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Drug-Induced Hepatotoxicity in COVID-19

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***Keywords*— Acute liver damage. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Drug-induced acute liver injury.**

***Abstract*—** *Objective: The aim of this research is to map the scientific evidence on drug-induced hepatotoxicity in COVID-19.Method:This is an integrative literature review study, through a systematic search performed by the reviewers to identify all relevant studies on the different causes of liver failure in patients with COVID-19, published from June 16, 2021 to July 27, 2021.Results and Discussion: After analyzing the articles, six categories emerged, namely: 1) Drug-induced liver injury; 2) hepatotoxicity caused by Hydroxochloroquine in COVID-19; 3) the hepatotoxicity caused by Ivermectin in COVID-19; 4) hepatotoxicity caused by Tocilizumab in COVID-19; 5) hepatotoxicity caused by Azithromycin in COVID-19; 6) the hepatotoxicity caused by Remdesivir in COVID-19. Conclusion: COVID-19 has put the health systems of many countries under great pressure and has been particularly challenging due to the lack of predictive parameters and effective pharmacotherapies for the treatment of COVID-19 in advanced liver disease. Despite the common descriptions of liver enzyme alterations observed in patients with COVID-19, the frequency, intensity and impact of liver damage are discreet and of little clinical significance in relation to morbidity or mortality of this disease.*

I. INTRODUCTION

Liver damage was reported as a common complication of New Coronavirus disease in 2019 (COVID-19). [1] The spectrum of liver damage in COVID-19 can be caused by direct infection, either by hepatotropism of the virus, or indirectly, such as systemic inflammation, hypoxic changes, iatrogenic causes, mechanical ventilation, exacerbation of underlying liver disease or hepatotoxicity of drugs used to combat the disease. [2]

Abnormality of liver enzymes is common in patients with the New Coronavirus, in addition to the virus itself, it is also possible that liver failure is due to hepatotoxicity of the drugs used to fight the infection, as well as to inflammation mediated by the immune system, with sudden increase and intense inflammatory substances and decreased oxygen associated with pneumonia, both of which can contribute to liver damage or even progress to liver failure in patients with COVID-19 who are severely ill. [1]

There are many drugs that can affect liver function, some of them may cause liver enzymes to rise asymptomatically, or may cause acute hepatitis. Liver damage may depend on the dosage of the drug used or it may be independent of the dosage of the drug used. Among the medications that can damage the liver, there are commonly used medications such as antibiotics, anti-inflammatory and antivirals. [3]

Drug-induced liver injury is potentially fatal and is also known as drug-induced hepatotoxicity, which is an important cause of acute liver failure, whose COVID-19 positive inpatients may undergo pharmacological polytreatment, making clinical management even more complex. In this context, information about the potential for hepatotoxicity of the drugs in use is important to prevent liver dysfunction and the side effects of the drugs used in its treatment. [4]

A percentage of patients with COVID-19 may have an asymptomatic course of viral infection, a good percentage may have fever and use antipyretics such as paracetamol or other analgesics, with potential hepatotoxicity, which is associated with the risk of liver damage that can occur in the later stages of COVID-19 infection and can result in a very dangerous synergy. [5]

In the Brazilian context, other drugs were used both in the hospital context and prescribed to the population, such as Azithromycin, Hydroxychloroquine, Paracetamol, Lopinavir and Remdesivir, drugs with already documented potential for hepatotoxicity. [6]

Thus, the objective of this research is to map the scientific evidence on drug-induced hepatotoxicity in COVID-19.

II. METHOD

It is an integrative literature review type research, which aims to gather and synthesize research results on a delimited topic, in a systematic and orderly manner, being an instrument for deepening knowledge about the investigated topic, allowing the synthesis of multiple published studies and general conclusions about it. [7]

A systematic search was performed by the reviewers to identify all relevant studies on the different causes of liver failure in patients with COVID-19 published from June 16, 2021 to July 27, 2021.

The methodological outline involves the exception of the following steps: (1) documentation of defined research objectives and research strategy, (2) identification and selection of peer-reviewed research articles, (3) final selection of peer-reviewed research articles from according to the defined eligibility criteria and according to the purpose of the review, (4) organizing and reporting the data and findings of peer-reviewed research articles in different sections and (5) discussion of results and conclusion.

