients with severe COVID-19
Du et al ²⁵	Retrospective observational	Wuhan, China	85	35.3% (30)	ALT = 72.9 (199.5)† AST = 94.4 (263.3)† TBIL = 18.44 (13.61)†	-	-
Fu et al ¹⁵	Prospective case-cohort	Wuhan and Fuyang, China	355	28.5% (101)	ALT = 23.0 (15.0-42.0)* AST = 29.0 (23.0-54.0)* TBIL = 10.9 (8.0-16.2)*	Male sex, old age, diabetes mellitus, lymphopenia	Patients who were critically ill had higher levels of ALT (33.0 [19.0-61.0]* U/L) and AST (49.0 [35.0-80.0]* U/L) than those who were not. Liver injury at an early stage of disease increased death risk
Li et al ¹⁴	Retrospective observational	Beijing, China	85	38.8% (33)	ALT = 28.0 (19.5-44.5)* AST = 29.0 (20.5-38.5)* TBIL = 9.2 (6.4-12.1)*	Old age, drinking history, increased CRP, decreased lymphocyte count	Liver injury was more commonly seen in patients with severe COVID-19
Li et al ²⁶	Retrospective observational	Wuhan, China	25	20% (5)	ALT = 24 (16.5-46)* AST = 37 (29.5-57.5)*	-	In addition to the lungs, the liver was the third most commonly damaged organ in deceased patients
Lian et al ²⁷	Retrospective observational	Zhejiang, China	465	13.1% (61)	ALT = 27.95 (22.49)† AST = 28.37 (17.56)† TBIL = 11.52 (7.02)†	-	-
Zhou et al ³⁵	Retrospective observational	Sichuan, China	366	-	-	Chronic liver disease	Chronic liver disease is a risk factor for the development of severe disease
Yang et al ¹⁹	Retrospective observational	Wuhan, China	92	16.3% (15)	ALT = 27 (3-1693)* AST = 31 (11-6000)* TBIL = 13.6 (4.2-439.0)*	-	Liver injury was commonly seen in deceased patients with COVID-19
Yang et al ²⁸	Retrospective observational	Wuhan, China	52	29% (15)	-	-	Liver dysfunction was commonly seen in critically ill patients with COVID-19. Survivors' TBIL was lower than that of non-survivors (13.1 [4.3]† vs 19.5 [11.6]† µmol/L)
Yang et al ²⁸	Retrospective observational	Wuhan, China	52	29% (15)	-	-	Liver dysfunction was commonly seen in critically ill patients with COVID-19. Survivors' TBIL was lower than that of non-survivors (13.1 [4.3]† vs 19.5 [11.6]† µmol/L)
Wang et al ³⁷	Retrospective observational	Wuhan, China	339	-	ALT = 27 (17-44)* AST = 32 (23-46)*	-	Patients who died had higher AST levels than survivors (43 [30-68]* vs 29 [22-43]* U/L). There was no significant difference in ALT levels between the two groups
Wu et al ⁴⁶	Retrospective cohort	Wuhan, China	201	-	ALT = 31.00 (19.75-47)* AST = 33.00 (26-45)* TBIL = 11.45 (9-14.75)*	-	Liver function indices in patients with ARDS were increased as compared to those without ARDS, ie, TBIL (difference: 1.90 µM; 95% CI=0.60-3.30 µM; P=0.004)
Qi et al ⁶⁰	Case series	Hubei, China	3	-	ALT = 26 (19-44)* AST = 42 (41-103)* TBIL = 40.4 (22.2-62.5)*	Decompensated liver cirrhosis	-

Abbreviations: 95% CI = 95% confidence interval; ALT = alanine aminotransferase (U/L); ARDS = adult respiratory distress syndrome; AST = aspartate aminotransferase (U/L); COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; IQR = interquartile range; SD = standard deviation; TBIL = total bilirubin (µmol/L)

* Data are shown as median and IQR (in parentheses)

† Data are shown as mean and SD (in parentheses)

