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Drug-induced liver injury and COVID-19: A review for clinical practice

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Abstract

Coronavirus disease 2019 (COVID-19) consists of a systemic disease that can present many complications. The infection presents broad clinical symptoms and a high rate of transmissibility. In addition to severe acute respiratory syndrome, the patients manifest complications beyond the respiratory system. The frequency of liver damage in COVID-19 patients ranges from 14.8% to 53% of patients. One should pay attention to drug-induced liver injury (DILI) in patients with COVID-19, especially considering the off-label use of drugs in prophylactic and therapeutic regimens applied on large scales. This review aims to present relevant information on the medication used so far in COVID-19 patients and its possible hepatotoxicity. We reviewed liver damage in patients with COVID-19 on PubMed and Virtual Health Library to investigate DILI cases. Four studies were selected, involving the medicines remdesivir, tocilizumab and a pharmacovigilance analysis study. The hepatotoxicity profile of drugs presented in the literature considers use in accordance to usual posology standards for treatment. However, drugs currently used in the management of COVID-19 follow different dosages and posology than those tested by the pharmaceutical industry. The deficiency of
uniformity and standardization in the assessment of hepatotoxicity cases hinders the publication of information and the possibility of comparing information among healthcare professionals. It is suggested that severe liver injury in COVID-19 patients should be reported in pharmacovigilance institutions, and physicians should pay attention to any considerable abnormal liver test elevation as it can demonstrate unknown drug hepatotoxicity. Liver disorders in COVID-19 patients and the use of several concomitant off-label medications — with a potential risk of further damaging the liver - should at least be a warning sign for rapid identification and early intervention, thus preventing liver damage from contributing to severe impairment in patients.

Core Tip: Coronavirus disease 2019 (COVID-19) is a multisystemic disease, and liver manifestations are an important aspect to be considered. One should pay attention to drug-induced liver injury, especially considering the off-label use of drugs in prophylactic and therapeutic regimens applied on large scales. A review of liver damage in patients with COVID-19 returned three studies involving remdesivir, tocilizumab, and a pharmacovigilance study. Liver disorders in COVID-19 patients and the use of several concomitant off-label drugs - potentially causing further liver damage - should be a warning sign for rapid identification and early intervention, thus preventing severe impairment in patients.

INTRODUCTION

In December 2019, the world watched severe acute respiratory syndrome (SARS) spread from an epidemic in China to a pandemic with global catastrophic effects[1]. The virus causing the syndrome has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new pathogen in the coronavirus family, and the disease is called coronavirus disease 2019 (COVID-19)[2]. On January 31, 2021, COVID-19 was already present in 223 countries/territories, with over one hundred million confirmed cases and two million deaths. The United States presents more than 40% of confirmed cases worldwide, followed by India and Brazil[2].

The infection presents broad clinical symptoms and a high rate of transmissibility. The overall signs can vary from fever, cough, shortness of breath, body pain, and diarrhea to severe pneumonia[3]. COVID-19 is a multifactorial systemic disease with rapid progression, leading a patient to the intensive care unit (ICU) in a matter of days[4]. In mild cases of the disease, symptomatic treatment is indicated. In moderate to severe cases, support measures and the use of experimental/off-label treatments should be performed[5].

In addition to SARS, patients with COVID-19 manifest complications beyond the respiratory system[6]. The virus hosts the angiotensin-converting enzyme receptor 2 (ACE-2), which despite being expressed in 80% of lung cells, it is also located in tissues such as vascular endothelium, gastrointestinal tract, squamous epithelium of the nasal, oral mucosa, and nasopharynx[7,8]. Therefore, COVID-19 consists of a systemic disease that can present complications such as thromboembolic episodes, arrhythmias, and myocardial dysfunction, prolongation of the QT interval, acute coronary syndrome, kidney injury, hepatocellular damage, hyperglycemia, and ketoacidosis, neurological symptoms, sepsis and, in more severe cases, multiple organ failure[9].
The frequency of liver damage in COVID-19 patients ranges from 14.8% to 53% of patients[10]. In a systematic review analyzing 12882 hospitalized patients, 41.1% had elevated aspartate aminotransferase (AST), and 29.1% increased alanine aminotransferase (ALT). Elevation of AST and ALT three times above the normal upper limit is significantly associated with greater chances of unfavorable clinical outcomes [11]. Other publications demonstrate the increase in ALT/AST ratio in 16% to 62% of cases and elevated total bilirubin by 5% to 21% of the patients. Elevation of AST and ALT presented is about two times above the normal upper limit[12]. Studies suggest that aminotransferase elevations occur more frequently in severe patients[9].

