

## COVID-19 and Liver injury: hepatology perspectives.

Natassia Vianna Bocchese<sup>1</sup>, Noele Gurgel Dávila<sup>1</sup>, Maria Beatriz Maia Rodrigues<sup>1</sup>, Irami Araújo-Neto<sup>1</sup>, Mariana de Oliveira Costa<sup>2</sup>, Diniz de Meiroz Grillo Barbalho<sup>3</sup>, Amália Cinthia Meneses Rêgo<sup>4</sup>, Irami Araújo-Filho<sup>5</sup>

<sup>1</sup>Undergraduate Student of Medicine at UnP - Potiguar University - Laureate International Universities – Natal/Brazil;

<sup>2</sup>Undergraduate Student of Medicine at the Federal University of Rio Grande do Norte, Natal/Brazil;

<sup>3</sup>Physician, Potiguar University, UnP - Laureate International Universities – Natal/Brazil;

<sup>4</sup>Postgraduate Program in Biotechnology at Potiguar University / UnP - Laureate International Universities. Teaching and Research Manager - School of Health - League Against Cancer Natal - RN / Brazil. Ph.D. in Health Science;

<sup>5</sup>Postgraduate Program in Biotechnology at Potiguar University/ UnP - Laureate International Universities; Full Professor Department of Surgery, Federal University of Rio Grande do Norte. Full Professor, Department of Surgery, Potiguar University. Ph. D in Health Science/ Natal-RN, Brazil.

**\*Corresponding Author:** Irami Araújo-Neto, Undergraduate Student of Medicine at UnP - Potiguar University - Laureate International Universities – Natal/Brazil.

**Received date:** May 26 2020; **Accepted date:** June 12, 2020; **Published date:** June 19, 2020

**Citation:** Natassia Vianna Bocchese, Noele Gurgel Dávila, Maria Beatriz Maia Rodrigues, Irami Araújo-Neto, Mariana de Oliveira Costa, Diniz de Meiroz Grillo Barbalho, Amália Cinthia Meneses Rêgo, Irami Araújo-Filho. *Clinical Medical Reviews and Reports*. 2(3); DOI: [10.31579/2690-8794/020](https://doi.org/10.31579/2690-8794/020)

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### Abstract

SARS-CoV-2, a severe acute respiratory syndrome caused by Coronavirus 2, discovered in 2019 in China, is responsible for the current pandemic declared by the WHO since March 2020. The clinical syndrome caused by Covid-19 has a broad spectrum of severity. The most common clinical manifestations are fever, dry cough, dyspnea, fatigue, and anosmia. The virus binds to receptors for angiotensin-converting enzyme 2 (ECA2) and serine protease TMPRSS2 for protein S initiation, which are expressed not only in the lungs but also in the liver, colonic, esophageal and biliary epithelial cells. In this context, the liver is a potential target for COVID-19 infection. Liver damage occurs during the course and treatment of viral infection in patients with or without previous liver disease. Therefore, the characteristics of liver injury associated with COVID-19 were reviewed based on research related, in the context of the pandemic.

**Keywords:** covid-19 virus infection; sars-cov-2 infection; coronavirus infections; liver; liver diseases; liver dysfunctions.

### Introduction

In December 2019, a new RNA virus appeared in the world through the coronavirus mutation, known as SARS-Cov-2, capable of causing the severe acute respiratory syndrome, initially detected in a province of China, in the city of Wuhan. As of March 5, 2020, 96,000 cases of the disease and 87 affected countries had already been reported [1].

The infection is acquired by inhaling droplets containing the virus or through fomites, being able to remain alive on surfaces for a long time. Viral particles were detected in the feces, making fecal-oral transmission possible. The incubation period varies from 7 to 14 days [1].

Clinical manifestations vary, from asymptomatic to respiratory failure. The most prevalent signs are fever (50%) and cough (38%). The severity of the disease is related to the increase in inflammatory cytokines, such as IL1, IL6, IL8, and TNF-alpha. Headache, nausea, vomiting, and diarrhea have also been reported [1,2].

