



VIRAL AND DRUG LIVER INJURY CAUSED BY COVID-19

INJÚRIA HEPÁTICA VIRAL E MEDICAMENTOSA CAUSADA PELA COVID-19

LESIÓN HEPÁTICA VIRAL Y FARMACOLÓGICA CAUSADA POR COVID-19

Débora Dantas Nucci Cerqueira¹, Giuliene Rocha de Medeiros², João Victor Cordeiro Farias³, Penelopy Rodrigues de Macedo⁴

Submetido em: 26/06/2021

e26442

Aprovado em: 16/07/2021

ABSTRACT

The current pandemic caused by SARS-CoV-2 originated in the city of Wuhan, China with an outbreak of pneumonia. The reported symptoms were mostly respiratory, but mounting evidence began to indicate that COVID-19 could reach other organs and systems. Among the gastrointestinal symptoms, liver involvement appears to be more common, with changes in liver enzymes (ALT and AST) being the first sign. Therefore, the present study aims to evaluate and discuss the hepatic manifestations in COVID-19 as the infection, manifestations, and drug effects. The study was based on a literature review, of a qualitative nature and an exploratory type. Articles were selected, according to some criteria, from databases such as PUBMED, MEDLINE and Google Scholar. The mechanism that SARS-CoV-2 uses to reach the liver is still uncertain, there are currently 3 hypotheses: ACE2 receptors in cholangiocytes, cytokine storm, and drug-induced liver injury, due to the increase in the indiscriminate use of hepatotoxic drugs without scientific comprovação like hydroxychloroquine who can lead to fulminant hepatic failure and azithromycin potentiates these effects, the role of remdesivir on the liver are still uncertain. Liver damage in mild cases of COVID-19 can be transient, but doctors should monitor and be alert to any changes in liver enzymes. When severe liver damage occurs, liver protective drugs have usually been given to these patients. Thus, this review provides a review of hepatic impairment and the management of patients considering the main studies carried out to date.

KEYWORDS: SARS-CoV-2. Hepatic manifestations. Liver enzymes. Drugs

RESUMO

A atual pandemia causada pelo SARS-CoV-2 teve origem na cidade de Wuhan, na China, com um surto de pneumonia. Os sintomas relatados foram principalmente respiratórios, mas crescentes evidências começaram a indicar que a COVID-19 poderia atingir outros órgãos e sistemas. Entre os sintomas gastrointestinais, o envolvimento hepático parece ser mais comum, sendo as alterações das enzimas hepáticas (ALT e AST) o primeiro sinal. Portanto, o presente estudo tem como objetivo avaliar e discutir as manifestações hepáticas no COVID-19 como a infecção, manifestações e efeitos de drogas. O estudo baseou-se em uma revisão da literatura, de natureza qualitativa e do tipo exploratório. Foram selecionados artigos, de acordo com alguns critérios, de bases de dados como PUBMED, MEDLINE e Google Acadêmico. O mecanismo que o SARS-CoV-2 utiliza para chegar ao fígado ainda é incerto, existem atualmente 3 hipóteses: receptores ACE2 em colangiócitos, tempestade de citocinas e lesão hepática induzida por drogas, devido ao aumento do uso indiscriminado de drogas hepatotóxicas sem comprovação científica, como a hidroxiclóricoquina, que pode levar à insuficiência hepática fulminante e a azitromicina potencializa esses efeitos, já o papel do remdesivir no fígado ainda é incerto. Os danos ao fígado em casos leves de COVID-19 podem ser transitórios, mas os médicos devem monitorar e estar alertas a quaisquer alterações nas enzimas hepáticas. Quando ocorre lesão hepática grave, geralmente são administrados medicamentos de proteção ao fígado a esses pacientes. Assim, este estudo fornece uma revisão do comprometimento hepático e do manejo dos pacientes, considerando as principais pesquisas realizados até o momento.

¹ Universidade de Pernambuco - UPE

² Universidade de Pernambuco - UPE

³ Universidade de Pernambuco - UPE

⁴ Centro Universitário Brasileiro - UNIBRA



PALAVRAS-CHAVE: SARS-CoV-2. Manifestações hepáticas. Enzimas hepáticas. Drogas.

RESUMEN

La pandemia actual causada por el SARS-CoV-2 se originó en la ciudad de Wuhan, China, con un brote de neumonía. Los síntomas informados fueron principalmente respiratorios, pero la creciente evidencia comenzó a indicar que COVID-19 podría llegar a otros órganos y sistemas. Entre los síntomas gastrointestinales, la afectación hepática parece ser más común, siendo el primer signo los cambios en las enzimas hepáticas (ALT y AST). Por lo tanto, el presente estudio tiene como objetivo evaluar y discutir las manifestaciones hepáticas en COVID-19 como la infección, las manifestaciones y los efectos de los fármacos. El estudio se basó en una revisión de la literatura, de carácter cualitativo y de tipo exploratorio. Los artículos fueron seleccionados, según algunos criterios, de bases de datos como PUBMED, MEDLINE y Google Scholar. El mecanismo que utiliza el SARS-CoV-2 para llegar al hígado aún es incierto, actualmente existen 3 hipótesis: receptores ACE2 en colangiocitos, tormenta de citocinas y daño hepático inducido por fármacos, debido al aumento del uso indiscriminado de fármacos hepatotóxicos sin Compromiso científico, como la hidroxiclороquina que puede provocar insuficiencia hepática fulminante y la azitromicina potencia estos efectos, el papel del remdesivir en el hígado aún es incierto. El daño hepático en casos leves de COVID-19 puede ser transitorio, pero los médicos deben vigilar y estar alerta a cualquier cambio en las enzimas hepáticas. Cuando se produce un daño hepático severo, a estos pacientes generalmente se les han administrado medicamentos protectores del hígado. Así, esta revisión proporciona una revisión de la insuficiencia hepática y el manejo de los pacientes considerando los principales estudios realizados hasta la fecha.