The liver injury pattern consists of increased AST/ALT and less frequently decreased serum albumin, increase total bilirubin, gamma-glutamyltransferase (GT range), and alkaline phosphatase[13,14]. Liver histopathological alterations demonstrated microvesicular steatosis, portal fibrosis, inflammatory infiltration in the hepatic and ductular lobe, and multifactorial acute liver necrosis[9]. The high transmissibility of the virus and the absence of protocols for the protection of health professionals at the beginning of the pandemic made it difficult to perform autopsies and liver biopsies of patients with COVID-19 — leading to scarce histopathological data in the literature[15]. Another difficulty in establishing a liver injury pattern is the scarcity of publications reporting liver signs and symptoms in addition to laboratory findings such as jaundice, hepatomegaly, and ascites.

Liver involvement in patients with COVID-19 is currently limited to moderate to severe cases, and its damage may be transient, with liver tests returning to normal without the need for specific treatment[9,15]. The occurrence of acute or chronic liver failure is yet to be investigated. Nevertheless, the higher the serum level of AST/ALT and total bilirubin, the severer the disease, the higher the risk of a patient requiring admission to the ICU or prolonged hospital stay[16], and the greater the mortality risk[14].

Reasons for the occurrence of liver damage in COVID-19 patients are multifactorial[9]. The first hypothesis was the cytopathic injury caused directly by the virus[9]. Although the liver damage pattern found in COVID-19 patients suggests hepatocellular damage, ACE-2 is expressed in only 2.6% of hepatocytes, in contrast to the relevant expression in cholangiocytes (59%), which would suggest cholestatic damage[13]. However, the bile duct has a role in liver regeneration and immune response, and direct damage to cholangiocytes can impair this function. The presence of the virus in the vascular endothelium causes a state of hypercoagulation; thus, there is the possibility of liver damage caused by thrombosis in the porta-hepatic system[9,11].

The manifestation of hypoxemia due to pneumonia may cause liver damage due to hypoxia-reoxygenation[13]. In cardiac, circulatory or respiratory distress passive congestion and decreased blood flow to the liver may occur. Theoretically, hypoxia rescue and reperfusion of organs cause the availability of a large amount of oxygen suddenly increases the presence of reactive oxygen species, causing the release of pro-inflammatory factors and thus facilitating the occurrence of blood hyperviscosity, which aggravates microvascular lesions in the liver[13]. Septic shock is a common complication in severe COVID-19 patients and functional imbalance may be responsible for liver damage[17].

It is a consensus among experts that functional changes caused by SARS-CoV-2 in patients with moderate to severe disease may be related to systemic inflammatory response syndrome[9]. The development of an uncontrolled immune-mediated inflammatory reaction occurs by the increase in plasma cytokines and other inflammatory reagents [interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor]. This mechanism affects several organs and has supported the clinical use of anti-inflammatory corticosteroids[8].

The role of chronic liver disease (CLD) in COVID-19 patients is still controversial. Cirrhosis is a risk factor for mortality in general, with clinical complications such as sepsis and respiratory stress[18]. The prevalence of non-alcoholic fatty liver disease is increasing worldwide, and the patient’s profile is similar to the SARS-CoV-2 risk group: advanced age and presence of comorbidities such as hypertension, diabetes, obesity, and cardiovascular distress[19]. CLD may interfere with the findings of liver enzyme alterations to some extent in COVID-19 — if not directly responsible, acting together with the virus to worsen liver function. Despite this scenario, liver damage might occur regardless of liver disease’s previous existence[18].