The levels of liver enzymes and bilirubin are abnormal in severe infections, with difficulties in the management of patients with liver disease, especially those with autoimmune hepatitis or cirrhosis using immunosuppressants [3-5].

The definition of liver injury by COVID-19 is not standardized in the scientific community; some scholars consider any change in liver function parameters as injury, and others require the need to raise the hepatogram's standard limit by three times [4,6].

Thus, it is necessary to study the hepatic manifestations in patients with COVID-19, from the mechanism by which the liver is injured, the tools for rapid recognition of the injury, including changes in the management of patients with previous liver disease.

### Methods

The research was carried out in Pubmed / Medline, Scopus, Scielo, Embase, and Web of Science databases, in addition to searching Google Scholar, considered as a source of gray literature, as it does not contain peer-reviewed articles. The articles were selected according to the focus of the study: hepatic repercussions of COVID-19 and research on fecal-oral transmission. The studies were chosen by combining the following keywords: *COVID-19 virus infection, SARS-CoV-2 infection; Coronavirus Infections; Liver; Liver Diseases; Liver Dysfunctions*. All relevant studies published between January 2019 to the present were included in the cohort, systematic review, case-control, cross-sectional, case series studies, reviews, and editorials. The filters chosen were studies carried out in humans, complete articles, and published in the last year, totaling 24 articles. The analysis, review, and selection of articles was

carried out in pairs, separately, based on the reading of the title and summary of the study, with a third reviewer in case of disagreement between the other two reviewers.

## Results and discussion

### Pathophysiology

SARS-CoV uses the angiotensin-converting enzyme 2 (ACE2) and the serine protease TMPRSS2 to initiate protein S. ACE2, and TMPRSS2 is not only expressed in the lung, but also the epithelia of the small intestine, upper esophagus, liver, colon, and bile duct cells [5,6].

After viral binding to the respiratory epithelium, the expression of ACE2 becomes lower in this tissue, concomitantly with the period in which the individual progresses to acute respiratory failure, a condition present in severe forms of the disease [7-9].

In the gastrointestinal tract, an association was observed between viremia, diarrhea, and other enteric manifestations. Even after viral bleaching, clinical signs attributed to epithelial changes and disabsorption caused by Covid-19 persisted [7,8].

Liver manifestations do not have an exact mechanism. It is believed that liver damage can be caused by cytopathic damage induced directly by the virus by binding to ACE2. They were also found in patients with SARS-CoV-2, high expression of ACE2 in cholangiocytes concerning hepatocytes (59.7% x 2.6%) [6, 8].

In addition to the mechanism, as mentioned earlier, the inflammatory response to COVID-19 contributes to liver damage through the exacerbated production of pro-inflammatory cytokines [7-9].

On the other hand, studies have shown a relationship between critically ill patients infected with COVID-19 and increased levels of creatinine kinase, lactate dehydrogenase, and myoglobin. Therefore, the possibility was raised that elevations of aminotransferases did not result only from liver damage. Still, that infection by COVID-19 could cause a myositis similar to that which occurs in cases of severe flu [9,10].

Pathological studies in patients with SARS confirmed the presence of the virus in liver tissue, although the viral titer was relatively low because no viral inclusions were observed [8]. In this context, a liver biopsy performed on a patient who died due to infection presented microvesicular steatosis, mild lobular, and portal inflammation, findings commonly found in sepsis [9,10].

### Hematological and hepatic changes

Blood cellularity changes with the onset of the disease and indicates severity. In a study with 1099 patients, 83.2% had lymphopenia, 36.2% thrombocytopenia, and 33.7% leukopenia. In contrast, an increase in ALT and AST levels was found, indicating liver injury, especially in severe cases [2,8,11-13].

Some studies have revealed the presence of mild steatosis, attributed mainly to drug-induced liver damage and not to the virus [12,13]. Also, inflammation mediated by the immune system, such as cytokine storm and hypoxia associated with pneumonia, contributes to mild liver damage or liver failure in severely affected patients with COVID-19 [8]. There is evidence that the virus can replicate in the liver and influence normal liver functions, as well as multiple respiratory infections [13,14].