Electronic databases such as PubMed, Cochrane Library, Google Scholar, Scopus and Web of Science were searched for potentially relevant studies using the health descriptors: acute liver injury, liver injury, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), new coronavirus disease 19 (COVID-19), liver disease and prognosis.

The retrieved studies were carefully examined to omit overlapping data or possible duplication. Those written in other languages without complete data and accessible information were excluded. The studies included in this review were published in the last 2 years in specialized journals, written in English and Portuguese, with reported clinical findings. Observational articles reporting the prevalence or incidence of drug-induced acute liver injury in adults, as well as randomized and nonrandomized interventions performed in different populations were included in this review article.

Studies reported on the findings and main drugs used in the COVID-19 pandemic and their likelihood of causing liver damage were also included.

Were identified 147 articles through the database, 87 were excluded due to duplication and 08 articles were selected for review.

The guiding question for the elaboration of this integrative review consisted of: What are the available scientific productions on liver injury induced by drugs used in COVID-19?

III. RESULTS AND DISCUSSION

In this integrative literature review, 08 original scientific articles were selected that strictly met the previously established sample selection and showed approximations with the object of this study. These were organized in alphanumeric codes, from CV01 to CV08, for better presentation and understanding of the results.

Table 1: Distribution of studies.

Nº	Base	Language	Author. Title. Periodical. Year	Objective	Methodology
CV01	Google Scholar	English	Orly, Alexander. et al.Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. Drug Safety. 2020.	Correlate potential hepatotoxicity of drugs that were used as treatment for COVID-19.	Experience report of Nursing students in the development of the curricular internship, which took place from April to July 2020.
CV02	PubMed	English	Hanafy, Amr. et al. Challenges in COVID-19 drug treatment in patients with advanced liver diseases: A hepatology perspective. World Journal of Gastroenterology. 2020.	Propose a review of medications that could be suitable for advanced liver disease.	Guideline for a step-by-step approach to treating COVID-19 in advanced liver disease.
CV03	PubMed	English	Vitiello, Antonio et.al. The risks of liver injury in COVID-19 patients and pharmacological management to reduce or prevent the damage induced. Egyptian Liver Journal. 2021.	Describe the pharmacological management in order to preserve the liver or reduce the damage caused by treatments with COVID-19 and anti-COVID-19.	Literature review
CV04	PubMed	English	Leegwater, Emiel et al.Drug-induced Liver Injury in a Patient With Coronavirus Disease 2019: Potential Interaction of Remdesivir With P-Glycoprotein Inhibitors. Clinical Infectious Diseases. 2021.	Propose a relationship with a drug-drug interaction between Remdesivir and P-glycoprotein inhibitors.	Case report of a critically ill patient with COVID-19 who developed hepatotoxicity after Remdesivir therapy.
CV05	PubMed	English	Boeckmans, Joost et al. COVID-19 and drug-induced liver injury: a problem of plenty or a petty point? Archives of toxicology, 2020.	Reflect on COVID-19 and drug-induced liver damage.	Literature review
CV06	PubMed	English	Cerqueira, et al. Viral and drug liver injury caused by COVID-19. Obesity Medicine. 2020.	Evaluate and discuss hepatic manifestations in COVID-19 such as infection, manifestations and drug effects.	Literature review
CV07	Google Scholar	Portuguese	Macedo, et al. Medicamentosconsiderados no tratamento da COVID-19 durante o período de pandemia no Brasil. RECIMA. 2021.	Bring a review of the current types of drugs used in the treatment of COVID-19 in Brazil, highlighting the importance of further	Literature review

				therapeutic studies on the disease.	
CV08	LILACS	English	Brito, Barros e Lopes. Mechanisms and consequences of COVID-19 associated liver injury:What can we affirm?World Journal of Hepatolog. 2020.	To review currently available data on liver damage in patients with COVID-19.	Literature review

Source: Author, 2021.

Table 2: Evidence from studies.