One should pay attention to drug-induced liver injury (DILI) in patients with COVID-19, especially considering the off-label use of drugs in prophylactic and therapeutic regimens applied on large scales. DILI is an adverse reaction to medications, and patients using five or more drugs - for example, critically ill ICU patients with COVID-19 - are more likely to experience this type of reaction[20].
Although rare, often ranging from 1 case in 10000-100000\cite{21}, physicians and pharmacists should monitor the occurrence of this event in COVID-19 patients since the side-effect prolongs hospital stay, a critical situation in a hospital bed shortage moment\cite{22}.

Finally, the DILI adverse event can play a crucial role in COVID-19 patients. This review aims to present relevant information on the medication used so far in COVID-19 patients and its possible hepatotoxicity. We intend to condense information that supports decision-making and patient management in clinical practice in the hospital environment and make remarks on liver manifestations in light of the DILI subject.

**LITERATURE REVIEW**

**Review of liver damage in patients with COVID-19**

A review of liver damage in patients with COVID-19 on PubMed for general information on hepatic manifestations in SARS-CoV-2 was performed using the terms (“Liver Diseases” [MeSH]) AND (“sars cov 2” [MeSH]). Secondly, PubMed and VHL (Virtual Health Library) were used to explore DILI cases in COVID-19. VHL was used to expand the search for Latin American cases. The search strategy for PubMed combined the descriptors as follows (“Chemical and Drug Induced Liver Injury”[MeSH]) AND (“sars-cov-2”[MeSH]) AND (“covid-19”[MeSH]). There was no limitation by language, year of publication, or study design. The search strategy for VHL combined the descriptors as “Chemical and Drug Induced Liver Injury” AND “coronavirus infections”. The first search was performed on January 6th, 2021, and was then updated on April 17, 2021.

The studies’ eligibility was defined by identifying DILI cases due to medications used to treat patients with COVID-19. The studies’ selection was performed by two independent reviewers, MWB and KHS, and in three sequential stages — title, abstract, and full-text readings. A third reviewer, CRB, resolved the disagreements. The following variables were analyzed: Drug, patient characteristics, assessment of liver enzymes, DILI diagnosis criteria.

The search returned 53 articles — 22 articles from the VHL and 31 articles from the PubMed database. After excluding duplicate articles and review articles, 10 available abstracts and full texts were assessed. One excluded article assessed adverse drug reactions but did not mention DILI. Another two excluded articles assessed liver injury but no mention to the medication used; a retrospective study analyzing antiviral treatment was excluded since no causality was assessed. Six studies were selected — five case reports and a pharmacovigilance analysis study of VigiBase, the World Health Organization’s individual case safety reports database, as summarized in Table 1.

The results found are related to the attempt to treat critically ill patients, either by eliminating the virus or by decreasing the inflammatory manifestations developed. Tocilizumab is an IL-6 receptor antagonist and has been proposed to treat severe forms of COVID-19. IL-6 plays an important role in COVID-19-induced cytokine storm\cite{23}. Remdesivir is a nucleotide analogue RNA polymerase inhibitor, originally developed and tested for Ebola virus disease. The drug showed antiviral activity against a broad spectrum of human coronaviruses in cell cultures and mouse models, including SARS. Recently, the Food and Drug Agency recommended Remdesivir for the treatment of patients hospitalized with severe coronavirus disease\cite{24,26,28}.

**Risk of hepatotoxicity of medicines on COVID-19 patients**

It is challenging to find data on hepatotoxicity. This data includes clinical trials, observational studies, series and case reports. In the case of DILI, clinical trials do not focus on assessing causality, so it is not accurate in this identification, even because it is not the objective of this study design. Retrospective observational studies have a known bias regarding data collection. However, prospective observational studies and case series are essential for the detection and understanding of DILI. In this context, the analysis of the evidence synthesis is a difficult task to perform. In terms of access, the LiverTox® database\cite{29} website is a valuable reference for a quick consultation\cite{30}. It classifies medicines according to the following scale: Category A (over 50 published reports), B (over 12 but less than 50), C (over four but less than 12), and D (one to three cases).

Some reservations emerged concerning the frequencies of risk of hepatotoxicity when confronted with a large series of prospective cases — mainly related to drugs presenting a risk of hepatotoxicity when it was impossible to rule out other
CIOMS/RUCAM: Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method; DILI: Drug induce liver injury; EASL: European Association for the Study of the Liver; TCZ: Tocilizumab; RDV: Remdesivir.

