

EVALUATION OF THE CLINICAL AND LABORATORY REPERCUSSIONS OF COVID-19 IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT: **BACKGROUND:** The COVID-19 pandemic managed, in a short time, to mark the history of science as one of the most relevant problems in recent decades, given that its mortality and morbidity is intensified in individuals with a pre-existing disease. Therefore, it takes more studies to make a correlation between

some pathologies, such as hepatic diseases and COVID-19. **OBJECTIVE:** Thus, the present study aims to evaluate the clinical and laboratory repercussions in patients with liver cirrhosis who were infected by SARS-COV-2. **METHODS:** The research followed the ethical standards of the Nuremberg Code and the Declaration of Helsinki, and it is classified as a cross-sectional, prospective, and observational study. Epidemiological data, such as gender and age, patient perceptions about their own health, laboratory and/or image tests were analyzed. **RESULTS:** It was seen that asthenia was the most frequent post-COVID-19 symptom among the participants. In addition, about 8% of them reported damage in their health status, and 16% reported that it had no changes compared to pre-COVID-19. It was noticed that the laboratory parameters which showed most worsening was cholesterol, triglycerides, total bilirubin and Gamma-GT. Furthermore, there was a reduction in transamins and creatinine, an insignificant decrease in hemoglobin and no changes in the platelets. **CONCLUSION:** Ultimately, it can be concluded that patients with cirrhosis who survive COVID-19 may have no worsening of their underlying liver disease or long-

term prognosis. It is important to carry out more studies that compare, in more detail, the interferences of COVID-19 in the natural history of liver cirrhosis.

KEYWORDS: COVID-19, Liver Cirrhosis, Epidemiology.

AValiação DAS REPERCUSSões CLíNICAS E LABORATORIAIS DA COVID-19 EM PACIENTES COM CIRROSE HEPÁTICA

RESUMO: **CONTEXTO:** A pandemia da COVID-19 conseguiu, em pouco tempo, marcar a história da ciência como um dos agravos mais marcantes das últimas décadas, dado que sua mortalidade e morbidade é intensificada em indivíduos portadores de algumas comorbidades. Portanto, são necessários mais estudos que possam possibilitar a correlação de certas patologias, como as hepáticas, e sua relação com a COVID-19. **OBJETIVOS:** Portanto, o presente estudo visa avaliar as repercussões clínicas e laboratoriais de pacientes portadores de cirrose hepática previamente infectados pelo vírus da COVID-19, o SARS-CoV-2. **MÉTODO:** A pesquisa seguiu os padrões éticos do Código de Nuremberg e Declaração de Helsinque e caracteriza-se como um estudo transversal, prospectivo e observacional. Foram avaliados os dados epidemiológicos, como sexo e idade, percepções do paciente sobre a própria saúde, exames laboratoriais e/ou de imagem da rotina desses pacientes. **RESULTADOS:** Observou-se que a astenia foi o sintoma pós-COVID-19 mais prevalente entre os participantes do estudo, ademais, cerca de 8% destes relataram piora no seu estado de saúde e 16% referiram não ter tido nenhuma alteração comparado ao pré-COVID-19. Notou-se que os parâmetros laboratoriais que mais apresentaram piora foram o colesterol, triglicérides, bilirrubinas totais e Gama-GT. Além disso, houve uma redução nas transaminases e na creatinina, uma diminuição pouco expressiva na hemoglobina e níveis inalterados de plaquetas. **CONCLUSÃO:** Por fim, conclui-se que pacientes com cirrose que sobrevivem à COVID-19 podem não ter piora de sua doença hepática subjacente ou prognóstico a longo prazo. Ressalta-se a importância da realização de mais estudos que comparem de maneira mais minuciosa as interferências da COVID-19 na história natural da cirrose hepática.

PALAVRAS-CHAVE: COVID-19, Cirrose Hepática, Epidemiologia.

