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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

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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.

Key Words: Liver injury; Chemical and drug-induced liver injury; COVID-19; SARS-CoV-2; Pharmacovigilance

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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.

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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[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[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[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[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[29] website is a valuable reference for a quick consultation[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

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

Ref.	Study/site	Patient profile	Medication	DILI	Outcome
Muhović <i>et al</i> [23]	Case report; Montenegro	Man, 52-yr-old	Chloroquine, lopinavir/ritonavir, methylprednisolone, ceftriaxone and azithromycin. After 6 d: methylprednisolone, ceftriaxone, azithromycin	CIOMS/RUCAM: scored 8 points for a 'probable' cause of DILI by TCZ. Hepatocellular form of DILI diagnosed using the EASL guidelines	TCZ had a positive effect on clinical and laboratory parameters, with transaminases values normalizing in 10 d
Zampino <i>et al</i> [24]	Case series; Naples, Italy	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	Before and during RDV treatment, 4 of 5 patients also received hydroxychloroquine patient 2 and 4 received ceftazidime-avibactam plus daptomycin and patient 3 meropenem and linezolid	Significant increase in AST/ALT	Adverse effect neither progressed to severe liver damage nor induced liver failure. In no cases, RDV was discontinued because of liver injury
Durante-Mangoni <i>et al</i> [25]	Case series; Naples, Italy	Four patients	All patients had been previously treated with LPV/r or darunavir/cobicistat (DRV/c) and also received hydroxychloroquine	3 patients experienced ALT and AST increase (5 times to 8 times the upper normal limit)	RDV was prematurely discontinued in patient 1 because of a <i>torsade de pointes</i> requiring cardiac resuscitation and in patient 3 because of death due to multiple organ failure. The study suggests a significant burden of adverse events
Montastruc <i>et al</i> [26]	Cross-sectional study; United States, Europe	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	In the majority of cases (122, 94%), RDV was the sole suspected drug	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	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
Yamazaki <i>et al</i> [27]	Case reported; Japan	73-yr-old man. History of hypertension, hyperlipidemia, gastric ulcer, benign prostatic hyperplasia, and alcoholic hepatitis	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	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	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)
Leegwater <i>et al</i> [28]	Case report; The Netherlands	A 64-yr-old male patient. History of hypertension and hypercholesterolemia	Remdesivir	5 d after start of remdesivir ALT was 1305 IU/L, AST 1461 U/L, alkaline phosphatase 269 U/L, total bilirubin 8 μ mol/L, gammaglutamyltransferase 227 U/L and creatine kinase 103 U/L	Remdesivir toxicity was suspected based on the time-relation, the positive dechallenge, the known <i>in vitro</i> toxicity of remdesivir and the absence of alternative causes of hepatotoxicity. After stop of remdesivir the ALT/AST ratio reached normal values

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.

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

go unnoticed, as the data is generally related to internal reports by regulatory agencies. Despite this bias, the LiverTox® database is still the most practical way of obtaining information on hepatotoxicity. The expansion of its use and knowledge can improve the quality of publications and more accurate detection and assessment of DILI's causality.

The evidence of hepatotoxicity available in the LiverTox® database[29] was organized considering drugs for COVID-19 treatment. Table 2 presents some of the most studied drugs for the COVID-19 treatment according to hepatotoxicity information and DILI case probability. Table 3 presents drugs that enhance the effectiveness of medical treatment.

DISCUSSION

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 $> 3 \times$ ULN with an increase in bilirubin $> 2 \times$ 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 $5 \times >$ 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

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

Drug	Evidence of hepatotoxicity	Probability
Azithromycin	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 discontinuance. 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	A
Lopinavir/ritonavir	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	D
Hydroxy-chloroquine	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	C
Tocilizumab	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	C
Remdesivir	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 discontinuance and were not associated with a clinically apparent injury	D
Nevirapine	Associated with significant elevations in ALT (above 5 times the ULN) in 4% to 20% of patients and symptomatic elevations in 1% to 5%	A
Ivermectin	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	D

Adapted from LiverTox[®] database[27]. A: Well known 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

Drug	Evidence of hepatotoxicity	Probability
Heparin	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	NR
Enoxaparin	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	E
Cortico-steroids	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 discontinuance. Some cases have progressed to acute liver failure, resulting in death or the need for emergency liver transplantation	A
Voriconazole	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 discontinuance 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	B
Anidulafungin	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	D
Colchicine	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	C

Adapted from LiverTox[®] database[27]. A: Well known 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-previous 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 data 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 patients and the use of several concomitant off-label drugs should be at least a warning sign of potential further liver damage. Rapid identification and early intervention can prevent liver damage contributing to severe impairment in patients.