Histopathological findings of liver injury in COVID-19

Histopathological findings of autopsied liver samples have provided evidence of direct viral invasion and changes secondary to hypoxia, sepsis, and pro-inflammatory and pro-coagulant states. Wang et al¹¹ revealed the presence of hepatic apoptosis, occasional bi- or multi-nucleated hepatocytes, mitochondrial swelling, and decreased glycogen granules. These findings strongly suggest direct cytopathic effects of COVID-19 on the liver. Electron microscopy also showed the presence of viral particles. Other non-specific findings have included varying degrees of steatosis,^{11,12,49-52} mild portal lymphocytic infiltration,^{11,36,50,51} mild sinusoidal dilation,^{36,51,53} and inflamed cells within the sinusoids.¹² However, samples obtained via needle biopsy did not facilitate effective determination of the histology of the ductal epithelium, which carries a higher density of ACE2Rs.⁵¹ Ductal pathology was highlighted by Lax et al,⁵² indicating the presence of canalicular cholestasis and mild nuclear pleomorphism of cholangiocytes. Patterns of both massive and focal patchy necrosis were reported in the periportal and centrilobular areas.^{51,52} The authors suggested that sepsis and systemic inflammation might be responsible for acute hepatic necrosis. Furthermore, reverse transcription-polymerase chain reaction of one liver sample was positive for COVID-19.⁵¹ In that case, an ultrasound-guided autopsy observed centrilobular congestion (which was likely attributable to shock), ischaemic necrosis, portal tract inflammation, and Kupffer cell activation.⁵¹

The watery degeneration of some hepatocytes observed by Cai et al¹² was likely due to ischaemia and hypoxia. The presence of thrombi within the liver, among other organs, also demonstrates the possibility of COVID-associated coagulopathy.⁵² Liver involvement with COVID-19 infection may further elaborate the inflammatory cascade and alter the secretion of coagulation factors, thus playing a role in causing widespread thrombosis.⁵² Endotheliitis, acute and chronic vascular changes, and sinusoidal arterialisation due to pressure elevation observed in the liver further support the involvement of underlying endothelial pathology in causing coagulative derangements.^{53,69}

Liver injury as a marker of the severity of COVID-19

Studies have consistently shown liver injury to be associated with severe COVID-19.^{11-16,34,42-44} Deranged LFTs have also been linked to prolonged hospital stays¹⁸ and worse clinical outcomes.^{19,38,40,45} Disease severity is most likely linked with the elevation of AST rather than ALT.^{20,21,45} Additionally, hypoproteinaemia and cholestasis in early-stage disease have been shown to increase the risk of

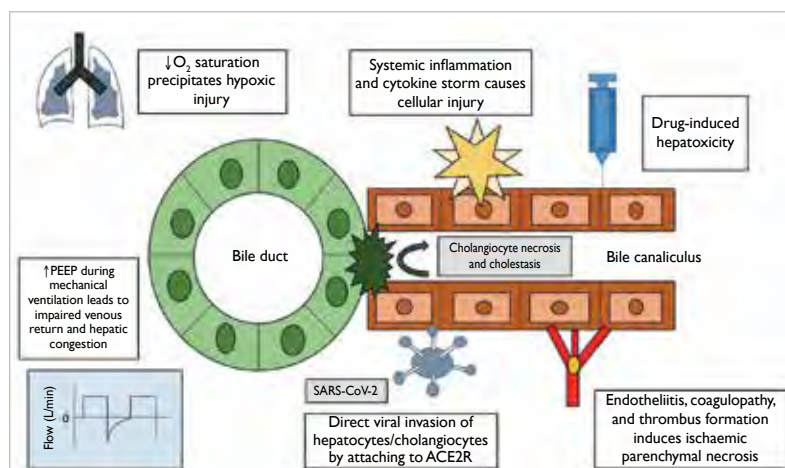


FIG 2. Pathogenesis of COVID-19-associated liver dysfunction

Abbreviations: ACE2R = angiotensin-converting enzyme 2 receptor; COVID-19 = coronavirus disease 2019; O₂ = oxygen; PEEP = positive end expiratory pressure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

death.¹⁵ However, the impact of AST on mortality has been controversial.^{22,46}

These findings cannot reliably establish that elevated LFT levels were solely caused by COVID-19 infection, as many studies did not exclude patients with CLD, nor did they consider other possible reasons for liver enzyme elevation. Furthermore, there is still not enough evidence to suggest that mild derangement has a high likelihood of progressing into fulminant liver failure. Yet, patients with deranged LFT patterns of the hepatocellular or mixed types at the time of admission or during hospitalisation were more likely to progress to severe disease,^{12,47} thus necessitating adequate monitoring.^{38,44,45,48} Additionally, there is no evidence that liver dysfunction can directly cause mortality in patients with COVID-19.