1 | INTRODUCTION

Different infectious diseases have emerged at various times in history. However, with globalization, the spread of pathological agents has grown exponentially. It increased the complexity of disease containment, leading to real public health challenges. In December 2019, in the Chinese city of Wuhan, a third outbreak of pneumonia caused by an unidentified microorganism was unexpectedly reported., with tests carried out confirmed that it was a new species of coronavirus, SARS-CoV-2(1). The coronavirus disease (COVID-19) rapidly spread across the world, and its widespread transmission was recognized by the World Health Organization as a pandemic(2)

While most patients with COVID-19 have mild illness, 10 to 15% of them require hospitalization, and few develop respiratory failure, septic shock or multiorgan dysfunction,

with a mortality rate ranging from 3 to 8%, furthermore, liver involvement, as suggested by direct organ infection(3) and compromised liver enzymes, was seen in more than 1/3 of these individuals(4). In addition, hypoxia, a condition often observed in the disease, can induce a decrease in cell activity and oxygen free radicals, resulting in liver damage. Therefore, patients with COVID-19 and pre-existing liver dysfunction are theoretically more susceptible to poor prognosis(5)

In this context, liver cirrhosis, a serious public health problem and a significant source of mortality, attracts special attention. The disease represents the main indication for liver transplantation in the United States and Europe, and it is the 23rd cause of death in the world(6). All chronic liver diseases are characterized by their ability to progress to cirrhosis, in which there is excessive collagen deposition, resulting in qualitative and quantitative changes in the extracellular matrix. In it, there is a structural subversion in the liver, and, in advanced stages, it is a condition with very limited treatment options(7).

Advanced liver disease also leads to immune deficiency and persistent systemic inflammation, a process reflected by the presence of active immune cells in the circulation and increased serum levels of pro-inflammatory cytokines(8). This condition can predispose them to the uncontrollable production of inflammatory cells(9), an important fact, considering that one of the main factors of severity of COVID-19 is its hyperinflammatory response, the dreaded “cytokine storm”(10). Many patients with cirrhosis may also have an underlying hepatopulmonary syndrome, portopulmonary hypertension or hepatic hydrothorax, which itself increases the risk of respiratory failure(11). Thus, in these people, the severity of COVID-19 and the rate of complications, potentially leading to increased liver-related mortality, may be more pronounced than in the general population(12,13).

Likewise, elevations in gamma-glutamyl transferase (GGT), alkaline phosphatase and total bilirubin values were also observed, data that suggest possible liver injury. Overall, patients with pre-existing liver disease were at increased risk of mortality (12% compared with 4% of patients without LD) and hospitalization (52% with DH; 30% without LD)(14). The relative risk was even greater in patients with cirrhosis(5). The results were like those reported for other carriers of already established comorbidities within risk groups, such as hypertension, diabetes, or cardiovascular disease(14)

Another research carried out in Italy clearly demonstrated that patients with COVID-19 who have liver cirrhosis have a worse prognosis(15). The main causes of death were respiratory complications and the sudden worsening of liver function, leading to end-stage liver disease, in addition, acute liver injury was observed in almost 50% of the individuals with previously normal transaminase values(15). The injury appears to be related to a potential direct cytopathic effect, as SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter and damage the target organ, and the liver contains a large amount of these receptors(15).

These researches show results that have important implications for the risk

stratification of patients with liver cirrhosis worldwide during the COVID-19 pandemic, and clinicians should be aware of the deleterious effects that the disease can have on this group of people. However, the number of analyzes in this context is still scarce, and little is known about the perception that these individuals have during the infection. Therefore, this study aims to evaluate the impact of COVID-19 on the health of patients with liver cirrhosis through the analysis of clinical and laboratory parameters.

2 | METHODS

This study is complied with the ethical precepts of the Declaration of Helsinki and the Nuremberg Code, as well as the rules for research involving human beings (Res. CNS 466/12) of the National Health Council, and took place upon approval of the draft by the Center for Research, Extension and Graduate Studies in Medicine (NUPEM), by the Research Ethics Committee (REC) of the State University of Pará (UEPA) and by the Research Ethics Committee (REC) of the Santa Casa de Misericórdia do Pará Foundation (FSCMPA), CAAE 50827721.7.3001.5171 committee opinion number 5.081.509. The research was supported by a Term of Commitment for Data Use (TCDU) and a Term of Free and Informed Consent (TFIC).

This is an observational, prospective, cross-sectional, descriptive study with a quantitative and qualitative approach. The study sample consisted of 25 participants, who underwent medical follow-up at the Liver Outpatient Clinic of Santa Casa de Misericórdia do Pará (FSCMPA). Patients diagnosed with liver cirrhosis according to clinical and/or laboratory and/or endoscopic and/or imaging criteria, over 18 years old, regardless of gender, previously treated at the Liver Outpatient Clinic of Santa Casa do Pará and infected by Sars-CoV-2, according to the Ministry of Health's(16), verified by clinical, clinical-epidemiological, clinical-imaging and/or laboratory criteria were included in the study.

