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OPINION REVIEW

Mechanisms and consequences of COVID-19 associated liver injury: What can we affirm?

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Abstract

Since the first reports of coronavirus disease 2019 (COVID-19) cases in December 2019 in China, numerous papers have been published describing a high frequency of liver injury associated with severe acute respiratory syndrome coronavirus 2 infection, many of them proposing a link between these findings and patient outcomes. Increases in serum aminotransferase levels (ranging from 16% to 62%) and bilirubin levels (ranging from 5% to 21%) have been reported and seem to be more often observed in patients with severe forms of COVID-19. Although absolute changes in these parameters are frequently seen, other variables, such as the ratio above the upper limit of normal, the onset of liver injury as a complication in severe cases and histopathological findings, reinforce that liver changes are of dubious clinical relevance in the course of this disease. Other factors must also be considered in these analyses, such as the repercussions of hemodynamic changes, the presence of thrombotic events, and, mainly, the possible drug-induced liver injury with the current, yet off-label, treatment. This paper aimed to analyze the currently available data on liver injury in patients with COVID-19.

Key words: COVID-19; SARS-CoV-2; Liver injury; Liver enzymes; Drug induced liver

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Core tip: The coronavirus disease 2019 (COVID-19) pandemic has affected millions worldwide, with high lethality. Papers have been describing liver injury but with divergent results; some have suggested a positive relationship between liver involvement and severity of infection. To evaluate this matter, some aspects, such as the frequency and severity of liver enzyme abnormalities, should be analyzed according to clinical and histopathological findings; other associated factors, such as interactions with the drugs used in COVID-19 treatment, should be analyzed as well. An overview of the aspects related to liver injury during COVID-19 infection was analyzed in this study according to evidence known to date.

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INTRODUCTION

The first reports of what is now known as coronavirus disease 2019 (COVID-19) came out in December 2019 in China, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the COVID-19 etiologic agent, subsequently spread worldwide. Currently, more than 200 countries have been affected, with approximately 3 million confirmed cases and more than 200000 deaths to date (as of May 5th, 2020). Severe disease is observed in up to 20% of affected patients with a lethality rate that may eventually exceed 10%[1-4].

Recently, many papers have been published reporting gastrointestinal manifestations, including acute liver injury, with increased levels of aminotransferases, in COVID-19 patients; these manifestations have been reported more frequently in patients with severe forms of this disease. However, there is a wide variation of these findings in different studies[5-18].

Despite frequent reports of liver injury in patients with COVID-19, some questions remain: What is the liver enzymes' curve and how often do they rise above the upper limit of normal (ULN) serum level? Are these abnormalities correlated with COVID-19 disease severity? Can increased serum aminotransferase levels reflect the degree of injury? What is the liver injury frequency in cases with a severe course of disease with complications and death? What do histopathological findings suggest? Are the liver parenchymal changes due to the systemic disease consequences or a direct effect of SARS-CoV-2? May drug use for COVID-19 be the cause of liver injury?

FREQUENCY OF INCREASE IN LIVER FUNCTION ENZYMES IN COVID-19 PATIENTS

Liver injury related to SARS-CoV-2 disease has been defined by increased liver enzyme serum levels, mainly aminotransferases and bilirubin, during the infection course in patients with or without previous liver disease[5-18]. Wide variability in deviations of liver enzyme serum levels from normal values is observed in infected patients, with an elevation frequency ranging from 16% to 62% for aminotransferases and from 5% to 21% for bilirubin. These abnormalities are seen mostly in severe forms of COVID-19 (Tables 1 and 2)[6,10,12,14,16].

In fact, the study by Guan *et al*. found high aminotransferase serum levels in 22% of 757 hospitalized patients, with elevated aspartate transaminase (AST) in 18.2% (112/615) of non-severe patients, in 39% (56/142) of severe patients and in 50% (26/52) in those with complicated outcomes such as intensive care unit (ICU) hospitalization, mechanical ventilation or death. In addition, bilirubin values above the ULN were present in 13.3% of non-severe patients and 20.8% of severe patients[6].