REFERENCES

- Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: [32015507](#) DOI: [10.1038/s41586-020-2012-7](#)]
- World Health Organization**. WHO Coronavirus Disease (COVID-19) Dashboard 2021. [cited 31 Jan 2021]. In: World Health Organization [Internet]. Available from: <https://covid19.who.int/>
- Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: [32091533](#) DOI: [10.1001/jama.2020.2648](#)]
- CDC COVID-19 Response Team**. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 343-346 [PMID: [32214079](#) DOI: [10.15585/mmwr.mm6912e2](#)]
- World Health Organization**. Clinical management of Covid-19: interim guidance, 27 May 2020. [cited 31 Jan 2021]. In: World Health Organization [Internet]. Available from <https://apps.who.int/iris/handle/10665/332196>
- Thakur V**, Ratho RK, Kumar P, Bhatia SK, Bora I, Mohi GK, Saxena SK, Devi M, Yadav D, Mehariya S. Multi-Organ Involvement in COVID-19: Beyond Pulmonary Manifestations. *J Clin Med* 2021; **10** [PMID: [33498861](#) DOI: [10.3390/jcm10030446](#)]
- Chai X**, Hu L, Zhang Y, Han W, Lu Z, Ke A. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. 2020 Preprint. Available from: [bioRxiv:2020.02.03.931766](https://www.biorxiv.org/content/2020.02.03.931766)
- Metawea MI**, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. *Dig Liver Dis* 2021; **53**: 146-152 [PMID: [32988758](#) DOI: [10.1016/j.dld.2020.09.010](#)]
- Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: [32651579](#) DOI: [10.1038/s41591-020-0968-3](#)]
- Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: [32145190](#) DOI: [10.1016/S2468-1253\(20\)30057-1](#)]
- Sharma A**, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, Honganur NS, Akbar A, Deol A, Francis B, Patel S, Mehta D, Jaiswal R, Singh J, Patel U, Malik P. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. *Ann Hepatol* 2021; **21**: 100273 [PMID: [33075578](#) DOI: [10.1016/j.aohp.2020.10.001](#)]
- Brito CA**, Barros FM, Lopes EP. Mechanisms and consequences of COVID-19 associated liver injury: What can we affirm? *World J Hepatol* 2020; **12**: 413-422 [PMID: [32952870](#) DOI: [10.4254/wjh.v12.i8.413](#)]
- Yang RX**, Zheng RD, Fan JG. Etiology and management of liver injury in patients with COVID-19. *World J Gastroenterol* 2020; **26**: 4753-4762 [PMID: [32921955](#) DOI: [10.3748/wjg.v26.i32.4753](#)]
- Wu Y**, Li H, Guo X, Yoshida EM, Mendez-Sanchez N, Levi Sandri GB, Teschke R, Romeiro FG, Shukla A, Qi X. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. *Hepatol Int* 2020; **14**: 621-637 [PMID: [32710250](#) DOI: [10.1007/s12072-020-10074-6](#)]
- Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: [32170806](#) DOI: [10.1111/liv.14435](#)]
- Portincasa P**, Krawczyk M, Machill A, Lammert F, Di Ciaula A. Hepatic consequences of COVID-19 infection. Lapping or biting? *Eur J Intern Med* 2020; **77**: 18-24 [PMID: [32507608](#) DOI: [10.1016/j.ejim.2020.05.035](#)]
- Li J**, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 2020; **8**: 13-17 [PMID: [32274341](#) DOI: [10.14218/JCTH.2020.00019](#)]
- Hanafy AS**, Abd-Elsalam S. Challenges in COVID-19 drug treatment in patients with advanced liver diseases: A hepatology perspective. *World J Gastroenterol* 2020; **26**: 7272-7286 [PMID: [33362383](#) DOI: [10.3748/wjg.v26.i46.7272](#)]