The first stage of data collection took place after approval by the Research Ethics Committee (REC) through the application of the questionnaire referring to the epidemiological profile and the patients' perception of their own health status in the pre- and post-COVID-19 period. Then, the clinical evaluation of the patients was performed. Regarding the laboratory parameters used in this research, they were already stored in the electronic medical records of patients with liver cirrhosis being followed up at the Liver Outpatient Clinic of Santa Casa do Pará.

The data obtained were recorded in research protocols, organized in the Microsoft Office Package 2016, and later submitted to statistical analysis. The results were organized in graphs and tables to facilitate the interpretation of the results. For the present study, Artificial Intelligence was not used to prepare the text.

3 | RESULTS

Of the 25 research participants, 15 were female (60%) and 10 were male (40%), with the average age being 55.7 years (22 – 77) (TABLE 3). Regarding the etiology of cirrhosis, most patients were due to Hepatitis C infection (48%), followed by Autoimmune Hepatitis (16%), Non-Alcoholic Hepatitis (12%), and finally, Hepatitis B, alcoholic, and of unknown causes, all with 8% each (GRAPH 2).

Most patients reported during the survey that there was no change in their health status according to their own perception (64%), however, 8 patients reported a worsening of their health status after COVID-19 infection (32%) (GRAPH 1). Regarding symptoms after SARS-COV-2 infection, the most reported were asthenia/fatigue (36%), memory loss (20%) and headache (20%) (TABLE 1).

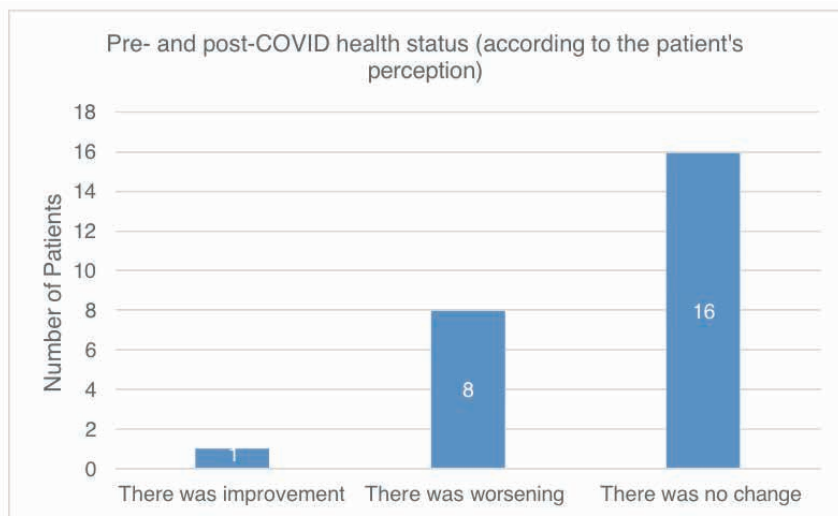
Regarding laboratory parameters, there was a difference in the means of the tests before and after COVID-19 infection, especially in relation to Total Cholesterol (165 – 184), Triglycerides (65 – 75), Total Bilirubin (0.85 – 0.98) and Gamma-GT (43 – 67) (TABLE 2).

POST-COVID SYMPTOMS YES

<i>Asthenia/fatigue</i>	9 (36%)
<i>Memory loss</i>	5 (20%)
<i>Headache</i>	5 (20%)
<i>Abdominal pain</i>	2 (8%)
<i>Ascites</i>	2 (8%)
<i>Cough</i>	3 (12%)
<i>Diarrhea</i>	3 (12%)
<i>Dizziness</i>	3 (12%)
<i>No symptoms</i>	5 (20%)

TABLE 1 – Main post-COVID-19 symptoms found in the patients of this study expressed in absolute numbers and in percentage

SOURCE: Research protocol.