Table 1 Different studies that evaluates liver enzymes according to disease severity and treatment protocol

	n	Disease severity, *n* (%)	Death, *n* (%)	Complications, *n* (%)	Treatment (%), Antiviral therapy; Antibiotic therapy; Antimalarial	Treatment (Drugs)
Xie *et al*[12]	79	Moderate: 51 (64.5%), Severe: 28 (2.5%)	0	NR	NR	NR
Huang *et al*[5]	41	Non-severe: 28 (68.3%), Severe: 13 (31.7%)	6 (15%)	Acute respiratory distress: 12 (29%); Acute cardiac injury: 5 (12%); Acute kidney injury: 3 (7%); Secondary infection: 4 (10%); Shock: 3 (7%)	All patients: AV (93%); AB (100%) Non-ICU care: AV (93%); AB (100%) ICU care: AV (92%); AB (100%)	Antiviral: Oseltamivir Antibiotic: NR
Guan *et al*[6]	1099	Non severe: 926 (84.3%), Severe: 173 (15.7%)	15 (1.4%)	Acute respiratory distress: 37 (3.4%); Acute kidney injury: 6 (0.5%); Septic Shock: 12 (1.1%); Disseminated intravascular coagulation: 1 (0.1); Rhabdomyolysis: 2 (0.2)	All patients: AV (35.8%); AB (58%) Non-severe: AV (33.8%); AB (53.8%) Severe: AV (46.2%); AB (80.3%)	Antiviral: Oseltamivir Antibiotic: NR
Zhang *et al*[13]	115	Non severe: 84 (73%), Severe: 31 (27%)	1 (0.9%)	NR	NR	NR
Cao *et al*[31]	128	Non severe: 107 (83.6%), Severe: 21 (16.4%)	0%	NR	NR	NR
Chen *et al*[9]	99	Non severe: 76 (77%), Severe (ICU): 23 (23%)	11 (11%)	Acute respiratory injury: 8 (8%); Acute kidney injury: 3 (3%); Septic Shock: 4 (4%); Ventilator-associated pneumonia: 1 (1%)	All patients: AV (76%), AB (71%)	Antiviral: Oseltamivir, ganciclovir, lopinavir/ritonavir Antibiotic: Cephalosporins, quinolones, carbapenems, tigecycline, linezolid
Richardson *et al*[18]	5700	Non severe: 4414 (77.4%), Severe (ICU): 1286 (22.6%)	553/2634 (21%)	Acute kidney injury: 1370 (24%); Acute Hepatic injury 89 (1.6%)	NR	NR
Zhang *et al*[10]	221	Non severe: 166 (75%), Severe: 55 (25%)	12 (5.4%)	Acute respiratory injury: 48 (21.7%); Acute kidney injury: 10 (4.5%); Acute cardiac injury: 17 (7.6%); Arrhythmia: 24 (11%); Shock: 15 (6.8)	All patients: AV (88.7%) Non-severe: AV (88%), Severe: AV (90.9%)	Antiviral: NR Antibiotic: NR
Bhatraju *et al*[11]	24	Severe: 24 (100%)	12 (50%)	Shock: 17 (71%)	All patients: AV (29.2%)	Antiviral: Remdesivir
Zhou *et al*[8]	191	General: 72 (38%), Severe: 66 (35%); Critical: 53 (28%)	54 (28%)	Sepsis: 112 (59%); Respiratory failure: 103 (54%); Heart failure: 44 (23%); Septic shock: 38 (20%); acute cardiac injury: 33 (17%); Acute kidney injury: 28 (15%); Secondary infection: 28 (15%)	All patients: AV (21%), AB (95%) Survivors: AV (21%), AB (93%)Non-survivors: AV (22%), AB (98%)	Antiviral: Lopinavir/ritonavir Antibiotic: NR
Pan *et al*[15]	204	NR (total)	36 (17.6%)	NR	All patients: AV (90.2%), AB (64.7%)	Antiviral: Lopinavir/ritonavir Antibiotic: NR
Wang *et al*[7]	138	Non severe: 102 (74%), Severe (ICU): 36 (26%)	6 (4.3%)	Respiratory failure: 27 (19.6%); Arrhythmia: 23 (16.7%); Shock: 12 (8.7%); Acute cardiac injury: 10 (7.2%); Acute Kidney injury: 5 (3.6%)	All patients: AV (89.9%); AB (100%) Non-ICU care: AV (88.2%); ICU care: AV (94.4%)	Antiviral: Oseltamivir Antibiotic: Moxifloxacin, ceftriaxone, azithromycin
Fu *et al*[16]	350	Common: 211 (60.3%), Severe: 88 (25.2%); Critical ill: 51 (14.5%)	34 (9.8%)	NR	NR	NR
Chen *et al*[17]	113	NR	113 (41%)	Type I respiratory failure: 18/67 (27%), Sepsis: 179 (65%), Acute cardiac injury: 89/203 (44%), Heart failure: 43/176 (24%), Acute kidney injury: 29 (11%)	All patients: AV (86%); AB (91%); Recovered: AV (91%); AB (89%) Deaths: AV (79%); AB (93%)	Antiviral: Oseltamivir, arbidol, lopinavir/ritonavir Antibiotic: Moxifloxacin, cefoperazone, or azithromycin