Risk factors for liver injury in COVID-19

Studies have reported associations between multiple risk factors and liver injury in the setting of SARS-CoV-2 infection:

1. Abnormal white blood cell parameters, including elevated neutrophils and decreased lymphocytes, have been associated with elevated risk of liver injury.^{14,15,17,22} The loss of lymphocytes responsible for suppression of the immune response during viral infection may have contributed to the damage.¹⁴ Similarly, high levels of C-reactive protein and procalcitonin were associated with increased risk of liver damage.^{14,17,18} The cytokine storm and systemic inflammation might be implicated, as they result in leukocyte activation and the release of a large quantity of inflammatory mediators that directly or indirectly damage cells.¹⁴
2. The use of hepatotoxic drugs, including antivirals,

- hydroxychloroquine, tocilizumab (discussed below),^{12,16,18,58} and antifungals for superimposed infections has been established as a risk factor for liver dysfunction.²² Systemic corticosteroids were also associated with an increased risk of AST elevation,²² perhaps due to drug-induced lymphopenia and alteration of the immune response.
3. A correlation between the severity of lung involvement and the incidence of liver injury has also been noticed.¹⁷ As severe lung lesions indicate a robust inflammatory state, the liver might be affected for the same reason (ie, a hyperinflammatory state).¹⁷ That study did not indicate the role of hypoxia, which is also a possible contributing factor to hepatic damage.
 4. Non-modifiable risk factors such as male sex (odds ratio=1.60; $P<0.001$) and old age (odds ratio=1.01; $P=0.031$) have been linked to a higher risk of liver damage.^{22,23}
 5. Patients with elevated ALT levels were more likely to have a history of drinking ($P=0.032$).¹⁴ However, that study did not comment on elevation of AST, the dominant enzyme involved in both alcoholic liver disease and COVID-19. Furthermore, that study's very small sample size necessitates further investigation of this risk factor.
 6. Patients with gastrointestinal symptoms were more likely to have liver injury than those without such symptoms ($P=0.035$).²⁴
 7. Diabetes mellitus was a risk factor for cholestasis in patients with COVID-19 ($P=0.044$),¹⁵ which is predicted to be a possible mechanism of liver injury in the setting of viral infection.⁶⁵
 8. Invasive mechanical ventilation increased the risk of LFT elevation⁴² and acute liver injury.³³ Such injury may be caused by hepatic congestion that results from elevated right atrial pressure, which in turn is caused by high levels of positive end expiratory pressure.⁶⁸

Drug-induced hepatotoxicity in COVID-19

The drugs currently used to manage COVID-19 infection also carry hepatotoxic potential. Muhović et al⁵⁶ reported a 40-fold rise in transaminases following two doses of tocilizumab, an interleukin-6 receptor antagonist, which regressed 10 days later. Morena et al⁵⁹ also reported elevated liver enzymes in 29% of patients who were receiving tocilizumab. In addition, Falcão et al⁵⁸ reported a 10-fold elevation in transaminases following two doses of hydroxychloroquine. Upon withdrawal, the enzyme levels dropped to near normal after 5 days.

Antivirals have also been demonstrated to cause liver toxicity. In one study, people receiving lopinavir/ritonavir had a higher incidence of liver dysfunction compared with those in whom these

drugs were not administered (51.8% vs 31.3%, respectively).¹⁸ Similarly, Young et al⁵⁵ reported abnormal LFTs in three out of five patients receiving lopinavir/ritonavir. According to Cai et al,¹² the use of lopinavir/ritonavir increased the likelihood of liver injury 4-fold. Durante-Mangoni et al⁵⁴ reported that remdesivir caused elevation of liver enzymes in three out of four patients, and Weber et al⁵⁷ suggested that drugs may play a role in precipitating acute liver failure. Administration of lopinavir/ritonavir and interferon was followed by progressive worsening of LFTs. This effect may have been attenuated by the use of Ramipril for arterial hypertension.⁵⁷ Additionally, Lei et al²² showed that elevated AST and ALP levels were associated with the use of antifungal medications. The above findings are from case reports, retrospective studies, and very small-scale prospective studies. Further large-scale prospective studies, including randomised controlled trials, need to be conducted to establish their efficacy and safety in patients with COVID-19.