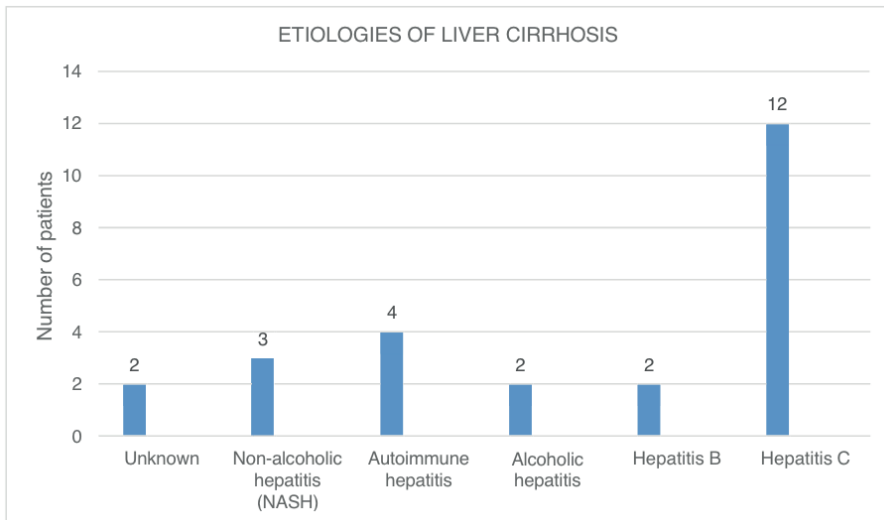
GRAPH 1 - Result of the questionnaire about the perception of the post-covid health status, according to the patients who participated in this research

SOURCE: Research protocol

LABORATORY	PRE-COVID	POST-COVID
<i>Hemoglobin (g/dL)</i>	12,8 (8,1 – 18,6)	12 (7,8 – 18,3)
<i>Platelets (/mm³)</i>	120 thousand (50 – 208 thousand)	120 (69 – 291 thousand)
<i>Leukocytes (/mm³)</i>	4900 (2000 – 6000)	4000 (1600 – 4800)
<i>TGO/AST (IU/L)</i>	54,5 (17 – 145)	34 (21 – 76)
<i>TGP/ALT (IU/L)</i>	36 (16 – 193)	26 (13 – 58)
<i>Gamma GT-GGT (IU/L)</i>	43 (24 – 352)	67 (19 – 168 thousand)
<i>Total Bilirubins (mg/dL)</i>	0,85 (0,4 – 2,6)	0,98 (0,4 – 2,2)
<i>Creatinine (mg/dL)</i>	0,8 (0,4 – 1,1)	0,78 (0,3 – 4,55)
<i>INR</i>	1,2 (1,02 - 1,62)	1,07 (1,02 – 1,57)
<i>Total Cholesterol (mg/dL)</i>	165 (140 – 224)	184 (100 – 249)
<i>Triglycerides (mg/dL)</i>	65 (50 – 129)	75 (41 – 153)

TABLE 2 – Quantitative data obtained from the patients' records expressed as median and the variation found in the respective parameters.

SOURCE: Research protocol.



GRAPH 2 – Proportion of liver cirrhosis etiologies found in the patients of this study.

SOURCE: Research protocol.

DEMOGRAPHIC VARIABLES

<i>GENDER</i>	FEMALE = 15; MALE = 10
<i>AVERAGE AGE</i>	55,7 YEARS OLD (22 – 77)

TABLE 3 – Demographic data regarding gender and age found in the researched sample

SOURCE: Research protocol

4 | DISCUSSION

Liver cirrhosis is the most common end-stage of most liver diseases, and its complications are estimated to be responsible for over 1,3 million deaths worldwide, making it the fourteenth most common cause of death globally(17). With the onset of the COVID-19 pandemic, research investigating the impact of Sars-CoV-2 on patients with cirrhosis has begun to be conducted, as these patients are more susceptible to virus-induced liver injury and have impaired regenerative capacity(18,19).In this study, it was possible to make a comparison between clinical and laboratory parameters of patients with liver cirrhosis before and after infection with COVID-19, as well as the general symptomatology presented in the two periods studied.

In total, 25 patients were eligible, a group formed mostly by women (60%), with a mean age of 55,7 years old (Table 3). The most common cause of cirrhosis was hepatitis C found in 48% of patients, followed by autoimmune hepatitis accounting for 16%, and non-alcoholic hepatitis (NASH) in 8% (Graph 2). It is important to note that the increased availability of direct-acting antivirals to treat hepatitis C virus (HCV) infection has decreased the prevalence of cirrhosis worldwide(20), but the sample studied did not show the same

trend, possibly reflecting poor control of the disease. In Brazil, the target for treatments for hepatitis C fell by 50% in 2020, in part reflecting the consequences of the COVID-19 pandemic(21).