PALABRAS CLAVE: SARS-CoV-2. Manifestaciones hepáticas. Enzimas del hígado. Drogas

INTRODUCTION

At the end of 2019 the World Health Organization (WHO) received notification of a cluster group of patients affected by pneumonia due to an unknown cause from Wuhan, China (Del Rio, 2019). On January 9, 2020, it was reported that this novel type of coronavirus, termed as “novel coronavirus-2019” (SARS-CoV-2), was responsible for the outbreak (Chakraborty, 2020) leading the WHO in March 11, 2020 to characterize the infection as a pandemic (WHO, 2020).

A report by Hubei initially summarized the clinical characteristics of 138 patients at early stage of this disease. The authors found that the most common symptoms were fever (98.6%), fatigue (69.6%) and dry cough (59.4%) (Whan, 2020) and less common symptoms were sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%) (In, 2020).

The SARS-CoV-2 infects the human cells by spike glycoprotein binding to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) (Ge, 2020). As for the spike protein of SARS-CoV-2, it contains two regions, S1 subunit and S2 subunit. The S1 domain is linked to the receptor binding domain (RBD) while the S2 domain is linked to cell membrane fusion (Morse, 2020). The infection seems to be determined by the affinity between RBD viral and the ACE2 of human cells (Whan, 2020).

Mounting evidence indicates that patients might also report extra-pulmonary manifestations (Dorrell *et al.*, 2020). A study by Wang (2020) showed that 39.6% of 140 confirmed COVID-19 patients had gastrointestinal (GI) symptoms and liver inflammation to be even more prevalent than GI symptoms with 24% of patients having elevated transaminases. Despite being frequently overlooked, involvement of the gastrointestinal (GI) tract and the hepatic system is now being increasingly reported (Cha, 2020).



Liver function tests (LFTs) include measures of hepatocyte injury such as Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT), bile duct injury or cholestasis like alkaline phosphatase, and gamma-glutamyltransferase, (GGT), markers of hepatic clearance/biliary secretion capacity (bilirubin), as well as measures of synthetic capacity (prothrombin time and albumin) (Bertolini, 2020). A varying degree of liver test abnormalities has been described in COVID-19 affected patients (Guan, 2020), elevated markers of liver cell injury (ALT, AST) are more common (Fan *et al.*, 2020).

There is not an effective antiviral drug for COVID-19, symptomatic and supportive treatments are crucial, many patients are treated with antiviral and antipyretic drugs, however, both drugs have adverse reactions, including liver injury (Fan *et al.*, 2020). Thus, it is important for clinicians not to be distracted by minimally elevated liver enzymes and focus on general management and supportive care (Cha, 2020).

COVID-19 is a new disease and its mechanisms of infection and symptoms are still unclear after one year of its appearance. The involvement of the hepatic system by Sars-CoV-2 has been underestimated but in the last few months, there has been a significant increase in evidence demonstrating that the coronavirus can affect the liver in several ways and if not identified and treated quickly it can lead to consequences and death. In this review, the characteristics' explanations of hepatic involvement caused by SARS-CoV-2 infection, the drug's effects used as treatment, and the patients' management are summarized.

METHODOLOGY

The study is a narrative bibliographic review, of a qualitative nature, with an exploratory characteristic as recommended by Pereira *et al.* (2018). Consisting of articles selected through searches in national and international databases, such as Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine (PUBMED), in addition the Google Academic tool, with publication date from 2014 to 2021 and include the keywords used (Covid-19; Sars-CoV-2 liver infection; Drug induced liver injury (DILI); Patient's management).

LIVER INFECTION BY SARS-CoV-2

The liver is a unique organ that it is supplied by both arterial and venous blood which allows these two blood supplies to mix and to bathe the various structures and cells in the liver with their content it is critical for the production of proteins, for the metabolism of nutrients, and for the clearance of toxins (Kubes, 2020).

The angiotensin-converting enzyme 2 (ACE2) is broadly expressed in nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder, and ileum, and these human organs are more vulnerable (Zhou, 2020). Liver damage in patients with coronavirus infections might be directly caused by the viral infection of liver cells (Zhang, 2020).



A study by Chai *et al.* (2020) showed a higher expression of ACE2 in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6% of cells), ACE expression level in cholangiocytes is comparable to Alveolar Type 2 cells which is the major SARS and 2019-nCoV targeting cell type in lung, suggesting that SARS-CoV-2 can bind directly to cholangiocytes with ACE2 present on its surface to deregulate liver function. Cholangiocytes are involved in many aspects of liver physiology, including regeneration and adaptive immune response mechanisms, and the disruption of cholangiocyte function can cause hepatobiliary damage (Alqahtani & Schattenberg, 2020).

COVID- 19- Associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID- 19 in patients with or without pre-existing liver disease. Approximately 2–10% of patients with COVID-19 present with diarrhea and SARS-CoV-2 RNA has been detected in stool and blood samples, this evidence implicates the possibility of viral exposure in the liver (Yeo, 2020).

Pathological studies confirmed the presence of the virus in liver tissue, although the viral title was relatively low because viral inclusions were not observed (Zhang, 2020). A study by Sun (2020) with liver biopsy specimens of patients deceased as a result of severe COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity, indicating that the injury could have been caused by either SARS- CoV- 2 infection or drug- induced liver injury (DILI).

Immune-mediated inflammation, such as cytokine storm, pneumonia-associated hypoxia, reactivation of pre-existing liver disease or drug-induced liver injury might also contribute to liver damage or even develop into liver failure in patients with COVID-19 who are critically ill (Zhang, 2020; Sun, 2020).