Nº	**Evidências**
CV01	Five main medications were widely used in COVID-19. Coronavirus has characteristics of hepatotropism, in addition most drugs are metabolized by the liver and in a pandemic context, due to the novelty of the disease, numerous prescriptions were made wrongly. This generated a higher rate of hepatotoxicity cases caused by medications.
CV02	In clinical trials of chloroquine for prevention and treatment with COVID-19, there were no reports of hepatotoxicity and the rates of serum enzyme elevations during treatment with chloroquine were low and similar to patients receiving placebo or standard care. Evaluation of previous studies indicates that, to date, no acute viral infections have been successful with chloroquine treatment in humans.
CV03	The mechanism by which Ivermect in can cause liver damageis still unknown. Single-dose therapy with Ivermect in has been associated with a low rate of serumamino transferaseelevations, in trials of Ivermect in to prevent SARS-CoV-2 infection and to improve the course of early and severe COVID-19, amino transfer asee levations Serum serum were notun common, butwerenot more frequent among patients who received Ivermect in than among those who received placebo or a drug comparator.
CV04	Literature data have shown that, in most cases, severe liver damage has been observed when Tocilizumab is combined with other hepatotoxic medicinal products and that liver failure and liver transplantation may occur in patients treated with Tocilizumab. Liver injury occurred as an unpredictable reaction, suggesting the need for careful monitoring during and after treatment.
CV05	Azithromycin can rarely cause clinically apparent liver damage. Because Azithromycin has become so commonly used, it has also become one of the most common causes of drug-induced liver damage and resembles that described with other macrolides. Azithromycin has not been approved for the treatment of viral infections, but some studies have supported its antiviral activity. Recently, few studies are emphasized with the use of Azithromycin in combination with Chloroquine/Hydroxychloroquine for the treatment of COVID-19.
CV06	Studies suggest that Redesemvir has the potential to cause liver damage. Remdesivir therapy given for 7 to 14 days was associated with smaller increases in serum aminotransferase but no other evidence of liver damage. Thus, elevations in serum aminotransferases are common during Remdesivir therapy but are usually asymptomatic, fully reversible, and not associated with jaundice.
CV07	The drugs used for treatment are still uncertain. One of the first drugs mentioned in the literature for the treatment was Chloroquine (CQ) and Hydroxychloroquine (HCQ). Additionally, Azithromycin (AZI), Nitazoxanide (NTZ) and Methylprednisolone (MPDN) are also considered therapeutic alternatives in Brazil. Therefore, it is necessary to identify an efficient treatment against COVID-19, and further research is needed on the drugs used to combat SARS-CoV-2.
CV08	Increases in serum aminotransferase levels (ranging from 16% to 62%) and bilirubin levels (ranging from 5% to 21%) have been reported and appear to be more frequently observed in patients with severe forms of COVID-19. Although absolute changes in these parameters are often seen, other variables, such as the proportion above the upper limit of normal, the onset of liver injury as a complication in severe cases and histopathological findings, reinforce that the liver changes are of dubious clinical relevance in the course. of this disease. Other factors

	should also be considered in these analyses, such as the repercussions of hemodynamic changes, the presence of thrombotic events and, mainly, possible drug-induced liver damage with the current treatment.

Source: Author, 2021.

After analyzing the articles, six categories emerged, namely: 1) Drug-induced liver injury; 2) hepatotoxicity caused by Hydroxochloroquine in COVID-19; 3) the hepatotoxicity caused by Ivermectin in COVID-19; 4) hepatotoxicity caused by Tocilizumab in COVID-19; 5) hepatotoxicity caused by Azithromycin in COVID-19; 6) the hepatotoxicity caused by Remdesivir in COVID-19.

The characteristics of these studies can be observed, in which articles in English are predominant (80%), such as clinical trials (60%), published in international journals (80%) and indexed in the PubMed database (62%).

Main drugs used that have hepatotoxic potential described in the literature were: Chloroquine, Azithromycin, Paracetamol, Lopinavir, Tocilizumab and Remdesivir.