Approximately one third of patients reported a worsening post-COVID19 health status, a fact usually accompanied by the onset of symptoms such as asthenia/fatigue, memory loss and headache (Table 1). In a study that looked at the consequences of Sars-Cov-2 infection over 6 months, more than 30% of individuals affected by COVID- 19 had persistent symptoms after their recovery⁽²²⁾. In this context, post-COVID fatigue may affect up to 1 in 3 people affected by the disease, and it is unrelated to its severity. The main risk group for the development of the symptom is women with some pre- existing comorbidity(23), profile that is like the sample of this research, mostly female patients with cirrhosis. In this study, 36% of the patients reported the presence of this symptom, which corroborates the existing literature.

In addition, 5 patients reported memory loss, which is a complaint also present in the group of diseases called Post-Acute Sequelae of Covid-19 (PASC)(24). In the cognitive domain, studies have shown that up to one in four patients experienced a range of symptoms that has become colloquially known as the “COVID fog,” including problems with attention, memory, executive functions, among others(25).

It is important to point out, however, that it is not possible to delimit the true origin of the appearance or worsening of a specific symptom. Fatigue, for example, is a common symptom in patients with liver disease, which is considered multifactorial and whose pathogenesis is poorly understood(26). Another 4 patients had ascites and/or abdominal pain, symptoms present in the clinical picture of liver cirrhosis(27). Thus, the reported symptoms could be late consequences of COVID-19, be part of the natural history of cirrhosis, or have been worsened by these two overlapping factors.

The laboratory data that showed worsening were total cholesterol, triglycerides, total bilirubin, and Gamma-GT. In a recent study describing the impact of the pandemic on the prognosis of patients with NAFLD-related cirrhosis found worsening bilirubin levels, but no change in the lipid profile of these patients, furthermore, worsening metabolic status was not identified as a risk factor for cirrhosis decompensation(28).

A study that compared patients with cirrhosis who had COVID-19 and patients who did not showed that the mortality and risk of decompensation of the two groups was similar, furthermore, patients who had COVID-19 had slightly higher levels of hemoglobin and lower levels of platelet count, ALT/TGP, and serum creatinine(29). In the present study, a decrease in transaminases, a slight decrease in hemoglobin, unchanged mean levels of platelet count, and the same trend of decrease in serum creatinine after COVID-19 were demonstrated (Table 2).

In contrast, a Chinese study reported persistence of abnormal liver enzymes up to 2 months after infection and association with worse recovery of patients with COVID-19(30).

This data, when compared to the result of this research, indicates an acute and transient increase in transaminases, since this took into account the late effects. Another study corroborating this finding demonstrated that patients with cirrhosis who had COVID-19 had a significantly higher risk of mortality, decompensation and UTI admission in 3 months compared to those who never had the disease. However, the 1-year follow-up of these individuals did not show an increase in these risks(31). That is, patients with cirrhosis who survive COVID-19 may not experience worsening of their underlying liver disease or long-term prognosis.

Also, regarding transaminases, a report on the impact of SARS-CoV-2 infection on ALT/TGP levels in patients with cirrhosis showed that acute liver injury was observed in almost 50% of patients with previously normal liver enzyme values(13). Moreover, an outbreak of hepatitis was not uncommon at the time of COVID-19 diagnosis(15). Therefore, the short-term effects of the disease should not be underestimated.

5 | CONCLUSION

From the present study, it is concluded that the most prevalent etiology of liver cirrhosis among the survey participants was hepatitis C. In addition, it was observed that about a third of the patients reported worsening in their health status after COVID19. However, this perception was not accompanied by major changes in laboratory parameters. This fact should be better studied considering that the change in these factors may have occurred transiently. Therefore, a serial follow-up of these exams is necessary for more reliable conclusions.

Furthermore, the comparison of clinical, laboratory, and radiological parameters before and after COVID-19 was hampered by incomplete electronic medical records, as well as the absence of some of the tests evaluated by the research protocol.

The present research sought to observe changes comparing the same individuals, in different periods, which makes it one of the pioneers in the current scenario. Therefore, it is vitally important to conduct further studies that thoroughly analyze the repercussions that COVID-19 can have on the well-being of patients with liver cirrhosis.

AUTHORS' CONTRIBUTION

VIANA EC: project management, survey execution, writing of text. SANTOS MCF: project management, survey execution, writing of text. MOTA, LO: project management, writing of text. MOIA LJMP: editing and review.

CONFLICT OF INTERESTS

There isn't.

SUBSIDY OR FINANCIAL SUPPORT

There isn't.

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