Table 1 Reports of drug-induced liver injury in patients with coronavirus disease 2019 (PubMed/Virtual Health Library)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study/site</th>
<th>Patient profile</th>
<th>Medication</th>
<th>DILI</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muhović et al[23]</td>
<td>Case report; Montenegro</td>
<td>Man, 52-yr-old</td>
<td>Chloroquine, lopinavir/ritonavir, methylprednisolone, ceftriaxone and azithromycin. After 6 d: methylprednisolone, ceftriaxone, azithromycin</td>
<td>CIOMS/RUCAM: scored 8 points for a ‘probable’ cause of DILI by TCZ. Hepatocellular form of DILI diagnosed using the EASL guidelines</td>
<td>TCZ had a positive effect on clinical and laboratory parameters, with transaminases values normalizing in 10 d</td>
</tr>
<tr>
<td>Zampino et al[24]</td>
<td>Case series; Naples, Italy</td>
<td>None of the 5 treated patients had history of liver disease, visceral obesity, viral hepatitis, or prior hepatotoxic medication or alcohol intake. Liver ultrasound did not show signs of advanced liver disease. Patient 1 and 2 had history of hypertension and asthma</td>
<td>Before and during RDV treatment, 4 of 5 patients also received hydroxychloroquine patient 2 and 4 received ceftazidime–avibactam plus dapto mycin and patient 3 meropenem and linezolid</td>
<td>Significant increase in AST/ALT</td>
<td>Adverse effect neither progressed to severe liver damage nor liver failure. In no cases, RDV was discontinued because of liver injury</td>
</tr>
<tr>
<td>Durante-Mangoni et al[25]</td>
<td>Case series; Naples, Italy</td>
<td>Four patients</td>
<td>All patients had been previously treated with LPV/r or darunavir/ritonavir resistant (DRV/c) and also received hydroxychloroquine</td>
<td>3 patients experienced ALT and AST increase (5 times to 8 times the upper normal limit)</td>
<td>RDV was prematurely discontinued in patient 1 because of a torsade de pointes requiring cardiac resuscitation and in patient 3 because of death due to multiple organ failure. The study suggests a significant burden of adverse events</td>
</tr>
<tr>
<td>Montastruc et al[26]</td>
<td>Cross-sectional study; United States, Europe</td>
<td>387 reports with RDV side effects in VigiBase: 130 hepatic adverse effects, 87 from the United States; 43 from Europe; mostly men (81, 62%), mean age of 54.9 yr</td>
<td>In the majority of cases (122, 94%), RDV was the sole suspected drug</td>
<td>Increased hepatic enzymes (114, 88%), involving AST and ALT in 79 cases (61%) and bilirubin in 4 cases (3%). Other cases were reported as hepatic failure or hepatitis</td>
<td>Most cases were serious (94, 72%), resulting in hospitalization or prolongation of hospital stay. The use of RDV was associated with an increased risk of reporting hepatic disorders</td>
</tr>
<tr>
<td>Yamazaki et al[27]</td>
<td>Case reported; Japan</td>
<td>73-yr-old man. History of hypertension, hyperlipidemia, gastric ulcer, benign prostatic hyperplasia, and alcoholic hepatitis</td>
<td>Favipiravir was the suspected drug. Dosage was 6000 mg on day 1 and 2400 mg/d from day 2 onward, for a total of 14 d. Patient was using previously lopinavir/ritonavir combined with interferon-β-1b, vancomycin and antithrombin III. After started favipiravir two more drugs were added Trimethoprim–sulfamethoxazole and micafungin</td>
<td>Transaminases were elevated until day 4: Aspartate aminotransferase (AST) from 70 U/L (day 0) to 112 U/L (day 4) and alanine aminotransferase (ALT) from 37 U/L to 59 U/L, respectively. Total bilirubin (T-Bil) increased until day 3 from 5.2 mg/dL to 12.6 mg/dL. On day 11, however, transaminases peaked again (AST, 268 U/L; ALT, 115 U/L) and total bilirubin was also rising</td>
<td>A case of cholestatic liver injury in the early stages of favipiravir treatment for COVID-19. Based on the CIOMS/RUCAM scoring system, it was classified as a cholestatic liver injury, with a score of 6 (possible)</td>
</tr>
<tr>
<td>Leegwater et al[28]</td>
<td>Case report; The Netherlands</td>
<td>A 64-yr-old male patient. History of hypertension and hypercholesterolemia</td>
<td>Remdesivir</td>
<td>5 d after start of remdesivir ALT was 1305 IU/L, AST 1461 U/L, alkaline phosphatase 269 U/L, total bilirubin 8 µmol/L; gamma-glutamyltransferase 227 U/L and creatine kinase 103 U/L</td>
<td>Remdesivir toxicity was suspected based on the time-relation, the positive dechallenge, the known in vitro toxicity of remdesivir and the absence of alternative causes of hepatotoxicity. After stop of remdesivir the ALT/AST ratio reached normal values</td>
</tr>
</tbody>
</table>