Category 1: DRUG-INDUCED LIVER INJURY

In a pandemic context, different therapies were being tested in patients with COVID-19, including antiviral drugs. Self-medication is not recommended for any disease, but with the COVID-19 pandemic and the uncertainties it brought, the practice of self-medication has gained many followers and the side effects of this practice can be very dangerous. One of them is drug hepatitis. [6]

Novo Coronavirus has characteristics of hepatotropism, the relationship between the liver and COVID-19 may be related to the direct cytopathic effect of the virus. The postulated mechanism of viral entry is through angiotensin converting enzyme 2 (ACE2) receptors, ACE2 receptors are expressed in the gastrointestinal tract, vascular endothelium and liver cholangiocytes. Another mechanism that can cause liver damage is through the drugs that were used for COVID-19. [8]

Drug-induced liver injury occurs through several different mechanisms, including the direct impairment of the structural and functional integrity of the liver and the production of a metabolite that alters the hepatocellular structure and function. [9] In a meta-analysis study carried out in Jamaica, involving 20,874 patients with COVID-19, the combined incidence of drug-induced liver injury was 25.4%. [10]

Drugs that have been over-prescribed and used in COVID-19 such as Chloroquine, Azithromycin, Paracetamol, Lopinavir, Tocilizumab and Remdesivir are all metabolized in the liver. It is important to recognize and remove the offending agent as soon as possible to prevent progression to chronic liver disease or acute liver failure. Adverse drug reactions are an important cause of liver injury that may require suspension of the offending agent, hospitalization or even liver transplant. [11]

The liver is responsible for the concentration and metabolization of most drugs, it is the main target of drug-induced damage. [12] Depending on the duration of the injury and the histological location of the damage, drug-induced liver injury is categorized as acute or chronic, as well as hepatitis, cholestatic, or a mixed injury pattern.[4]

Category 2: HEPATOTOXICITY CAUSED BY HYDROXOCHLOROQUINE IN COVID-19

Hydroxochloroquine is an anti-malarial drug, also used for rheumatoid arthritis, lupus erythrematosus, and amoebiasis, [13] which passively diffuses through cell membranes and into endosomes, lysosomes and Golgi vesicles, where it becomes protonated, trapping hydroxychloroquine in the organelle and raising the surrounding pH. [14] The high pH in endosomes prevents viral particles from using their activity for fusion and entry into the cell.

Hydroxychloroquine is a drug that interferes with lysosomal activity and autophagy, interacting with membrane stability and consequently altering signaling pathways and transcriptional activity, which can result in the inhibition of cytokine production and modulation of certain costimulatory molecules. [14] Regarding possible liver damage caused by the drug, hepatotoxicity in patients who used this drug is uncommon, but it is noteworthy that the drug may be associated with adverse cardiac, ophthalmological, hematological, neurological, musculoskeletal and gastrointestinal adverse effects, among others. [16]

Hydroxychloroquine's injury mechanism consists in the fact that it is metabolized in the liver and can alter the metabolism of other drugs, the toxicity may be due to reactive metabolites and oxidative stress induced by this drug or to an idiosyncratic or synergistic toxic effect associated with processes inflammatory. [15] Although the hepatotoxicity of this drug is rare, it was documented in a study carried out in Brazil, which concluded that there was a rapid normalization of liver enzymes after the withdrawal of hydroxychloroquine. [4]

In clinical trials of Hydroxychloroquine for prevention and treatment with COVID-19, there were no reports of hepatotoxicity and the rates of serum enzyme elevations during treatment with Hydroxychloroquine were low and similar to patients receiving placebo or comparator agents. [17] A study carried out in Brazil in March 2020 reported the case of a patient with severe COVID-19 pneumonia who developed hepatotoxicity associated with the use of hydroxychloroquine, marked by a 10-fold increase in transaminase levels; these levels regressed rapidly after drug withdrawal. [14]

An exception to this is the use of hydroxychloroquine in patients with porphyria cutaneatarda, and when used in relatively high doses, hydroxychloroquine can trigger an acute liver injury with sudden onset of fever and marked elevation of serum enzymes with increased excretion of porphyrins. [18] Therapy is unlikely to cause liver damage in normal individuals, but may trigger an acute worsening of porphyria cutaneatardain susceptible individuals. [19]

The effect of hydroxychloroquine on liver tissue appears ambiguous as it is used to treat liver infection with protozoa, but cases of fulminant liver failure have been reported.