NR: Not report; ICU: Intensive care unit; AV: Antiviral therapy; AB: Antibiotic therapy; AM: Antimalarial.

Moreover, among 24 hospitalized ICU patients, Bhatraju *et al*[11] found increases of 41% and 32% in AST and alanine transaminase (ALT) levels, respectively. Huang *et al*[5,7], when assessing the frequency of abnormalities among 41 patients, found AST alterations in 62% of ICU patients compared to 25% of non-ICU hospitalized patients, similar to the findings in other studies.

According to these findings, the frequency of aminotransferase elevation during COVID-19 is directly related to the disease severity; that is, the higher the COVID-19 severity, the greater the chance of liver enzyme elevation. Then, increases of aminotransferases serum levels would be a predictor factor of severity of SARS-CoV-2 infection.

SERUM LEVELS OF LIVER ENZYMES AND LIVER INJURY

It must be acknowledged, however, that in acute liver injury, hepatocyte necrosis extension is reflected by aminotransferase serum levels. Although these changes are often described in COVID-19 cases, the aminotransferase serum level abnormalities are discrete[6-8,10-16].

In a study by Cao *et al*[14] 107 non-severe COVID-19 patients had a mean AST of 30.63 U/L (30.63 ± 18.85), and even among the 21 severe cases, serum levels were lower than 100 U/L (44.13 ± 36.26)[14]. In another study involving 115 patients, 27% were categorized as severe, and among them, 85% had serum AST levels below 50 U/L, with no cases presenting an AST above 150 U/L and just one case with an ALT level above this value. For bilirubin, only seven cases presented with serum levels higher than ULN (> 21 μmol/L), and they did not exceed 31.5 μmol/L[13].

Using a stratification score for the variability in serum levels among 341 patients, Cai *et al*[19] found 25% of AST abnormalities at admission, with most of these cases (91%) having serum levels between one and two times above ULN; 8% had an elevation range of two and three times above ULN, and only 1% had an elevation above three times the ULN[19].

In the evaluation of cases that progressed to a fatal outcome, the same pattern persisted. In the study by Chen *et al*[17], 52% (59/113) of deceased patients presented an AST increase, with median serum levels of 45 U/L (IQR: 31.0-67.0). On the other hand, only 25 out of 161 (16%) patients who recovered presented AST levels higher than the ULN, with median serum levels of 25.0 (IQR: 20.0-33.3)[17].

In an analysis of 82 deaths, Zhang *et al*[10] compared the aminotransferases and bilirubin values at admission and 24 h before the fatal outcome. The alterations were higher close to the timing of death, with AST, ALT and bilirubin values above the ULN occurring in 70%, 40% and 30.6%, respectively. However, the absolute values

Table 2 Frequency and serum levels of hepatic enzymes abnormalities in different studies