Chronic liver disease and COVID-19

The effects of underlying liver disease on the severity of COVID-19 are controversial. Zhou et al³⁵ suggested the presence of CLD as a risk factor for severe COVID-19. However, that study included only eight known cases of CLD. Similarly, Qi et al⁶⁰ indicated that decompensated liver cirrhosis might be a risk factor for poor outcomes of COVID-19. In contrast, a meta-analysis by Wang et al⁷² that included five studies concluded that prior liver disease does not impact the severity of COVID-19. Likewise, the presence of pre-existing cirrhosis had no direct prognostic association in the setting of COVID-19.⁷³ Some studies in our review included patients with CLD, which may account for some of the LFT derangements observed in patients. A meta-analysis by Mantovani et al⁴¹ estimated that the baseline prevalence of CLD was 3%. This figure is much lower than the proportion of people with liver dysfunction. Hence, the role of CLD in worsening the prognosis of COVID-19 infection seems to be minor, if there is any.

Nevertheless, acute-on-chronic liver failure (ACLF) following COVID-19 infection has been reported. One case was a female patient with decompensated alcoholic cirrhosis (ACLF Grade 2) who developed a mixed hepatic and cholestatic pattern of liver dysfunction following COVID-19 infection. However, her prognosis was good.⁷⁴ Another patient was an older man with ACLF Grade 1 non-alcoholic cirrhosis. He developed hepatorenal syndrome-type acute kidney injury following COVID-19 infection. His liver failure subsequently progressed to Grade 2 after catheter-associated urinary tract infections and complicated paracentesis.⁷⁵

Oro-faecal transmission and liver injury

Cui et al⁶¹ revealed that anal swabs of an infant with liver injury remained positive for COVID-19 even after throat swabs returned to a negative state. However, polymerase chain reaction of stool samples was not performed in most of the articles included in our review. The association of liver dysfunction with the risk of oro-faecal transmission remains to be investigated. If transmission via this route is possible, existing isolation and discharge protocols may need to be revised.

Limitations and recommendations

Our review is subject to certain limitations. First, the majority of the included studies did not have any specific pre-defined clinical criteria for diagnosing liver injury in COVID-19. Moreover, the included studies did not distinguish between a history of liver disease (eg, CLD) and liver injury secondary to COVID-19. Hence, our results need to be interpreted cautiously, as they do not accurately describe the level of incidence of liver injury that is caused by COVID-19. Second, we did not include studies published in any language other than English, which might have provided additional insight. Third, the inclusion of a large number of studies prevented us from critically appraising the individual studies' sources of evidence. There is a need for a comprehensive systematic review or meta-analysis to summarise the statistics and provide a clearer picture of liver injury in SARS-CoV-2 infection. Transplant recipients, a group that is vulnerable to liver injury, were also not reviewed.

Many studies have defined 'liver injury' as non-specific elevation of LFTs above the upper limit of normal. Further, many of the investigated studies did not assess the bilirubin levels or coagulation profiles of patients with COVID-19, both of which are important indicators of liver function. Moreover, there have been no reports of liver failure or hepatic cell death secondary to COVID-19 to date. Hence, we recommend the use of scientifically relevant terms 'liver dysfunction' or 'liver enzyme derangement' to explain non-specific LFT abnormalities until an appropriate definition for liver injury is devised. Furthermore, we propose that pre-defined criteria for liver injury should be set and that mild, non-specific derangements of liver function should not be labelled as liver injury. Given the existing controversy in the literature, we recommend a thorough investigation into the pathogenesis of liver injury, especially the mode of direct viral invasion.

Additional studies are required to investigate whether mild derangement of liver function can cause hepatic failure in COVID-19. The reason for the hepatocellular pattern with predominant AST elevation also needs to be elucidated. Finally, the safety and efficacy of hepatotoxic drugs in COVID-19

should also be established via randomised controlled trials.

Conclusion

Liver injury is a common extrapulmonary feature of COVID-19. However, the absence of standardised clinical criteria for liver injury in this setting needs to be addressed. Derangements of LFT levels are markers of the severity of COVID-19 infection, but the association between LFT derangements and disease progression requires further investigation because to date, liver dysfunction has not been shown to directly cause mortality in patients with COVID-19. The pattern of injury is predominantly hepatocellular, accompanied by greater elevation of AST than of ALT. Possible pathogenetic mechanisms include direct viral invasion, hypoxia, systemic inflammation, endothelial dysfunction, and the use of mechanical ventilation. Histopathological findings in the liver support viral-induced pathology in addition to non-specific changes. Nevertheless, these studies are sparse, and more research is required. Potentially hepatotoxic drugs have also been observed to cause liver injury in patients with COVID-19, and thus, the administration of these drugs necessitates careful monitoring. Large-scale studies are needed to establish their role in the management of COVID-19.

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Critical revision of the manuscript for important intellectual content: T Bin Arif, H Sohail.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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