- 19 **Leoni S**, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. *World J Gastroenterol* 2018; **24**: 3361-3373 [PMID: [30122876](#) DOI: [10.3748/wjg.v24.i30.3361](#)]
- 20 **Council for International Organizations of Medical Sciences**. Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2020
- 21 **Björnsson ES**, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; **144**: 1419-1425, 1425.e1 [PMID: [23419359](#) DOI: [10.1053/j.gastro.2013.02.006](#)]
- 22 **Ranzani OT**, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, Bozza FA. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med* 2021; **9**: 407-418 [PMID: [33460571](#) DOI: [10.1016/S2213-2600\(20\)30560-9](#)]
- 23 **Muhović D**, Bojović J, Bulatović A, Vukčević B, Ratković M, Lazović R, Smolović B. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int* 2020; **40**: 1901-1905 [PMID: [32478465](#) DOI: [10.1111/liv.14516](#)]
- 24 **Zampino R**, Mele F, Florio LL, Bertolino L, Andini R, Galdo M, De Rosa R, Corcione A, Durante-Mangoni E. Liver injury in remdesivir-treated COVID-19 patients. *Hepatol Int* 2020; **14**: 881-883 [PMID: [32725454](#) DOI: [10.1007/s12072-020-10077-3](#)]
- 25 **Durante-Mangoni E**, Andini R, Bertolino L, Mele F, Florio LL, Murino P, Corcione A, Zampino R. Early experience with remdesivir in SARS-CoV-2 pneumonia. *Infection* 2020; **48**: 779-782 [PMID: [32418190](#) DOI: [10.1007/s15010-020-01448-x](#)]
- 26 **Montastruc F**, Thuriot S, Durrieu G. Hepatic Disorders With the Use of Remdesivir for Coronavirus 2019. *Clin Gastroenterol Hepatol* 2020; **18**: 2835-2836 [PMID: [32721580](#) DOI: [10.1016/j.cgh.2020.07.050](#)]
- 27 **Yamazaki S**, Suzuki T, Sayama M, Nakada TA, Igari H, Ishii I. Suspected cholestatic liver injury induced by favipiravir in a patient with COVID-19. *J Infect Chemother* 2021; **27**: 390-392 [PMID: [33402301](#) DOI: [10.1016/j.jiac.2020.12.021](#)]
- 28 **Leegwater E**, Strik A, Wilms EB, Bosma LBE, Burger DM, Ottens TH, van Nieuwkoop C. Drug-induced Liver Injury in a Patient With Coronavirus Disease 2019: Potential Interaction of Remdesivir With P-Glycoprotein Inhibitors. *Clin Infect Dis* 2021; **72**: 1256-1258 [PMID: [32594120](#) DOI: [10.1093/cid/ciaa883](#)]
- 29 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012– [PMID: [31643176](#)]
- 30 **Hoofnagle JH**, Serrano J, Knoben JE, Navarro VJ. LiverTox: a website on drug-induced liver injury. *Hepatology* 2013; **57**: 873-874 [PMID: [23456678](#) DOI: [10.1002/hep.26175](#)]
- 31 **Real M**, Barnhill MS, Higley C, Rosenberg J, Lewis JH. Drug-Induced Liver Injury: Highlights of the Recent Literature. *Drug Saf* 2019; **42**: 365-387 [PMID: [30343418](#) DOI: [10.1007/s40264-018-0743-2](#)]
- 32 **Hunt CM**, Papay JI, Stanulovic V, Regev A. Drug rechallenge following drug-induced liver injury. *Hepatology* 2017; **66**: 646-654 [PMID: [28295448](#) DOI: [10.1002/hep.29152](#)]
- 33 **Danan G**, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. *Int J Mol Sci* 2015; **17** [PMID: [26712744](#) DOI: [10.3390/ijms17010014](#)]
- 34 **Teschke R**, Frenzel C. Drug induced liver injury: do we still need a routine liver biopsy for diagnosis today? *Ann Hepatol* 2013; **13**: 121-126 [PMID: [24378275](#)]
- 35 **Teschke R**, Danan G. Prospective Indian Study of DILI with Confirmed Causality Using the Roussel Uclaf Causality Assessment Method (RUCAM): A report of Excellence. *Ann Hepatol* 2017; **16**: 324-325 [PMID: [28425398](#) DOI: [10.5604/16652681.1235471](#)]
- 36 **Wong YJ**, Tan M, Zheng Q, Li JW, Kumar R, Fock KM, Teo EK, Ang TL. A systematic review and meta-analysis of the COVID-19 associated liver injury. *Ann Hepatol* 2020; **19**: 627-634 [PMID: [32882393](#) DOI: [10.1016/j.aohp.2020.08.064](#)]
- 37 **Peng Y**, Tao H, Satyanarayanan SK, Jin K, Su H. A Comprehensive Summary of the Knowledge on COVID-19 Treatment. *Aging Dis* 2021; **12**: 155-191 [PMID: [33532135](#) DOI: [10.14336/AD.2020.1124](#)]
- 38 **Cavalcanti AB**, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E Silva PGM, Tramuja L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med* 2020; **383**: 2041-2052 [PMID: [32706953](#) DOI: [10.1056/NEJMoa2019014](#)]
- 39 **Björnsson ES**. Hepatotoxicity by Drugs: The Most Common Implicated Agents. *Int J Mol Sci* 2016; **17**: 224 [PMID: [26861310](#) DOI: [10.3390/ijms17020224](#)]
- 40 **Bunchorntavakul C**, Reddy KR. Drug Hepatotoxicity: Newer Agents. *Clin Liver Dis* 2017; **21**: 115-134 [PMID: [27842767](#) DOI: [10.1016/j.cld.2016.08.009](#)]
- 41 **David S**, Hamilton JP. Drug-induced Liver Injury. *US Gastroenterol Hepatol Rev* 2010; **6**: 73-80 [PMID: [21874146](#)]