Category 3: HEPATOTOXICITY CAUSED BY IVERMECTIN IN COVID-19

Ivermectin is an anti-infective agent with activity against several nematodes and parasites. [20] In Brazil, a wave of misinformation spread during this period and the drug was included in a list of drugs called “kit-covid-19”, although it has no proven efficacy in the treatment of COVID-19, it was widely used by the population. Ivermectin therapy has been associated with minor, self-limiting elevations in serum aminotransferase and very rare cases of clinically apparent liver damage. [5]

In cell culture, Ivermectin has activity against several viruses, including Novo Coronavirus, in view of the increasing burden of serious diseases represented by COVID-19, drugs with antiviral activity against SARS-CoV-2 in vitro have often been tried to improve the course and prevent mortality. Ivermectin has been evaluated in several open-label studies with evidence suggestive of benefit, but in more carefully designed studies, Ivermectin at doses of 20 to 14 mg per day for 3 to 5 days had little or no effect in preventing infection or improving infection your result. [21]

Single-dose therapy with Ivermectin was associated with a low rate of serum aminotransferase elevations. A single case of clinically apparent liver injury has been reported after the use of Ivermectin, the onset of injury one month after a single dose and was characterized by a hepatocellular pattern of serum enzyme elevations without jaundice. Recovery was quick and complete. [24]

In trials of Ivermectin to prevent SARS-CoV-2 infection and to improve the course of early and severe COVID-19, serum aminotransferase elevations were not uncommon, but were not more frequent among patients receiving Ivermectin than among patients those who received placebo or a medicine comparator. Ivermectin is generally well tolerated and liver damage reported with its use was mild and self-limited in course, the reported occurrence of acute liver injury should be clarified and related to the severity of COVID-19. [23]

Category 4: HEPATOTOXICITY CAUSED BY TOCILIZUMAB IN COVID-19

Tocilizumab (TCZ) is a recombinant monoclonal antibody used to block the IL-6 signal transduction pathway [24]. Interleukin-6 (IL-6) plays an important role in the pathogenesis of cytokine storm and the progression of COVID-19, whose increased levels of IL-6 are key to cytokine storm stimulation and predict an increased risk of respiratory failure and death. [25]

Clinical studies have shown very good effects of TCZ on clinical and biochemical parameters in patients with COVID-19, but the most common side effects of TCZ include headache and hypertension, but hepatotoxicity ranging from mild elevation of transaminases to severe injury may rarely occur drug-induced liver disease, data on TCZ hepatotoxicity in COVID-19 disease are limited and inconclusive (26)

TCZ is used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis, it was proposed for the treatment of COVID-19 when it came to the understanding that the virus not only attacked the lungs, but also provoked an exacerbated body response in an attempt to contain the virus, this mechanism was related to the cytokine storm syndrome (27)

The pathological immune response depends on the cytokine group, but IL-6 is considered an important mediator in the pathogenesis of CRS. TCZ was previously approved for the treatment of severe or life-threatening CRS induced by chimeric antigen receptor T cells. Therefore, in the absence of specific antiviral therapy, TCZ was included in the treatment of COVID-19, with the aim of interrupting the progression of systemic inflammation and CRS by blocking IL-6 (28)

A study in a hospital in Italy reported seven cases of patients with elevated liver enzymes at baseline who received TCZ for severe COVID-19 disease with

improved liver and lung function. In registry trials, serum aminotransferase elevations occurred in a high proportion (10–40%) of patients who received TCZ and, after licensing, were associated with several cases of clinically apparent liver damage with jaundice. (26)

Side effects with the use of TCZ include potential hepatotoxicity, literature data have shown that, in most cases, severe liver damage was observed when TCZ was combined with other hepatotoxic drugs that can cause liver failure. In most cases, TCZ has resulted in severe liver damage when used in combination with other potentially hepatotoxic drugs. (26)