The liver is an important organ in the human body. Although COVID-19 is a respiratory disease, several evidences show that it can affect other organs, including the liver. The mechanism of infection by Sars-CoV-2 is still uncertain, most authors suggest that the virus penetrates cholangiocytes due to the expression of the ACE2 protein as well as the lungs. However, other forms of liver injury in COVID- 19 are reported as cytokine storm, hypoxia and DILI.

HEPATIC MANIFESTATIONS

The elevation of hepatic biomarkers, such as AST, ALT and total bilirubin has been reported in several studies (CHA, 2020; ALQAHTANI & SCHATTENBERG, 2020 ;). Elevated *lactate dehydrogenase* (LDH), creatinine kinase or myoglobin, abnormal prothrombin time and high GGT were also reported at intensive care units (ICU) or normal care units (NCU) during hospitalization (Portincasa, 2020).

Elevated hepatic biomarkers are seen in 15-70% of patients and >90% of patients during the course of the illness and these manifestations were mostly found in the USA and China. A recent meta-analysis of 107 studies consisting of 20,874 COVID-19 positive patients, the incidence of elevated liver enzymes was 23.1% (Kulkarni *et al*, 2020).



In a cohort of patients with COVID-19 who were admitted to an American academic medical center, 69% had abnormal liver biochemistry on admission and 93% developed liver biochemistry above the upper limit of normal during hospitalization. The pattern of liver biochemistry was generally consistent with hepatocellular lesion, with predominance of AST (Bloom, 2020).

Evidences suggest that there is a strong correlation between the severity of the viral infection and the degree of liver enzyme elevation (Zhang, 2020; Mantovani, 2020; Clark, 2021). According to Bloom (2020), aminotransferase elevations not only mirror COVID-19 severity but also raise the possibility that the pattern of AST-dominant elevation reflects a unique virally-mediated mechanism of hepatic injury. Notably, the prevalence of an elevated AST was substantially higher among patients with severe COVID-19 disease (45.5%) compared to those with mild disease (15.0%) (Yip, 2020). Mild cases of the virus may have no abnormality or only slightly elevated aminotransferase levels (Mantovani, 2020), but a large study estimated that the occurrence of liver injury during COVID-19 infection is associated with a 9-fold greater risk of severe infection (CAI, 2020).

A retrospective study done with 515 patients aged >18 years tested positive for SARS- CoV- 2 infection at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome to investigate the prevalence of liver damage shows that GGT elevation was present in 13.6% of patients, these alterations are associated with the risk of ICU admission, being a possible indicator of more severe clinical evolution, but not with mortality, and tend to normalize over time (Ponziani, 2020). In severe COVID-19 cases, hypoalbuminemia is common and correlates with worse patient outcomes. Additionally, increased bilirubin levels and liver stiffness measured by transient elastography were found to be associated with more severe outcome (Saviano; Wrensch; Ghany; Baumert, 2021).

Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment (Zhang, 2020). Still, surveillance of viral clearance in the liver and long-term outcome of COVID-19 is required (Wang, 2020).

Abnormal blood tests on the liver were found in most patients with COVID-19, studies have shown that ALT, AST, LDH and GGT are elevated and that the predominance of AST may indicate severe liver injury. Thus, at the slightest sign of changes in liver exams, liver involvement should be considered and intensive care started.

OTHER PATHWAYS TO LIVER INJURY DURING COVID-19

While the cause of liver injury related to SARS-CoV-2 infection is unclear, some potential causes have been hypothesized. Dysregulation of the innate immune response can be one aspect of liver injury in COVID-19 (Alqahtani & Schattner, 2020), which is characterized as an over activation of the immune system, dysfunction of T Helper 17 and regulatory T cells prompting an enhanced secretion of pro-inflammatory cytokines, in an event known as “cytokine storm” (Campos *et al.*, 2020). Patients exhibit abnormal levels of C-reactive protein (CRP), lymphocytes, neutrophils and cytokines IL-6, IL-10, IL-2 and IFN- γ (Liu *et al.*, 2020). In COVID- 19, it is hypothesized that the presence of SARS- CoV2 activates the innate and adaptive immune system, which results in the release of IL- 6, arising during



illness and declining during recovery, and levels correlate with disease severity (Di Mauro, Scavone, Rafaniello, *et al.*, 2020; Diao, Wang, Liu *et al.*, 2020).

If not diagnosed and treated early, the cytokine storm can reach to the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammatory syndrome (Rumende, 2020) that can potentially injure the lungs, gut, and liver (evidenced by elevation of liver enzymes) and lead to death (Clarck, 2020). In a retrospective study at Beijing You'an Hospital, China, patients with liver damage had higher elevated CRP levels while T cell counts dropped to the lowest levels, serum level of inflammatory cytokines reached their peaks a few days after the onset of COVID-19. The author suggests that inflammatory cytokines are involved in the process at an early stage, which can explain the reason for the patients with mild liver injury (Li *et al.*, 2020).

A retrospective, observational study by Da *et al.* (2020) that included consecutive adult patients (>18 years old) diagnosed with severe or critical COVID-19, with or without evidence of liver injury, admitted to Mount Sinai Hospital in New York City, NY who underwent testing for cytokine release syndrome (CRS) blood markers (IL-6, IL-8, TNF- α , and/or IL-1 β) showed that median peak inflammatory markers were generally higher in the liver injury group (CRP: 247 vs. 168 mg/L; LDH: 706 vs. 421 U/L), ferritin was nearly 4-fold higher in the liver injury cohort (2,973 vs. 751 ng/mL). Ferritin is an inflammatory acute-phase reactant and it was the single most distinguishing inflammatory marker, with levels greater than 4 times higher in those with liver injury compared to those without. And the cytokines measured, IL-6 levels were higher in the liver injury group compared to the control group but there was no significant difference in IL-8, TNF- α , and IL-1 β levels between the two cohorts. The authors findings suggests that IL-6 is the main cytokine that is associated with higher liver enzymes in COVID-19 may be related to the accuracy of IL-6 in detecting inflammatory response, which results in liver injury but the IL-6 role in the disease it is unclear (Da, Kushner, El Halabi, *et al.*, 2020)

Other cause of some liver abnormalities in COVID-19 is Drug-induced liver injury (DILI), given the fact that the liver is involved in the metabolism of many drugs, including nucleoside analogs and protease inhibitors that are currently used to treat COVID-19, hepatotoxicity from these drugs could have arisen (Alqahtani & Schattenberg, 2020; Boeckmans, 2020).