Xie et al. observed among hospitalized patients with moderate COVID-19 (without the need for intensive care or mechanical ventilation), there was an increase in transaminases above 30%, with an elevation of AST slightly higher than that of ALT (35.4% x 31, 6%, respectively). There was also an increase in bilirubin in 5.1% of patients, with an average age of 60 years, and 1/3 had comorbidities [15].

Another trial conducted in China showed that of 13 patients in the intensive care unit, 62% had elevated AST compared to 28 patients who were not serious, where only 25% of these showed such change [4].

Patients with more severe changes demonstrated on chest computed tomography; liver changes were also more significant. In this respect, a more intense inflammatory response causes a systemic imbalance, promoting liver damage. Therefore, it is prudent that the liver function of these patients with moderate or severe lung damage is monitored early [15].

Other hepatic manifestations caused by COVID-19 were hypoproteinemia and changes in coagulation, with an extension of prothrombin time [7,16,17]. This phenomenon is believed to occur due to a viral tropism in the liver tissue, causing acute viral hepatitis, or even secondary to the use of hepatotoxic drugs [7,16-18].

The disseminated intravascular coagulation (DIC), the elevation of D dimer, and thrombocytopenia were found in 36.2%-46.4% of critically ill patients, determining a worse prognosis [18,19].

The changes in the coagulation cascade are explained by the imbalance between the pro and anticoagulant factors induced by the systemic inflammatory response to the virus. There is an increase in the production of fibrinogen, factors II, III, and X [18-20].

Changes in ferritin were observed as a nonspecific marker of inflammation and changes in iron metabolism secondary to the activation of macrophages. [9]

In addition to hepatocytes, the bile ducts are affected by the coronavirus, since viral RNA could be found in the intrahepatic bile ducts [7,8]. Children may have hematochezia as a symptom of infection with the new coronavirus. However, the most common in the general population is that manifestations, such as diarrhea and vomiting, are seen. [8,16]

Finally, biopsies performed on patients with liver disorders; lymphocytic were observed, in addition to dilation of sinusoids in symptomatic patients with COVID-19 [17-19].

### Hepatopathy/risk factor

Asia and China, in particular, have a high incidence of Hepatitis B; however, data is scarce regarding its influence on COVID-19. One report suggests that about 2% of severe cases had Hepatitis B infection compared to those with mild disease (0.06%) [12].

Patients with previous hepatitis B or C infected with COVID-19 are more likely to develop severe hepatitis, just as patients with cirrhosis are more susceptible to the development of severe immunodeficiency infection [6,8,13]. Liver disease patients have a leukocytosis with neutrophilia and elevated C-Reactive Protein compared to others, who develop leukopenia and lymphocytosis more commonly [15].

People with primary gastrointestinal neoplasms have a higher expression of angiotensin two receptors, which contributes to a higher risk of infection with the new coronavirus since it has been shown to enter the cell through this enzyme. However, angiotensin 2 acts in the modulation of the systemic inflammatory response at the gastrointestinal tract level, which could contribute to regulate this response [16].

Vulnerable groups are liver transplantation, in the use of immunosuppressants, cirrhosis, chronic-acute liver failure, immune dysfunction, and those with hepatocellular carcinoma. Patients with non-alcoholic steatohepatitis associated with diabetes and cardiovascular disorders are at high risk of being infected and progressing to severe SARS-CoV-2. [12].

It is essential to highlight that data on other underlying chronic liver diseases, non-alcoholic fatty liver disease, alcohol-related liver disease, and autoimmune hepatitis and its prognostic effect in the face of COVID-19, need to be better evaluated [13].

Jin et al. point out that among patients with chronic liver disease, 10.81% evolved with gastrointestinal manifestations. In comparison, only 2.85% did not have such expressions, demonstrating a significant relationship between previous liver disease and gastrointestinal symptoms [19].

Coronavirus-infected patients exhibited elevated serum levels of monocyte-1 chemoattracting protein (MCP-1), known to aggravate COVID-19-promoted steatohepatitis [14].

