Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTER TO THE EDITOR

Covid-19 and hepatic injury: A systematic review

After observing patients with pneumonia of unknown cause in Wuhan (China), a novel Coronavirus was identified as 2019 novel coronavirus (COVID-19). Gastrointestinal symptoms are common in COVID-19 and can be present in up to 26% of patients in some populations; the most common is diarrhoea, followed by nausea and/or vomiting and abdominal pain. A few studies recently described liver impairment as a common manifestation of the virus; therefore, a correlation between the severity of the disease and liver injury is being sought up.

Previous studies showed that liver injury could be detected using the elevated level of Alanine Aminotransferases (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TBil) followed by slightly decreased Albumin levels [1]. As underlined by Al-Busafi et al. the serum ALT and AST are the best markers of hepatocellular injury, so their elevated values tend to show more severe liver damage [2]. Liver injury is defined by an increase of over twice the upper limit of the normal range (2N) in serum alanine aminotransferase (ALT) or conjugated bilirubin, or a combined increase of aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin, provided one of them is above 2N.

Several authors suggested that liver abnormalities in COVID-19 patients could derive from the presence of viral infection in liver cells or drug toxicity and systemic inflammation.

Mao et al. [3] elaborated a systematic review and meta-analysis of emerging studies describing gastrointestinal symptoms and liver injury in COVID-19 patients with the aim of quantifying the effects of the virus on the digestive system. They analyzed 35 studies, including 6686 patients with COVID-19, mainly adult patients. The analysis of 12 studies showed a pooled prevalence of liver injury, ALT, AST, and Total Bilirubin respectively of 19%, 18%, 21% and 6%. On the one hand, the presence of gastrointestinal symptoms seemed to be associated with severe COVID-19 and with both an increased risk of acute respiratory distress syndrome and liver injury. On the other hand, digestive comorbidities did not determine any risk of severe disease. High levels of ALT, AST and total bilirubin, as indices of liver damage, was found particularly in patients with severe disease [3,4].

The meta-analysis carried out by Zhu et al. [5] summarized the clinical and laboratory characteristics of 8697 Chinese patients with COVID-19, with the aim of gaining a better understanding of the disease for clinical decisions and future research. The study showed as the male gender was the most represented (53,3%), fever and cough were the two major symptoms, and, in particular, abnormal liver function appeared in 26,4% of patients [5]. In the review of Xu et al. [6] about the risk factor of critical illness progression in COVID-19 patients, by the analysis of 20 articles, it emerged that, among the variables analyzed, higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (Tbil) were associated with severe disease. Moreover, the levels of lactate dehydrogenase (LDH), creatine kinase (CK) and D-dimer (D-D) increased significantly in severe patients. Since cytokine storms are involved in COVID-19 disease, the study of abnormal levels of liver enzymes in patients with this virus might be helpful to evaluate the severity of disease.

Xin et al. [7] compared the risk of abnormal liver function tests between severe and non-severe patients affected by the virus. They collected data from eight records, with an overall sample size of 7467 (2187 with severe disease and 5280 with a non-severe disease); the proportion of COVID-19 patients with abnormal ALT and AST levels was respectively of 29% and 29,2%. At the same time, COVID-19 patients with severe disease turned out to have a 37,1% of increase ALT and in 47,4% of increase AST. Also, abnormal TBil values was found in 18% of COVID-19 patients and in 19,8% of severe disease patients. The meta-analysis clenched the idea that the risk of elevated ALT, AST, TBil and LDH was higher for severe patients than in non-severe ones [7]. Parasa et al. [8] in their meta-analysis and systematic review, reported data about elevation of either AST or ALT levels at the time of patients' clinical presentation from 8 studies of 23.

The pooled prevalence of elevated ALT levels was 18,5% of patients and the one of AST levels was 17,7% of patients, when including all studies [8]. In many clinical surveys, liver disfunction has been observed, indicating a possibility that in patients with COVID-19 this may cause hepatic injury. Samidoust et al. [1] reported an occurrence of liver injury

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Table 1 Liver tests abnormalities in patients with SARS CoV-2 infection.

Reference	Sample size	Elevated ALT value	Elevated AST value	Elevated TBil value	Abnormal coagulation factors	Prevalence of liver injury in severe disease
Mao et al. [3]	1267	ALT (18%)	AST (21%)	TBil (6%)	NA	Yes
Zhu et al. [5]	8697	Yes	Yes	Yes	D-dimer (20,4%)	NA
Xu et al. [6]	4062	Yes	Yes	Yes	D-dimer	Yes
Xin et al. [7]	7467	ALT (29%)	AST (29,2%)	TBil (18%)	NA	Yes
Parasa et al. [8]	4805	ALT (18,5%)	AST (17,7%)	NA	NA	Yes (39,4%)
Samidoust et al. [1]	4191	Yes	Yes	Yes	NA	Yes

as a complication of COVID-19, ranged from 14,8% to 53%. It was accompanied by abnormal ALT/AST levels followed by elevated bilirubin levels. In addition, the proportion of liver injury in death cases and severe COVID-19 patients was higher than that in mild patients. The meta-analysis included 4191 COVID-19 patients and 288 death cases. The prevalence of liver injury was 19,5%, instead among the 288 death cases the prevalence of liver injury was 22,8%. Liver damage has been considered as an important risk factor for severe outcomes and death in some viral infections including MERS and SARS [1] (Table 1).

The descriptive study of Chen et al. [4] detected 49 patients with COVID-19, a great part of them reported organ functions damage and 43 patients showed differing degrees of liver function abnormality, with ALT or AST above the normal range, in particular one patient presented sever liver function damage, with ALT 7590 U/L and AST 1445 U/L [4].

Abnormalities in liver chemistries, including aspartate transferase (AST), alanine transferase (ALT), and total bilirubin (TBil), has been described since early observational studies. These data are particularly evident in patients with COVID-19 and severe diseases.

The direct assault of SARS-CoV-2 on hepatocytes could be the first reason that leads to abnormal values of liver enzymes. Even if it seemed that hepatocytes didn't express high-level of ACE2, instead, the expression of high level of ACE2 in cholangiocytes could represent an indirect cause of elevated liver enzymes, as well as a cholangiocyte dysfunction. Against this hypothesis, alkaline phosphatase has not been shown to be high in COVID-19 patients.

Several pro-inflammatory factors reach the liver via blood circulation, which can activate Kupffer cells and lead to more IL-6 release. IL-6 is, in particular, closely related to liver injury in severe COVID-19 patients [7]. Lastly, the occurrence of SARS can lead to hypoxic injury, mainly caused by severe pneumonia and drug-related, and to subsequent liver dysfunction.

A multicenter study in Chinese adults with COVID-19 pneumonia [9] reported a dynamic pattern of liver injury indicators, with a first increase of AST, followed by ALT in severe patients and mild fluctuations of total bilirubin levels independently from disease severity. In this study AST levels were significatively associated with the mortality risk. Despite the absence of a severe cholestatic pattern during COVID-19 disease, hyperbilirubinemia was observed in 11%—18% of cases [10].

Therefore, recent studies suggest that liver biochemical indicators may be used as predictors of severity and prognosis of COVID-19 patients. In the future they could be used as early markers of exacerbation and deterioration of patients with the disease.

Disclosure statement

The authors have nothing to disclose.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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