The most common drugs used during the course of the COVID-19 are antipyretic agents. Most of these medications contain acetaminophen, which is a drug recognized as being able to cause significant liver damage or induce liver failure (Feng *et al.*, 2020), an acute ingestion of >7.5 to 10 g of acetaminophen in adults or 150 to 200 mg/kg in children is likely to cause hepatotoxicity (Hodgman and Garrard, 2012).

A study by XU (2020) using liver biopsies from a COVID-positive patient treated with lopinavir and ritonavir as antiviral therapy showed moderate micro vesicular steatosis and mild lobular activity, indicate the possibility of drug-induced liver injury. Lopinavir administration is associated with moderate-to-severe elevations in serum aminotransferase levels ($> 5 \times$ ULN) in 3% to 10%. The pattern of serum enzyme elevations varies from hepatocellular to cholestatic or mixed (LiverTox, 2017; Olry, 2020) and



ritonavir, due to its enzymatic inhibitor properties, can enhance the plasmatic level of co-administered drugs which then raises the risk of their hepatotoxicity (LiverTox, 2012; Olry, 2020).

Chloroquine, and its less toxic version, Hydroxychloroquine are drugs indicated in the treatment and prevention of malaria as well as an anti-inflammatory agent for the treatment of rheumatoid arthritis and lupus erythematosus (Bakadia *et al.*, 2021) is also applied as an antiviral drug, by inhibiting a pre-entry step of the viral cycle by interfering with the binding of viral particles to their receptors on the cell surface (Ibáñez *et al.*, 2020). Chloroquine has an immunomodulatory ability on activated immune cells, it downregulates the expression of Toll-like receptors (TLRs) and TLR-mediated signal transduction and decreases or suppresses the release and production of TNF- α , IL-1, and IL-6, which facilitate the cytokines storm in COVID-19 (Savarino, 2003).

However, the main problem with the administration of Chloroquine\ Hydroxychloroquine is related to the side effects, which limit the use of these drugs in COVID-19. These adverse effects include prolonged QT interval, death, and transfer to intensive care with the persistence of virus after 6 days of treatment in more than 80 % of the patients and no significant difference in the rate of viral elimination between HCQ and standard of care (Molina *et al.*, 2020; Tang *et al.*, 2020). With sparse evidence in small clinical settings and the effects on hepatic tissue seems ambiguous, but cases of fulminant hepatic failure have been reported (Liu, 2020).

Azithromycin is antibiotic that would have additional effects to hydroxychloroquine because of additional properties on host-defense reactions by exerting the immuno modulation effects in chronic inflammatory diseases (Bakadia *et al.*, 2021), but there still are few pieces of evidence. A retrospective study with 18 patients with azithromycin-induced liver injury shows that azithromycin-induced liver injury occurs within 1–3 weeks after azithromycin initiation and is predominantly hepatocellular in nature, if not identified can lead to death or liver transplantation (Martinez *et al.*, 2015).

Remdesivir is an antiviral used in combination with other drugs to treat some viral infections like HCV and represents one of the most promising treatments of SARS-CoV-2 (Medeiros *et al.*, 2020). It has been recently recognized as a promising antiviral drug due to its effect of incorporates into nascent viral RNA chains and results in premature termination against a wide array of RNA viruses, including SARS/MERS-CoV5, infection in cultured cells, mice, and nonhuman primates (NHP) models (Wang *et al.*, 2020). This drug is not reported to cause liver injury in LiverTox (2018) and we have insufficient data about the potential hepatotoxicity of remdesivir. A study based on the use of remdesivir for patients hospitalized with severe COVID-19 shows that from the 53 patients whose data were analyzed clinical improvement was observed in 36/53 patients (68%) (Grein, 2020) but in another randomized double-blind, placebo-controlled, multicenter trial performed in China, mortality at day 28 was similar between the 2 groups (14% died in the remdesivir group vs. 13% in the placebo group) (Wang, 2020). Thus, the attribution of hepatotoxicity to remdesivir is challenging (Olry, 2020).

Respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ failure, due to COVID-19, may also cause hepatic ischemia and hypoxia-reperfusion dysfunction (Feng *et al.*, 2020). Under the conditions of ischemia and hypoxia, lipid accumulation, glycogen consumption



and adenosine triphosphate depletion of hepatocytes can inhibit cell survival signal transduction, rapidly leading to hepatocyte death (Tian & Ye, 2020).

PATIENTS' MANAGEMENT

According to the American association for the study of liver diseases (AASLD) physicians should rule out other etiologies unrelated to COVID-19, including viruses such as hepatitis A, B and C, and drug-induced liver injury when assessing patients with COVID-19 and elevated hepatic biomarkers. Regular monitoring of hepatic biomarkers should be performed in all hospitalized COVID-19 patients, regardless of baseline values. (Fix *et al.*, 2020).

For patients with severe and critical COVID-19 disease with liver damage, physicians should consider cytokine storms, ischemia or microcirculatory hypoxia as the cause. Therefore, respiratory and circulatory support must be strengthened. In cases of liver damage caused by drugs, the interruption or reduction of the quantity of suspected drugs and assessment of the degree of liver damage should be considered (Tian & Ye, 2020).