Category 5: HEPATOTOXICITY CAUSED BY AZITROMOCIN IN COVID-19

Azithromycin can also rarely cause clinically apparent liver damage. Azithromycin is a licensed, widely available, inexpensive and generally safe drug, it was proposed as a treatment for COVID-19 initially, as it had in vitro activity against Zika and Ebola viruses and in vivo in preventing severe respiratory tract involvement in infections viral, probably due to its immunomodulatory action (29). However, it has now been concluded that it has no proven efficacy against COVID-19. (30)

Azithromycin inhibits protein synthesis and experimentally reduces inflammation and viral replication, possibly because cytokines and viruses are made of proteins and use cellular ribosomes for protein translation. (31) Furthermore, inhibition of virus production can reduce viral transmission to other people, an important additional benefit (29).

The typical liver injury caused by Azithromycin resembles that described with other macrolides, typical symptoms are fatigue, jaundice, abdominal pain, itching, fever and eosinophilia may also be present, this form of liver injury caused by Azithromycin is generally benign, histology In these cases, the liver usually demonstrates bile duct loss, which, if severe, can result in disappearing bile duct syndrome and chronic cholestatic liver failure, ultimately requiring liver transplantation (32).

The hepatocellular forms of liver damage caused by Azithromycin can be severe and lead to acute liver failure and death or the need for emergency liver transplantation. However, in most cases, recovery occurs within 4 to 8 weeks, the cause of idiosyncratic liver injury due to Azithromycin is unknown, but the speed of onset suggests hypersensitivity as the cause (9).

Category 6: HEPATOTOXICITY CAUSED BY REMDESIVIR IN COVID-19

Remdesivir is a nucleotide analogue RNA polymerase inhibitor that has potent activity against the RNA-dependent RNA polymerases encoded by SARS-CoV-2 (34). This drug was developed for Ebola virus disease, and has shown some in vitro efficacy against SARS-CoV-2, Remdesivir therapy is given intravenously for 5 to 10 days and is often accompanied by transient and reversible mild to mild elevations moderate in serum aminotransferase levels, but only rarely has it been associated with cases of clinically apparent liver damage, its liver effects being overshadowed by the systemic effects of COVID-19 (35)

They claim that the results of liver toxicity have been contradictory, however, and it appears that Remdesivir can cause liver dysfunction. According to (3). Data regarding the potential hepatotoxicity of Remdesivir are currently limited, Remdesivir has been shown to be toxic to human hepatocytes, the Food and Drug Administration (FDA) has warned of the incidence of elevated liver enzymes in patients treated with Remdesivir, indicating a potential induced liver injury by drugs (36)

They described five cases of patients treated with Remdesivir with high levels of aminotransferases (TGO and TGP), suggesting hepatocellular damage, but without liver failure (11). Adverse events of Remdesivir therapy include mild to moderate degrees of nausea and vomiting, headache, fatigue, renal dysfunction, elevations in serum aminotransferases and rash, and rare cases of hypersensitivity reactions, liver dysfunction and damage have been reported (37)

Before attributing liver dysfunction to Remdesivir, it is imperative to extensively evaluate other etiologies not related to COVID-19, such as viral hepatitis, potential hepatotoxic drugs, and autoimmune diseases (11). The use of Remdesivir in patients hospitalized with COVID-19 is associated with a transient mild to moderate elevation in liver biochemistry with low rates of discontinuation. (3)

IV. CONCLUSION

COVID-19 has put the health systems of many countries under great pressure and has been particularly challenging due to the lack of predictive parameters and effective pharmacotherapies for the treatment of advanced liver disease. Despite the common descriptions of liver enzyme alterations observed in patients with COVID-19, the frequency, intensity and impact of liver damage are discreet and of little clinical significance in relation to the morbidity or mortality of this disease.

A better understanding of the natural history of liver involvement can be addressed in the near future with well-designed prospective studies on viral and immunological research. Thus, considering all these factors, respecting the rules set out above and excluding confounding factors, in particular those linked to the patient's behavior in times of crisis, should allow physicians to detect definitive drug-induced liver damage and avoid withdrawal inadequate use of a potentially useful drug.

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