	AST abnormalities %[F1]	Serum levelsAST U/L[F1]	ALT abnormalities %	Serum levelsALT U/L[F1]	Total bilirubinabnormalities %	Serum levels, Total bilirubin mol/L[F1]
Xie *et al*[12]	35.4%	[F2]All patients: 30 (20-50); Moderate: 28 (22-48); Severe: 35 (22-55)	31.6%	[F2]All patients: 34 (18-67); Moderate: 28 (21-43.5); Severe: 36.5 (17.5-71.5)	5.1%	[F2]All patients: 13.6 (8.8-17.6); Moderate: 13.9 (8.9-18.7); Severe: 12.7 (8.1-15.4)
Huang *et al*[5]	[F2]All patients: 37%, Non-ICU: 25%; ICU: 6%	[F2]All patients: 34 (26-48); Non-ICU: 34 (24-40.5); ICU: 44 (30-70)	NR	[F2]All patients: 32 (21-50); Non-ICU care: 27 (19.5-40); ICU care: 49 (29-115)	NR	[F2]All patients: 11.7 (9.5-13.9); Non-ICU care: 10.8 (9.4-12.3); ICU care: 49 (11.9-32.9)
Guan *et al*[6]	All patients: 22.2%; Non-severe: 18.2%; Severe: 39.4%; ICU/IMV/Death: 50%	NR	All patients: 21.3%; Non-severe: 19.8%; Severe: 28.1%; ICU/IMV/Death: 40.8%	NR	All patients: 10.5%; Non-severe: 9.9%; Severe: 13.3%; ICU/IMV/Death: 20.8%	NR
Zhang *et al*[13]	17%	[F2]All patients: 28.3 ± 15.6; ULN ≤ 50 U/L: 85%; 50-150 U/L: 15%; > 150: none	11%	[F2]All patients: 25.71 ± 21.8; ULN: ≤ 50 U/L: 90.4%; 50-150 U/L: 8.7%; > 150: 0.9%	6.96%	[F2]All patients: 11.31 ± 5.8; ULN: ≤ 21 μmol/L: 94%; 21-31.5 μmol/L: 6%
Cao *et al*[31]	NR	All patients: 30.63 ± 18.85; Non-severe: 27.98 ± 25.8; Severe: 44.13 ± 36.26	NR	All patients: 31.35 ± 20.36; Non-severe: 28.89 ± 31.83; Severe: 43.87 ± 47.8	NR	NR
Chen N *et al*[9]	35%	All patients: 34 (26-48)	28%	All patients: 39 (21-55)	18%	All patients: 15.1 ± 7.6
Richardson *et al*[10]	58.4%	All patients: 46 (31-71)	39%	All patients: 33 (21-55)	NR	NR
Zhang *et al*[10]	NR	All patients: 29 (22-49); Non-severe: 27 (20-38); Severe: 51 (29-78)	NR	All patients: 23 (16-39); Non-severe: 22 (14-33); Severe: 32 (22-57)	NR	All patients: 10 (8-14.2); Non-severe: 9.6 (7.9-13.8); Severe: 11.4 (8.6-17.4)
Bhatraju *et al*[11]	41%	NR	32%	NR	NR	0.6 (0.5-0.7)
Zhou *et al*[8]	NR	NR	All patients: 31% Survivor: 24%; Non-survivor: 48%	All patients: 30 (17-46); Survivor: 27 (15-40); Non-survivor: 40 (24-51)	NR	NR
Pan *et al*[15]	NR	All patients: 35.6 ± 59.6	NR	All patients: 35.8 ± 48.5	NR	All patients: 13.3 ± 10.2
Wang *et al*[7]	NR	All patients: 31 (24-51); Non-ICU: 29 (21-38); ICU: 52 (30-70)	NR	All patients: 24 (16-40); Non-ICU: 23 (15-36); ICU: 35 (19-57)	NR	All patients: 9.8 (8.4-14.1); Non-ICU: 9.3 (8.2-12.8); ICU: 11.55 (9.6-18.6)
Fu *et al*[16]	NR	Common: 16 (20-35); Severe: 29 (23-54); Critical ill: 49 (35-80)	NR	Common: 22 (14-35); Severe: 23 (15-36); Critical ill: 33 (19-61)	NR	[F2]Common: 10.4 (7.5-14.7) Severe: 10.9 (8.0-16.2); Critical ill: 12.6 (10.5-17)
Chen *et al*[17]	All patients: 31%; Deaths: 52%;	All patients: 16 (22-46);	All patients: 22%; Deaths: 27%;	All patients: 23 (15-38);	NR	All patients: 9.6 (6.7-13.5);

Recovered: 16%	Recovered: 25 (20-33.3); Deaths: 45 (31-67)	Recovered: 19%	Recovered: 20 (14.2-32); Deaths: 28 (18-57)	Recovered: 8.4 (5.8-11.2); Deaths: 12.6 (9.4-16.7)

[F1]Data is mean ± SD or median.