Various evidence shows that the indiscriminate use of medications can affect the liver and lead to more serious complications. With the pandemic caused by Sars-CoV-2, the rates of self-medication have increased about 200%, mostly drugs without scientific efficacy such as Chloroquine\Hydroxychloroquine, Azytromicine and vitamins (Remião, 2020). The consequences of self-medication can lead to aggravation of diseases, intoxications, drug resistance, increased liver enzymes and liver failure. Paracetamol, also known as acetaminophen, is a widely used antipyretic and analgesic, it is one of the active principles (alone or in combination) with the largest therapeutic administration worldwide. Sold without a prescription, it is responsible for thousands of medical admissions in the US due to poisoning that can lead to liver transplantation (Agrawal & Khazaeni, 2021).

Therefore, the use of medications must be done only when prescribed by a doctor according to the patient's needs and based on scientific evidence. The vaccine is the only effective treatment against COVID-19 today, social detachment and the use of masks continue to be essential to stop contamination by Sars-CoV-2.

FINAL CONSIDERATIONS

CoVs have caused three large-scale outbreaks over the past two decades: severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and now COVID-19. Since the declaration of the pandemic, ~141 million people have been infected with SARS-CoV-2, with >3 million deaths worldwide and global research efforts are rapidly being mobilized, each day resulting in new advances in basic and clinical research, therapy, diagnosis, vaccines and drug development, as well as epidemiology (Harrison, 2020).

Emerging evidence suggests that SARS-CoV-2 can involve multiple organs beyond lungs. There is still little data on direct liver disease predictions in the course of coronavirus infection, it has



been proposed that COVID-19 causes direct liver injury via a viral hepatitis, but studies showed that there are alternative explanations as cytokine storm, ischemia, hypoxia and drug hepatotoxicity (Bangash, Patel, & Parekh, 2020; Tian & Ye, 2020). Health professionals should be alert to the first sign of liver injury, such as changes in liver enzymes, and consider COVID-19.

Due to the lack of a scientifically effective drug to treat this disease, the prescription of test drugs is not contra-indicated but it should be done with caution as it can lead to DILI, liver failure, and future complications (El Ouali; Romero-Marrero & Regueiro, 2020). Thus, liver enzymes should be monitored regularly in all hospitalized COVID-19 patients, overall, liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment. However, when severe liver damage occurs, liver protective drugs have usually been given to such patients (Zhang, 2020).

New studies must be carried out in order to better understand the liver involvement by SARS-CoV-2, the other injury pathways must also be investigated, such as hypoxia, the mechanisms of hepatic injury to drugs such as Remdesivir should also be better elucidated.

REFERENCES

AGRAWAL, S.; KHAZAENI, B. Acetaminophen Toxicity. **StatPearlsPublishing**, jul. 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441917/>

BANGASH, M. N.; PATEL, J.; PAREKH, D. COVID-19 and the liver: little cause for concern. **The lancet. Gastroenterology & hepatology**, v. 5, n. 6, p. 529–530, 2020. DOI: [https://doi.org/10.1016/S2468-1253\(20\)30084-4](https://doi.org/10.1016/S2468-1253(20)30084-4)

BERTOLINI, A.; VAN DE PEPPEL, I. P.; BODEWES, F. A. J. A.; MOSHAGE, H.; FANTIN, A.; FARINATI, F.; FIOROTTO, R.; JONKER, J. W.; STRAZZABOSCO, M.; VERKADE, H. J.; PESERICO, G. Abnormal liver function tests in COVID-19 patients: relevance and potential pathogenesis. **Hepatology**, 2020. DOI: doi:10.1002/hep.31480

BAKADIA, B. M.; HE, F.; SOUHO, T.; LAMBONI, L.; ULLAH, M. W.; BONI, B. O.; AHMED, A., MUKOLE, B. M., & YANG, G. Prevention and treatment of COVID-19: Focus on interferons, chloroquine/hydroxychloroquine, azithromycin, and vaccine. **Biomedicine & pharmacotherapie**, v. 133, 2021. DOI: <https://doi.org/10.1016/j.biopha.2020.111008>

BLOOM, P. P.; MEYEROWITZ, E. A.; REINUS, Z.; DAIDONE, M.; GUSTAFSON, J.; KIM, A. Y.; SCHAEFER, E.; CHUNG, R. T. Liver Biochemistries in Hospitalized Patients With COVID-19. **Hepatology**, 2020. DOI: <https://doi.org/10.1002/hep.31326>

BOECKMANS, J.; RODRIGUES, R. M.; DEMUYSER, T.; PIÉRARD, D.; VANHAECKE, T.; ROGIERS, V. COVID-19 and drug-induced liver injury: a problem of plenty or a petty point?. **Archives of toxicology**, v. 94, n. 4, p. 1367-1369, 2020. DOI: <https://doi.org/10.1007/s00204-020-02734-1>

CAI, Q.; HUANG, D.; YU, H.; ZHU, Z.; XIA, Z.; SU, Y.; LI, Z.; ZHOU, G.; GOU, J.; QU, J.; SUN, Y.; LIU, Y.; HE, Q.; CHEN, J.; LIU, L.; XU, L. COVID-19: Abnormal liver function tests. **Journal of hepatology**, v. 73, n. 3, p. 566–574, 2020. DOI: <https://doi.org/10.1016/j.jhep.2020.04.006>



CAMPOS, L. N.; COSTA, A. C. S.; CERQUEIRA, D. D. N.; RANGEL, G. R.; ANDRADE, I. C. de F.; SOUZA, S. C. B. de; SILVA, J. C. D. de M.; COSTA, B. M. da; ROCHA, S. W. S. COVID-19 neurological manifestations: a narrative review on the mechanisms, pathogenesis, and clinical management. **Research, Society and Development**, v. 9, n. 12, e4291210724, 2020. DOI: <https://doi.org/10.33448/rsd-v9i12.10724>

CHA, M. H.; REGUEIRO M.; SANDHU D. S. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. **World J Gastroenterol**, v. 26, n. 19: p. 2323-2332, 2020. Disponível em: <https://www.wjnet.com/1007-9327/full/v26/i19/2323.htm>. DOI: <https://dx.doi.org/10.3748/wjg.v26.i19.2323>

CHAI X, HU L.; ZHANG, Y. *et al.* Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. **BioRxiv**, 2020. DOI: doi:10.1101/2020.02.03.931766.