hypotheses. Publication bias and lack of updating can also affect the assessment of the LiverTox® database[29] when considering a drug as low risk[21]. New drugs may also
Drug-induced liver injury and COVID-19

Healthcare professionals must consider DILI in COVID-19 patients when: (1) There is an elevation of ALT five times above the upper limit of normal (ULN); and (2) Increase in ALT > 3 × ULN with an increase in bilirubin > 2 × ULN with or without alteration of alkaline phosphatase levels or with hepatic signs[31]. DILI may be present when total bilirubin is > 2.5 mg/dL in the presence of AST and ALT elevation or when international normalized ratio > 1.5 with a concomitant increase in AST and ALT[32]. DILI can be classified as hepatocellular, cholestatic or mixed, as indicated by ALT and the alkaline phosphatase test[33]. Moreover, DILI can be mild, moderate, severe, or fatal; the worst outcomes are liver transplant or death[20]. Although there are three known types of DILI, there is no consensus of what type is the most common in COVID-19 patients.

Abnormal levels for aminotransferase in DILI without other signs and symptoms should only be monitored. If the patient presents ALT 5 × > ULN with jaundice, hepatomegaly, hyperbilirubinemia, or right-upper-quadrant pain, consider further clinical investigation and interruption of suspected DILI drug[9]. Patients under off-label drugs use and investigational treatments should be longitudinally monitored for liver tests. If resources are available, monitor liver tests of patients discharged from ICU to ensure no secondary damage will occur, and liver function will be fully restored[9,13]. Most DILI cases do not need drug therapy, and patients recover after drug discontinuance. Ursodeoxycholic acid 500 mg daily use is described in the literature for hepatic protection for elevated transaminases and serum total bilirubin in non-alcoholic liver disease, however its mechanism of action remain unclear[18].

Causality algorithms should be used in the assessment of adverse drug reactions. For DILI related to COVID-19 treatment, we strongly encourage using the Roussel Uclaf Causality Assessment Method (RUCAM) due to its specificity for liver injury[34]. Briefly, the RUCAM scale assigns points to seven domains, including temporal evolution of the liver injury, risk factors (age, alcohol use, and pregnancy), concomitant use of drugs that may be hepatotoxic, and the development of repeated liver damage after the new drug is administered[35]. RUCAM may also help in the differential diagnosis of other COVID-19 related etiologies that cause AST/ALT elevation, such as myositis, ischemia, cytokine-release syndrome, and previous CLD[9].

The mortality of COVID-19 relates to SARS. Nevertheless, extrapulmonary manifestations such as liver injury may contribute to a negative clinical prognosis. There is no sufficient data to consider liver injury caused by DILI as a risk factor for mortality, but it is a safety concern since it is related to severe cases of COVID-19[9,36], and it may increase hospital length of stay and expose patients to other comorbidities such as nosocomial infection. From a social and economic perspective, it also pressures the health system, as hospital bed shortages are a major concern in the pandemic, since resources are scarce worldwide.