[F2]Values on admission. ALT: Alanine transaminase; AST: Aspartate transaminase; NR: Not report; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; ULN: Upper limit of normal.

were not as high as supposed, with AST, ALT and bilirubin serum levels averaging 72 U/L (IQR: 30-71), 26 U/L (IQR: 18.5-47.5) and 13.6 μmol/L (IQR: 10-22.9) on admission, respectively, and 74.5 U/L (IQR: 35.5-184), 30.5 U/L (IQR: 22-102.5) and 26 μmol/L (IQR: 18.5-47.5) 24 h before death. Moreover, the authors also compared COVID-19 patients with 119 patients with community-acquired pneumonia due to other etiologies and did not observe significant differences in aminotransferase serum levels[10].

Although uncommon, there have been published reports of significant elevation in liver enzymes, such as the elevations described among 99 COVID-19 patients in the study by Chen *et al*[9], with one case (1%) presenting an ALT of 7590 U/L and an AST of 1145 U/L[9].

According to the studies published so far, liver enzyme serum levels are not very elevated during SARS-CoV-2 infection; most often they are below twice the ULN. These findings suggest that hepatocyte necrosis on the hepatic parenchyma is discrete and that liver injury does not seem to be very relevant. Likewise, serum levels appear to increase according to the progression time of the disease COVID-19 severity. To date, rare cases of high elevations of liver enzymes have been described during COVID-19.

HISTOPATHOLOGICAL FINDINGS

Therefore, the evidence shows that liver injury has little clinical relevance in the course of COVID-19 disease. Nevertheless, liver failure is a rare complication in severe cases, even though hypoxia and shock may contribute to hepatocyte damage. On the other hand, reports of acute respiratory failure, heart failure, acute cardiac injury, acute kidney injury and shock predominate in many studies as more frequent complications and causes of death[5-8,10,13,17,18].

Little is known about how hepatocytes are damaged during SARS-CoV-2 infection. However, years ago, evaluation of three patients with SARS-CoV confirmed the presence of coronavirus in liver tissue by RT-PCR, but the virus was present in low titles because no viral inclusions were observed ultrastructurally[20,21].

Additionally, postmortem histopathological studies show discrete changes in the hepatic parenchyma, and these findings may have multifactorial causes related to the viral mode of action, inflammatory response, adjacent repercussions of systemic

hemodynamic alterations, coagulation disorders or drug induced liver injury (DILI)[22-24].

In a study developed in Milan with 48 liver biopsies from postmortem COVID-19 patients, vascular changes in the portal vein were observed, with an increased number of portal branches, terminal vessel dilations, and thrombi found in portal and sinusoidal vessels. The inflammatory alterations were discrete, with mild portal and lobular infiltrates. The authors suggested that histopathological findings in COVID-19 are suggestive of changes in the intrahepatic blood vessel network secondary to systemic alterations induced by SARS-CoV-2 that could indicate that they are a target, in addition to the lung parenchyma or cardiovascular system. However, they conclude that liver failure is not a major concern in COVID-19 cases, and this organ is not a significant inflammatory injury target[23].

Moreover, some authors suggest that liver injury in COVID-19 may be triggered by viral replication itself within hepatocytes, since SARS-CoV-2 binds cells through the angiotensin-2-converting enzyme, especially in bile epithelium cells[23]. Nevertheless, the low serum aminotransferase levels observed in COVID-19 patients do not suggest that the exacerbated inflammatory response or direct viral injury to hepatocytes is relevant. The pattern of the aminotransferase curve during SARS-CoV-2 infection is different from those observed in hepatitis associated with other epidemic viruses that induce frequent and intense LFT elevations due to diffuse parenchymal necrosis, as found, for example, in patients with dengue or yellow fever[25-28]. In fact, the liver injury found in COVID-19 looks that one observed in other viruses, such as SARS, MERS and influenza[29-31].

Lastly, the liver histopathological findings observed in most patients with COVID-19 are suggestive of vascular abnormalities possibly resulting from increased arterial flow to the liver secondary to cardiac distress and thrombotic phenomena in the portal and sinusoidal vessels[23]. Nonetheless, eventually in some patients might be the involvement of some drug, as antibiotics or antivirals, in the induction of liver injury.