CHAKRABORTY, C.; SHARMA, A. R.; SHARMA, G.; BHATTACHARYA, M.; LEE, S. S. SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options. **European review for medical and pharmacological sciences**, v. 24, n. 7. P. 4016–4026, 2020. DOI: https://doi.org/10.26355/eurrev_202004_20871

CLARK, R.; WATERS, B.; STANFILL, A. G. Elevated liver function tests in COVID-19: Causes, clinical evidence, and potential treatments. **The Nurse practitioner**, v. 46, n. 1, p. 21–26, 2021. DOI: <https://doi.org/10.1097/01.NPR.0000722316.63824.f9>

DA, B. L.; KUSHNER, T.; EL HALABI, M.; PAKA, P.; KHALID, M.; UBEROI, A.; LEE, B. T.; PERUMALSWAMI, P. V.; RUTLEDGE, S. M.; SCHIANO, T. D.; FRIEDMAN, S.; SABERI, B. Liver Injury in Hospitalized Patients with COVID-19 Correlates with Hyper Inflammatory Response and Elevated IL-6. **Hepatology communications**, v. 5, n. 2, p. 177–188, 2020. DOI: <https://doi.org/10.1002/hep4.1631>

DEL RIO, C.; MALANI, P. N. Novel Coronavirus—Important Information for Clinicians. **JAMA**, v. 323, n. 11, p. 1039–1040, 2019. DOI: doi:10.1001/jama.2020.1490

DI MAURO, G.; SCAVONE, C.; RAFANIELLO, C.; ROSSI, F.; CAPUANO, A. SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment. **International immunopharmacology**, v. 84, 2020. DOI: <https://doi.org/10.1016/j.intimp.2020.106519>

DIAO, B.; WANG, C.; TAN, Y.; CHEN, X.; LIU, Y.; NING, L.; CHEN, L.; LI, M.; LIU, Y.; WANG, G.; YUAN, Z.; FENG, Z.; ZHANG, Y.; WU, Y.; CHEN, Y. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). **Frontiers in immunology**, v. 11, n. 827, 2020. DOI: <https://doi.org/10.3389/fimmu.2020.00827>

DORRELL, R. D.; DOUGHERTY, M. K.; BARASH, E. L.; LICHTIG, A. E.; CLAYTON, S. B.; JENSEN, E. T. Gastrointestinal and hepatic manifestations of COVID-19: A systematic review and meta-analysis. **JGH open: an open access journal of gastroenterology and hepatology**, 2020. DOI: <https://doi.org/10.1002/jgh3.12456>

EL OUALI, S.; ROMERO-MARRERO, C.; REGUEIRO, M. Hepatic manifestations of COVID-19. **Cleveland Clinic journal of medicine**, 2020. DOI: <https://doi.org/10.3949/ccjm.87a.ccc061>

FAN, Z.; CHEN, L.; LI, J.; CHENG, X.; YANG, J.; TIAN, C.; ZHANG, Y.; HUANG, S.; LIU, Z.; CHENG, J. Clinical Features of COVID-19-Related Liver Functional Abnormality. **Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association**, v. 18, n. 7, 1561-1566, 2020. DOI: <https://doi.org/10.1016/j.cgh.2020.04.002>

FENG, G.; ZHENG, K. I.; YAN, Q. Q.; RIOS, R. S.; TARGHER, G.; BYRNE, C. D. *et al.* COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. **J Clin Transl Hepatol**, v. 8, n. 1, p. 18-24, 2020. DOI: doi:10.14218/JCTH.2020.00018.



FERM, S.; FISHER, C.; PAKALA, T. *et al.* Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. **Clin Gastroenterol Hepatol**, jun. 2020. DOI: doi:10.1016/j.cgh.2020.05.049

FIX, O. K.; HAMEED, B.; FONTANA, R. J.; KWOK, R. M.; MCGUIRE, B. M.; MULLIGAN, D. C.; PRATT, D. S.; RUSSO, M. W.; SCHILSKY, M. L.; VERNA, E. C.; LOOMBA, R.; COHEN, D. E.; BEZERRA, J. A.; REDDY, K. R.; CHUNG, R. T. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. **Hepatology**, v. 72, n. 1, p. 287-304, 2020. DOI: <https://doi.org/10.1002/hep.31281>

GE, H.; WANG, X.; YUAN, X.; XIAO, G.; WANG, C.; DENG, T.; YUAN, Q.; XIAO, X. The epidemiology and clinical information about COVID-19. **European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology**, v. 39, n. 6, p. 1011–1019, 2020. DOI: <https://doi.org/10.1007/s10096-020-03874-z>

GUAN, G. W.; GAO, L.; WANG, J. W.; WEN, X. J.; MAO, T. H.; PENG, S. W.; ZHANG, T.; CHEN X. M.; LU, F. M. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. **Chin. J. Hepatol**, v. 28, 2020. DOI: doi:10.3760/cma.j.issn.1007-3418.2020.02.002.

GREIN, J.; OHMAGARI, N.; SHIN, D.; DIAZ, G.; ASPERGES, E.; CASTAGNA, A. Compassionate use of remdesivir for patients with severe covid-19. **N Engl J Med**, v. 382, p. 2327–2336, 2020.