The hepatotoxicity profile of drugs available in the literature considers approved therapeutic schemes applied in the medical routine. However, drugs currently used in the management of COVID-19 do not follow previously established therapies and posology when considering those tested by the pharmaceutical industry[37]. For example, in Brazil, reports of hepatotoxicity caused by ivermectin use 18 mg/d for a week as prophylaxis for COVID-19 are published in non-scientific media. Despite the small number of published cases according to Table 2, overdose — in the case of administration of non-studied dosage — may, over time, modify the risk of ivermectin hepatotoxicity. A similar situation may occur with several other drugs, leading to the need to review the frequency of adverse reactions described in the package leaflet. This scenario can be confusing in identifying DILI even when using well-established
Evidence of hepatotoxicity

Transient elevations in serum aminotransferase levels occur in 11% to 19% of patients on voriconazole. These elevations are usually self-limiting; however, fatal cases have been reported

Monitoring of liver tests during therapy is recommended, especially in patients with previous liver disease

Liver damage is usually self-limited cholestatic hepatitis, which appears 1 wk to 3 wk after starting treatment. It may also appear after some time following medicine discontinuation. Cholestasis and elevated transaminases can persist for up to 6 mo. Despite presenting the hepatocellular and cholestatic forms of injury, cholestatic is more often related to acute liver failure, death, or liver transplantation

It has not been associated with significant elevations in serum enzymes during therapy for rheumatic diseases. When used in relatively high doses, it can trigger an acute liver injury with a sudden onset of fever and marked elevation of serum enzymes. Post COVID-19 data have not been assessed

It has been associated with several cases of clinically apparent liver injury with jaundice. Although the liver injury was severe, it was usually self-limiting, with complete recovery within 2 mo to 3 mo. In at least one case, however, the affected patient died of liver failure. Current recommendations are patient monitoring by routine liver tests before medication. In registration trials, serum aminotransferase elevations occurred in a high proportion (10% to 50%) of patients

Between 10% and 50% of patients treated developed transient, mild-to-moderate serum ALT and AST elevations within 1 d to 5 d of starting therapy without changes in serum bilirubin or alkaline phosphatase levels. Elevations above 5 times ULN were reported in up to 9% of patients in several clinical trials, but the abnormalities resolved with discontinuation and were not associated with a clinically apparent injury

Associated with significant elevations in ALT (above 5 times the ULN) in 4% to 20% of patients and symptomatic elevations in 1% to 5%

Associated with minor, self-limiting elevations in serum aminotransferase and sporadic cases of clinically apparent liver damage. Post COVID-19 data have not been assessed

Table 2 Hepatotoxicity of the most common drugs used to treat coronavirus disease 2019

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence of hepatotoxicity</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Liver damage is usually self-limited cholestatic hepatitis, which appears 1 wk to 3 wk after starting treatment. It may also appear after some time following medicine discontinuation. Cholestasis and elevated transaminases can persist for up to 6 mo. Despite presenting the hepatocellular and cholestatic forms of injury, cholestatic is more often related to acute liver failure, death, or liver transplantation</td>
<td>A</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Clinically apparent liver disease occurs in 3% to 10% of patients. The onset of symptoms or jaundice is usually 1 wk to 8 wk, and the pattern of elevations in serum enzymes varies from hepatocellular to cholestatic or mixed. The injury is usually self-limiting; however, fatal cases have been reported</td>
<td>D</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>It has not been associated with significant elevations in serum enzymes during therapy for rheumatic diseases. When used in relatively high doses, it can trigger an acute liver injury with a sudden onset of fever and marked elevation of serum enzymes. Post COVID-19 data have not been assessed</td>
<td>C</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>It has been associated with several cases of clinically apparent liver injury with jaundice. Although the liver injury was severe, it was usually self-limiting, with complete recovery within 2 mo to 3 mo. In at least one case, however, the affected patient died of liver failure. Current recommendations are patient monitoring by routine liver tests before medication. In registration trials, serum aminotransferase elevations occurred in a high proportion (10% to 50%) of patients</td>
<td>C</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Between 10% and 50% of patients treated developed transient, mild-to-moderate serum ALT and AST elevations within 1 d to 5 d of starting therapy without changes in serum bilirubin or alkaline phosphatase levels. Elevations above 5 times ULN were reported in up to 9% of patients in several clinical trials, but the abnormalities resolved with discontinuation and were not associated with a clinically apparent injury</td>
<td>D</td>
</tr>
<tr>
<td>Neuravpine</td>
<td>Associated with significant elevations in ALT (above 5 times the ULN) in 4% to 20% of patients and symptomatic elevations in 1% to 5%</td>
<td>A</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Associated with minor, self-limiting elevations in serum aminotransferase and sporadic cases of clinically apparent liver damage. Post COVID-19 data have not been assessed</td>
<td>D</td>
</tr>
</tbody>
</table>

Adapted from LiverTox® database[27]. A: Well know hepatotoxicity; B: Highly likely hepatotoxicity; C: Probably hepatotoxicity; D: Possible hepatotoxicity; COVID-19: Coronavirus disease 2019; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limit of normal.