### **Clinical condition**

Clinical studies have shown an incidence rate of diarrhea between 2% -50% of cases, which may precede or accompany respiratory symptoms [5]. This evidence reinforces the liver's exposure to the virus with malabsorption syndrome [8].

Most patients had an average of three bowel movements per day. Besides, some patients experienced diarrhea in the absence of respiratory symptoms, which can induce underestimation of cases of COVID-19 [5].

The most common signs and symptoms found were fever, cough, dyspnoea, myalgia, headache, and diarrhea. Also, many of these patients had gastrointestinal syndromes as an initial manifestation of the clinical condition [20,21].

Gastrointestinal manifestations are more frequent in pregnant women and children when compared to adults; however, studies are needed to adequately map which age groups and sex correspond to those with the highest risks for liver involvement [22,23].

A statistically significant association was found between the presence of gastrointestinal symptoms at the presentation - defined as diarrhea, nausea, and vomiting - and a positive result from the COVID-19 test [20-22].

Gastrointestinal symptoms were associated with a 70% increased relative risk of positivity on the test. [24] Other related symptoms were epigastric pain, melena, and constipation [20].

Among patients positive for COVID-19, the presence of gastrointestinal symptoms was associated with longer disease duration, a tendency to lower ICU admission rates, and lower mortality during short-term follow-up [10-12].

These combined findings may suggest that gastrointestinal symptoms are associated with a more indolent form of COVID-19, although the conclusions at this point are preliminary [24,21].

Studies have observed an association between the presence of gastrointestinal manifestations and disease severity, comparing it to patients with milder clinical conditions [14].

### **Diagnosis**

The virus is detected through the molecular amplification tests in nasopharyngeal smears, endotracheal aspirates, and bronchoalveolar lavage. It can also be found in feces and blood. [1]

The polymerase chain reaction (PCR) is a method of high sensitivity and specificity, used routinely.[2]. Increasing evidence indicates possible oral-fecal transmission, indicating the need for a rapid and effective modification in the screening and diagnosis algorithms [5,12].

Ozma MA et al. demonstrated that at the beginning of the clinical picture, oral and rectal swabs were positive in 50% and 25% of patients, respectively. After a few days, the values found were 50% for an oral swab and 75% for a rectal swab, suggesting that at the end of the infection, it is more likely to find positivity in the feces [2,7].

In this sense, studies have shown that half of the individuals infected with SARS-CoV-2, who eliminated the respiratory tract infection, showed viral elimination in their fecal samples up to 15 days after the respiratory samples became negative [12,15].

### **Clinical management**

Patients should be stratified according to severity. Those with stable chronic liver disease have a low risk of complications. Patients with decompensated liver cirrhosis have high morbidity and mortality from COVID-19 infection [3,8].

Leo A et al. suggested that in patients with liver disease and using immunosuppressants, the dose of this medication should be reduced, especially in those with lymphopenia. Besides, patients should be managed in transplant centers in case of liver failure [1-3].

Hepatopaths should avoid access to the hospital, with postponing non-urgent medical appointments until the end of the state of emergency. Invasive procedures, such as paracentesis, should be performed by an experienced professional and preferably in centers that do not care for patients with COVID-19. It is also necessary to reiterate the importance of the vaccine against influenza and pneumococcus [3,17].

In patients with COVID-19 and autoimmune hepatitis, the effects of the administration of glucocorticoids on the prognosis of the disease are still unclear [8-10].

Liver damage in mild cases of COVID-19 is often transient and can return to normal without special treatment. However, when severe liver damage occurs, protective drugs are administered to these patients [5,8,24].

### **Conclusion**

In conclusion, according to the studies analyzed, it is possible to state that COVID-19 is a broad-spectrum disease, with manifestations that go beyond the pulmonary, including liver changes. Patients with abnormal liver function have a worse prognosis and are commonly admitted to the intensive care unit.