HARRISON, A. G.; LIN, T.; WANG, P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. **Trends in immunology**, v. 41, n. 12, p. 1100–1115, 2020. DOI: <https://doi.org/10.1016/j.it.2020.10.004>

HODGMAN, M. J.; GARRARD, A. R. A review of acetaminophen poisoning. **Crit Care Clin**, v. 28, p. 499-516, 2012. DOI: <https://doi.org/10.1016/j.ccc.2012.07.006>

IBÁÑEZ, S.; MARTÍNEZ, O.; VALENZUELA, F.; SILVA, F.; VALENZUELA, O. Hidroxicloroquina e cloroquina no COVID-19: devem ser usadas como terapia padrão?. **Clinical rheumatology**, v. 39, n. 8, p. 2461–2465, 2020. DOI: <https://doi.org/10.1007/s10067-020-05202-4>

IN, Y.; YANG, H.; JI, W.; WU, W.; CHEN, S.; ZHANG, W.; DUAN, G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. **Viruses**, v. 12, n. 4, p. 372, 2020. DOI: <https://doi.org/10.3390/v12040372>

JOTHIMANI, D.; VENUGOPAL, R.; ABEDIN, M. F.; KALIAMOORTHY, I.; RELA, M. COVID-19 and the liver. **Journal of hepatology**, v. 73, n. 5, p. 1231–1240, DOI: <https://doi.org/10.1016/j.jhep.2020.06.006>

KUBES, P.; JENNE, C. (2018). Immune Responses in the Liver. **Annual Review of Immunology**, v. 36, n. 1, 2018. DOI: doi:10.1146/annurev-immunol-051116-052415

KULKARNI A. V.; KUMAR, P.; TEVETHIA, H. V.; *et al.* Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. **Aliment Pharmacol Ther**, 2020. DOI: 10.1111/apt.15916. doi:10.1111/ apt.15916

LI, L.; LI, S.; XU, M. *et al.* Risk factors related to hepatic injury in patients with corona virus disease (2019). **medRxiv**, 2020. DOI: 10.1101/2020.02.28.20028514

LI, J.; FAN, J. G. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. **Journal of clinical and translational hepatology**, v. 8, n. 1, p. 13–17, 2020. DOI: <https://doi.org/10.14218/JCTH.2020.00019>



LIU, J.; LI, S.; LIU, J.; LIANG, B.; WANG, X.; WANG, H.; LI, W.; TONG, Q.; YI, J.; ZHAO, L.; XIONG, L.; GUO, C.; TIAN, J.; LUO, J.; YAO, J.; PANG, R.; SHEN, H.; PENG, C.; LIU, T.; ZHANG, Q.; HENG, X. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. **EBioMedicine**, v. 55, 2020. DOI: <https://doi.org/10.1016/j.ebiom.2020.102763>

LIU, J.; CAO, R.; XU, M.; WANG, X.; ZHANG, H.; HU, H.; LI, Y.; HU, Z.; ZHONG, W.; WANG, M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. **Cell discovery**, v. 6, n. 16, 2020. DOI: <https://doi.org/10.1038/s41421-020-0156-0>

LIVERTOX. **Clinical and Research Information on Drug-Induced Liver Injury**. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2012. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK547961/>

LIVERTOX. **Clinical and Research Information on Drug-Induced Liver Injury**. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2012. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548080/>

MARTINEZ, M. A.; VUPPALANCHI, R.; FONTANA, R. J.; STOLZ, A.; KLEINER, D. E.; HAYASHI, P. H.; GU, J.; HOOFNAGLE, J. H.; CHALASANI, N. Clinical and histologic features of azithromycin-induced liver injury. **Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association**, v. 13, n. 2, p. 369–376, 2015. DOI: <https://doi.org/10.1016/j.cgh.2014.07.054>

MANTOVANI, A; BEATRICE, G; DALBENI, A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. **Liver Int.**, v. 40, p. 1316-1320, 2020. DOI: <https://doi.org/10.1111/liv.14465>

MEDEIROS, G. R. de; FARIAS, I. C. C.; FARIAS, J. V. C.; MACEDO, P. R. de. Anti-HCV antiviral therapies as an alternative for the treatment of Covid-19. **Research, Society and Development**, v. 9, n. 10, e9489109406, 2020. DOI: <https://doi.org/10.33448/rsd-v9i10.940>

MOLINA, J. M.; DELAUGERRE, C.; LE GOFF, J.; MELA-LIMA, B.; PONSCARME, D.; GOLDWIRT, L.; DE CASTRO, N. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. **Medicine et maladies infectieuses**, v. 50, n. 4, p. 384. DOI: <https://doi.org/10.1016/j.medmal.2020.03.006>

MORSE, J. S.; LALONDE, T.; XU, S.; LIU, W. R. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. **ChemBioChem**, 2020. DOI: 10.1002/cbic.202000047

OLRY, A.; MEUNIER, L.; DÉLIRE, B.; LARREY, D.; HORMANS, Y.; LE LOUËT, H. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. **Drug safety**, v. 43, n. 7, p. 615–617, 2020. DOI: <https://doi.org/10.1007/s40264-020-00954-z>

PEREIRA, A. S.; SHITSUKA, D. M.; PARREIRA, F. J.; SHITSUKA, R. **Metodologia da pesquisa científica**. Santa Maria. Ed. UAB/NTE/UFSM, 2018. [e-book]. Available from: http://repositorio.ufsm.br/bitstream/handle/1/15824/Lic_Computacao_Metodologia-Pesquisa-Cientifica.pdf?sequence=1. Accessed on April 29.