Table 3 Hepatotoxicity of adjuvant therapy medications for coronavirus disease 2019 treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence of hepatotoxicity</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Associated with a transient elevation of 10% to 60%, but the values are generally less than 5 times the upper limit of normal and are rarely associated with symptoms or jaundice. Values above 5 times the upper limit of normal occur around 2% of those receiving high heparin doses</td>
<td>NR</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Associated with elevations in serum aminotransferases in 4% to 13% of patients, but values greater than 5 times the upper limit of normal are not common and occur in higher doses. The typical liver injury in patients receiving low molecular weight heparins occurred with rapid onset (within 3 d to 5 d of onset), rapid recovery (from 1 wk to 4 wk), and the absence of symptoms and jaundice. Some patients have mild increases in serum bilirubin and alkaline phosphatase but generally remain within the normal range</td>
<td>E</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>The use of glucocorticoids can result in hepatomegaly and steatosis. They can trigger or worsen non-alcoholic steatohepatitis. Long-term use can also exacerbate chronic viral hepatitis. High doses of intravenous corticosteroids, mainly methylprednisolone, have been associated with acute liver damage resulting in acute liver failure and death. Symptoms and jaundice develop 2 wk to 6 wk after discontinuation. Some cases have progressed to acute liver failure, resulting in death or the need for emergency liver transplantation</td>
<td>A</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Transient elevations in serum aminotransferase levels occur in 11% to 19% of patients on voriconazole. These elevations are generally asymptomatic and self-limited, but approximately 1% of patients require voriconazole discontinuation due to ALT elevations. Cases of acute liver failure have been described. Testing for serum bilirubin and aminotransferase levels is recommended at the time of initiation and weekly during the first month of therapy and monthly thereafter</td>
<td>B</td>
</tr>
<tr>
<td>Anidulafugin</td>
<td>Transient elevation of transaminases from 2% to 15%. There are rarely serious cases. Monitoring of liver tests during therapy is recommended, especially in patients with previous liver disease</td>
<td>D</td>
</tr>
<tr>
<td>Colchicine</td>
<td>It is rarely associated with elevations in serum aminotransferase or alkaline phosphatase. The cases of acute liver injury attributed to the overdose of colchicine were self-limiting, and the other toxicities of this agent, such as rhabdomyolysis, generally overshadowed the liver injury. No convincing cases of liver failure have been reported</td>
<td>C</td>
</tr>
</tbody>
</table>

Adapted from LiverTox® database[27]. A: Well know hepatotoxicity; B: Highly likely hepatotoxicity; C: Probably hepatotoxicity; D: Possible hepatotoxicity; E: Unlikely hepatotoxicity; NR: Not reported; ALT: Alanine aminotransferase.

causality algorithms, leading to sub notification, as drugs are used in non-previously indications.

When we analyzed Azithromycin and Hydroxychloroquine, we found that Azithromycin has a greater potential for hepatotoxicity, according to table 2.
Nevertheless, the Brazilian clinical trial ‘Coalition’ found a curious fact: Hydroxychloroquine alone or in addition with Azithromycin increased the levels of aminotransferases. Azithromycin was therefore not a confounder, but its interaction further increased the frequency of liver damage[38].