The approach towards chronic liver disease is still controversial, especially concerning the reduction of the dose of immunosuppressants. Still, it is a consensus that in these patients, attention should be focused on prevention, with strict control measures. Finally, the exact mechanisms of liver injury by the coronavirus are not yet fully understood, requiring further studies in this line of research.

### **Compliance with ethical standards**

### **Acknowledgments**

The authors thank the Ph.D. in Health Sciences and Teaching and Research Manager at League Against Cancer, Profa. Dra. Amália Rêgo, for her contribution and relevance to the scientific discussion and supervision of this review, acting as an expert consultant on the bibliographic survey, analysis, and scientific advice. We also thank all the study components for their dedication and effort to build a scientifically validated quality study.

### **Disclosure of conflict of interest**

There are no conflicts of interest to declare by any of the authors of this study.

## References

1. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr.* 2020;87(4):281-286.
2. Ozma MA, Maroufi P, Khodadadi E, Köse Ş, Esposito I, Ganbarov K, Dao S, Esposito S, Dal T, Zeinalzadeh E, Kafil HS. Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period. *Infez Med.* 2020 Ahead of print Jun 1;28(2):153-165.
3. Lleo A, Invernizzi P, Lohse AW, Aghemo A, Carbone M. Highlights for management of patients with Autoimmune Liver Disease during COVID-19 pandemia. *J Hepatol.* 2020;10.
4. Lee IC, Huo TI, Huang YH. Gastrointestinal and Liver Manifestations in Patients with COVID-19. *J Chin Med Assoc.* 2020;1.
5. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. *Clin Gastroenterol Hepatol.* 2020;8.
6. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab J Gastroenterol.* 2020;21(1):3-8.
7. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int.* 2020;40(5):998-1004.
8. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol.* 2020;5(5):428-430.
9. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol.* 2020;20.
10. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and Liver Manifestations of COVID-19. *J Clin Exp Hepatol.* 2020;10(3):263-265.
11. Yang X, Zhao J, Yan Q, Zhang S, Wang Y, Li Y. A case of COVID-19 patient with the diarrhea as initial symptom and literature review. *Clin Res Hepatol Gastroenterol.* 2020 Apr 15.
12. Sarin SK. "Fast, faster, and fastest: science on the run during COVID-19 drama"- "do not forget the liver". *Hepatol Int.* 2020;10.
13. Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, Wu KC, Chen MH; Chinese Society of IBD, Chinese Elite IBD Union; Chinese IBD Quality Care Evaluation Center Committee. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol.* 2020 May;5(5):425-427.
14. Boeckmans J, Rodrigues RM, Demuyser T, Piérard D, Vanhaecke T, Rogiers V. COVID-19 and drug-induced liver injury: a problem of plenty or a petty point? *Arch Toxicol.* 2020;94(4):1367-1369.
15. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver Int.* 2020 Apr 2.
16. Li LY, Wu W, Chen S, Gu JW, Li XL, Song HJ, Du F, Wang G, Zhong CQ, Wang XY, Chen Y, Shah R, Yang HM, Cai Q. Digestive system involvement of novel coronavirus infection: Prevention and control infection from a gastroenterology perspective. *J Dig Dis.* 2020 Apr;21(4):199-204.
17. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int.* 2020 Apr 2.
18. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol.* 2020;9;127:104362.
19. XL, Yu GD, Xu KJ, Wang XY, Gu JQ, Zhang SY et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut.* 2020;69(6):1002-1009.
20. Hormati A, Shahhamzeh A, Afifian M, Khodadust F, Ahmadvpour S. Can COVID-19 present unusual GI symptoms? *J Microbiol Immunol Infect.* 2020;21.
21. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol.* 2020;115(5):766-773.
22. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, Poucke SV, Liu WY, Zheng MH. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol.* 2020 Mar 28;8(1):18-24.
23. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R et al. Gastrointestinal Manifestations of SARS CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. *Gastroenterology.* 2020;3.
24. Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, Freedberg DE. Gastrointestinal Symptoms and COVID-19: Case-Control Study from the United States. *Gastroenterology.* 2020;12.