OTHER CAUSES OF LIVER INJURY IN SARS-CoV-2

Other factors may be involved in hepatic enzyme alterations. Several medications used to treat COVID-19, mainly antivirals such as lopinavir/ritonavir and remdesivir, chloroquine and hydroxychloroquine antimalarials, antibiotics including azithromycin, or immune-modulators such as tocilizumab, may lead to DILI. Therefore, physicians should be aware of the LFT profile in response to drug use to help attribute liver injury to the natural history of infection[19,32-39].

Antivirals such as lopinavir/ritonavir and remdesivir that have been recently used for COVID-19 may be associated with liver injuries. DILI from lopinavir/ritonavir has been reported in 2%-10% of patients[32]. Cai *et al*[19] published a trial in which 417 patients using lopinavir/ritonavir presented a higher risk for developing liver injury [OR of 4.44 (P < 0.01)] and higher levels of bilirubin and gamaGT during hospitalization (P < 0.004)[19].

The use of antimicrobials and antibiotics, frequently prescribed for suspicious or confirmed very ill COVID-10 patients, is considered a frequent etiology of DILI[33].

In the reviewed papers, antivirals and antimicrobials were often prescribed to COVID-19 patients, ranging from 21% to 93% and 58% to 100%, respectively and many times they were used simultaneously[5-11,13,17]. Liver enzymes abnormalities were often seen, even in the trials that less frequently used antiviral treatment[6,8,11]. In Zhou *et al*[8] trial, lopinavir/ritonavir was used in around 20% of the patients either they survive or not, and ALT abnormalities was observed in 24% and 48% respectively[8]. There is also a wide variability in antivirals prescribed to patients, such as oseltamivir, remdesivir, lopinavir/ritonavir and ganciclovir. The same is also observed with the use of antimicrobials, either alone or in combination with antivirals and other drugs. This does not allow us to stablish a clear causality relationship or even the amount of importance to the use of this drugs and the liver injury. Besides it the histopathological findings do not suggest a DILI pattern[23].

Hydroxychloroquine (HCQ) has been used, though still off-label, in several countries, despite the limited number of studies published so far and divergent opinions regarding its efficacy. Although hepatotoxicity in users of HCQ is uncommon, LFTs and severe liver dysfunction have been documented[37-40].

Makin *et al*[40] reported two cases of patients with rheumatological disease who, after 2 wk of using 400 mg of HCQ daily, were admitted with fulminant hepatitis; one required a liver transplant, and both patients died[40]. Recently, Falcão *et al*[37] reported

an increase in LFTs in very sick COVID-19 patients on drug treatment, with return to normal levels once the drugs were halted[37].

The mechanisms of hepatic injury related to HCQ are poorly established, and toxicity may be due to reactive metabolites and oxidative stress induced by this drug or an idiosyncratic toxic or synergistic effect associated with inflammatory processes induced by the infection itself[41-43].

More recently, azithromycin in association with HCQ has become a therapeutic option for COVID-19 patients[44,45]. Biliary and hepatocellular injury have been associated with azithromycin use[34-36]. Another report with 18 patients presenting with azithromycin-induced DILI described a wide range of histopathological abnormalities, including hepatitis, veno-occlusive changes and/or central venulitis acute cholestasis and cholestatic hepatitis[35].

Due to the significantly increased use of HCQ and azithromycin during COVID-19 disease treatment, liver toxicity related to these drugs must be considered, and liver abnormalities should not be solely attributable to SARS-CoV-2 infection itself; the high risk of DILI seen in these scenarios should not be neglected. If DILI is suspected, COVID-19 drugs should be promptly halted.

Additionally, it is highly difficult to stablish a causality relationship between a specific drug and liver injury during COVID-19 infection, because most of the times they are used as combination of antimalarials, antivirals, antimicrobials, anticoagulants and sometimes vasoactive drugs. It is also worth remembering that the most severe cases, which do not present favorable evolution, are those where more drugs are administered in the fight against the disease.

CONCLUSION

Despite the common descriptions of liver enzyme abnormalities observed in COVID-19 patients, the frequency, intensity and impact of liver injury are discrete and of little clinical significance regarding morbidity or mortality of this disease. A better understanding of the natural history of liver involvement may be addressed in the near future with well-designed prospective studies regarding viral and immunologic research.

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