PONZIANI, F. R.; DEL ZOMPO F.; NESCI, A. *et al.* Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2 positive patients. **Aliment Pharmacol Ther**, 2020. DOI: doi:10.1111/apt.15996



PORTINCASA, P.; KRAWCZYK, M.; MACHILL, A.; LAMMERT, F.; DI CIAULA, A. Hepatic consequences of COVID-19 infection. Lapping or biting?. **European journal of internal medicine**, v. 77, p. 18-24, 2020. DOI: <https://doi.org/10.1016/j.ejim.2020.05.035>

RAGAB, D.; SALAH ELDIN, H.; TAEIMAH, M.; KHATTAB, R.; SALEM, R. The COVID-19 Cytokine Storm; What We Know So Far. **Frontiers in immunology**, v. 11, 2020. DOI: <https://doi.org/10.3389/fimmu.2020.01446>

REMIÃO, F. O paracetamol e a COVID-19. **Revista de Ciência Elementar**, v. 8, n. 2, 2020.

RUMENDE, C. M.; SUSANTO, E. C.; SITORUS, T. P. The Management of Cytokine Storm in COVID-19. **Acta medica Indonesiana**, v. 52, n. 3, p. 306-313, 2020.

SAVIANO, A.; WRENSCH, F.; GHANY, M. G.; BAUMERT, T. F. Liver disease and COVID-19: from Pathogenesis to Clinical Care. **Hepatology**, 2021. DOI: <https://doi.org/10.1002/hep.31684>

SUN, J.; AGHEMO, A.; FORNER, A.; VALENTI, L. COVID-19 and liver disease. **Liver international: official journal of the International Association for the Study of the Liver**, v. 40, n. 6, p. 1278–1281, 2020. DOI: <https://doi.org/10.1111/liv.14470>

TANG, W.; CAO, Z.; HAN, M.; WANG, Z.; CHEN, J.; SUN, W.; WU, Y.; XIAO, W.; LIU, S.; CHEN, E.; CHEN, W.; WANG, X.; YANG, J.; LIN, J.; ZHAO, Q.; YAN, Y.; XIE, Z.; LI, D.; YANG, Y.; LIU, L.; XIE, Q. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. **BMJ**, v. 369, 2020. DOI: <https://doi.org/10.1136/bmj.m1849>

TIAN, D.; YE, Q. Hepatic complications of COVID-19 and its treatment. **Journal of medical virology**, v. 92, n. 10, p. 1818–1824, 2020. DOI: <https://doi.org/10.1002/jmv.26036>

XU, Z.; SHI, L.; WANG, Y.; ZHANG, J.; HUANG, L.; ZHANG, C.; LIU, S.; ZHAO, P.; LIU, H.; ZHU, L.; TAI, Y.; BAI, C.; GAO, T.; SONG, J.; XIA, P.; DONG, J.; ZHAO, J.; WANG, F. S. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. **The Lancet. Respiratory medicine**, v. 8, n. 4, p. 420-422, 2020. DOI: [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)

WAN, D. Y.; LUO, X. Y.; DONG, W.; ZHANG, Z. W. Current practice and potential strategy in diagnosing COVID-19. **European review for medical and pharmacological sciences**, v. 24, n. 8, p. 4548–4553, 2020. DOI: https://doi.org/10.26355/eurrev_202004_21039

WANG, M.; CAO, R.; ZHANG, L.; YANG, X.; LIU, J.; XU, M.; SHI, Z.; HU, Z.; ZHONG, W.; XIAO, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. **Cell research**, v. 30, n. 3, p. 269–271, 2020. DOI: <https://doi.org/10.1038/s41422-020-0282-0>

WAN, Y.; SHANG, J.; GRAHAM, R.; BARIC, R. S.; LI, F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. **J Virol**, 2020. DOI: doi.10.1128/jvi.00127-20

WANG, J. T.; SHENG, W. H.; FANG, C. T. et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. **Emerg Infect Dis**, v. 10, p. 818–824, 2004.

WANG, Y.; LIU, S.; LIU, H.; LI, W.; LIN, F.; JIANG, L.; LI, X.; XU, P.; ZHANG, L.; ZHAO, L.; CAO, Y.; KANG, J.; YANG, J.; LI, L.; LIU, X.; LI, Y.; NIE, R.; MU, J.; LU, F.; ZHAO, S.; ZHAO, J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. **Journal of hepatology**, v. 73, n. 4, p. 807–816, 2020. DOI: <https://doi.org/10.1016/j.jhep.2020.05.002>

WANG, Y.; ZHANG, D.; DU, G.; DU, R.; ZHAO, J.; JIN, Y. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. **Lancet**, v. 395, n. 10236, p. 1569–1578, 2020.



RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

VIRAL AND DRUG LIVER INJURY CAUSED BY COVID-19
 Débora Dantas Nucci Cerqueira, Giuliane Rocha de Medeiros,
 João Victor Cordeiro Farias, Penelopy Rodrigues de Macedo

WORLD HEALTH ORGANIZATION. **Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update**. Genebra: WHO, 2020. Available from: www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

YEO, C.; KAUSHAL, S.; YEO, D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible?. **The lancet. Gastroenterology & hepatology**, v. 5, n. 4, p. 335–337, 2020. DOI: [https://doi.org/10.1016/S2468-1253\(20\)30048-0](https://doi.org/10.1016/S2468-1253(20)30048-0)

YIP, T. C.; LUI, G. C.; WONG, V. W. *et al.* Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. **Gut**, 2020. DOI: doi:10.1136/gutjnl-2020-321726

ZHANG, C.; SHI, L.; WANG, F. S. Liver injury in COVID-19: management and challenges. **The lancet. Gastroenterology & hepatology**, v. 5, n. 5, p. 428-430, 2020. DOI: [https://doi.org/10.1016/S2468-1253\(20\)30057-1](https://doi.org/10.1016/S2468-1253(20)30057-1)

ZHOU, H.; WANG, S.; VON SEIDLEIN, L.; WANG, X. The epidemiology of norovirus gastroenteritis in China: disease burden and distribution of genotypes. **Frontiersof medicine**, v. 14, n. 1, p. 1-7, 2020. DOI: <https://doi.org/10.1007/s11684-019-0733-5>