Besides azithromycin, many antimicrobial agents applied in the treatment of respiratory infections may cause hepatotoxicity. Fluoroquinolones, especially ciprofloxacin and levofloxacin, are responsible for frequent causes of clinically apparent liver injury and bile duct paucity[39]. Amoxicillin-clavulanate is LiverTox® A category and the most common documented cause of non-acetaminophen idiosyncratic DILI in the United States and Spain[40]. The drug causes cholestasis or mixed pattern of liver injury with significant increased alkaline phosphatase and gamma glutamyl transpeptidase markers[40-42]. Antituberculosis agents such as isoniazid are well known for their hepatotoxicity[43]; in developing countries, patients with COVID-19 and tuberculosis might be at increased risk of poor respiratory outcomes and DILI occurrence. Physicians should be aware of the available date on general antimicrobial hepatotoxicity to evaluate risk-benefit of adjuvant drug therapy.

COVID-19 is a condition yet to be duly clarified as to its extent and consequences. Despite the evidence showing the benefits of dexamethasone for the treatment, its use also made conditions such as aspergillosis pneumonia more frequent. This increase has been associated with the increased use of corticosteroids. Therefore, the treatment protocol of some antifungal drugs is associated with respiratory conditions. With the increase in the use of antifungals, known to affect the liver, it is necessary to be aware of the increased frequency of DILI associated with these drugs that were not so often used before[44].

After Ivermectin, Nevirapine, and Hydroxychloroquine, now Colchicine is under study for the treatment of COVID-19[45]. Pre-pandemic, the concept of hepatotoxicity was reported as an unlikely or even non-existent cause. Nevertheless, COVID-19 has taught us that we need to be aware of possible new adverse effects when treating new pathologies — especially those stemming from new and dosage regimens.

Most DILI reports are concentrated in a hospital environment due to the availability of diagnostic resources[46]. In a non-pandemic context when most cases are identified in a hospital environment, 50% of DILI cases are poorly diagnosed[47]. In patients with COVID-19, this situation may be even more precarious since the off-label drug use in outpatient settings — drugs such as azithromycin, hydroxychloroquine, and ivermectin — will only alert to hepatotoxicity in severe cases when a patient already requires hospitalization.

Healthcare professionals must be aware of self-medication practices with over-the-counter medicines in the treatment of COVID-19 fever and pain, such as nonsteroidal anti-inflammatory drugs[48]. Acetaminophen overdoses cause harmful acute hepatocellular injury and even in adequate doses it can slightly elevate serum aminotransferases[49]. Liver injury can occur when acetaminophen is taken for several days in supratherapeutic doses[42]. Hepatotoxicity is worsened if the patient is critically ill, presents alcoholism, malnutrition or preexisting CLD[49]. Moreover, chronic use of diclofenac can increase ALT levels; nimesulide has been described in acute liver failure and ibuprofen is associated with cholestatic DILI[41].

Studies describe the increase in AST/ALT as a synonym for liver damage and hepatotoxicity in patients with COVID-19. However, for a relevant outcome in clinical practice, it is necessary to clarify the presence of signs and symptoms in those cases. The deficiency of uniformity and standardization in the assessment of hepatotoxicity cases hinders the publication of information and the possibility of comparing information among healthcare professionals[50]. In that scenario, RUCAM may help to guide more consistent and complete data on DILI, including COVID-19 cases, undergoing clinical features, treatments used, and current diseases. The World Health Organization strengthened the report of any drug adverse event and so, DILI should also be monitored and reported to local pharmacovigilance institutions to compose the VigiBase dataset. Physicians should pay attention to any considerable abnormal liver test elevation as it can demonstrate unknown drug hepatotoxicity. The only certainty that we have is that after COVID-19, knowledge about drug use and abuse will be updated. For that, we should pay attention to increasing DILI reports.

**CONCLUSION**

COVID-19 is a multisystemic disease, and liver manifestations are a crucial aspect to be considered. The pandemic moment experienced presents new clinical situations
that need different perspectives and approaches. It is important to verify the occurrence of hepatic manifestation in different populations, as there may be a relationship with the different therapeutic schemes used to treat the disease.

Pharmacovigilance actions using validated tools such as the RUCAM algorithm can establish a causal relationship between drugs and DILI and disseminate relevant information for clinical decision-making. The set of liver disorders in COVID-19 needs different perspectives and approaches. It is important to verify the occurrence of hepatic manifestation in different populations, as there may be a warning sign of potential further liver damage. Rapid identification and early intervention can prevent liver damage contributing to severe impairment in patients.

REFERENCES


Ortiz GX et al. Drug-induced liver injury and COVID-19