- 42 **Lee WM.** Drug-induced hepatotoxicity. *N Engl J Med* 2003; **349**: 474-485 [PMID: [12890847](#) DOI: [10.1056/NEJMra021844](#)]
- 43 **Metushi I,** Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. *Br J Clin Pharmacol* 2016; **81**: 1030-1036 [PMID: [26773235](#) DOI: [10.1111/bcp.12885](#)]
- 44 **Warris A,** Schwartz I. Editorial MMCR special issue 'Covid-19 associated pulmonary aspergillosis'. *Med Mycol Case Rep* 2021; **31**: 1 [PMID: [33589872](#) DOI: [10.1016/j.mmcr.2021.02.003](#)]
- 45 **Lopes MI,** Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, Gigante SL, Benatti MN, Rezek UC, Emrich-Filho LL, Sousa BAA, Almeida SCL, Luppino Assad R, Veras FP, Schneider A, Rodrigues TS, Leiria LOS, Cunha LD, Alves-Filho JC, Cunha TM, Arruda E, Miranda CH, Pazin-Filho A, Auxiliadora-Martins M, Borges MC, Fonseca BAL, Bollela VR, Del-Ben CM, Cunha FQ, Zamboni DS, Santana RC, Vilar FC, Louzada-Junior P, Oliveira RDR. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open* 2021; **7** [PMID: [33542047](#) DOI: [10.1136/rmdopen-2020-001455](#)]
- 46 **Becker MW,** Lunardelli MJM, Tovo CV, Blatt CR. Drug and herb-induced liver injury: A critical review of Brazilian cases with proposals for the improvement of causality assessment using RUCAM. *Ann Hepatol* 2019; **18**: 742-750 [PMID: [31130470](#) DOI: [10.1016/j.aohep.2019.03.010](#)]
- 47 **Meier Y,** Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier PJ, Fattinger K. Incidence of drug-induced liver injury in medical inpatients. *Eur J Clin Pharmacol* 2005; **61**: 135-143 [PMID: [15726344](#) DOI: [10.1007/s00228-004-0888-z](#)]
- 48 **Quispe-Cañari JF,** Fidel-Rosales E, Manrique D, Mascaró-Zan J, Huamán-Castillón KM, Chamorro-Espinoza SE, Garayar-Peceros H, Ponce-López VL, Sifuentes-Rosales J, Alvarez-Risco A, Yáñez JA, Mejia CR. Self-medication practices during the COVID-19 pandemic among the adult population in Peru: A cross-sectional survey. *Saudi Pharm J* 2021; **29**: 1-11 [PMID: [33519270](#) DOI: [10.1016/j.jsps.2020.12.001](#)]
- 49 **National Institute of Diabetes and Digestive and Kidney Diseases.** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Acetaminophen. [Updated 2016 Jan 28]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2016. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548162/>
- 50 **Andrade RJ,** Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, Devarbhavi H, Merz M, Lucena MI, Kaplowitz N, Aithal GP. Drug-induced liver injury. *Nat Rev Dis Primers* 2019; **5**: 58 [PMID: [31439850](#) DOI: [10.1038/s41572-019-0105-0](#)]



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