Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008375

Biomedical Implications of SARS COV 2 Infection in Context of Chronic Hepatic Diseases

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ARTICLE INFO

Received: October 04, 2023

Published: October 12, 2023

Citation: D Munteanu, A Vlase, R Ciorap, MI Ungureanu, G Statescu, B Anton and LI Pertea. Biomedical Implications of SARS COV 2 Infection in Context of Chronic Hepatic Diseases. Biomed J Sci & Tech Res 53(2)-2023. BJSTR. MS.ID.008375.

ABSTRACT

SARS-CoV-2 infection and the subsequent development of the COVID-19 pandemic, as is known, particularly affected certain segments of the population, respectively a series of systems and organs such as the lungs, kidneys, liver, heart, and brain, which were identified as priority organs. Liver diseases are considered a particular risk factor for the high mortality caused by the COVID-19 pandemic. In addition, liver damage, which previously coexisted with a chronic pathology, was demonstrated in a substantial proportion of patients with SARS-COV-2 infection, respectively COVID-19 disease, especially in those with severe clinical symptoms. Also added are antiviral drugs, immunosuppressive drugs after liver transplantation, pre-existing liver diseases, and chronic liver diseases such as cirrhosis, which have been implicated in the development of liver damage induced by viral infection. As a result, some precautions have been taken to prevent, monitor the virus and avoid immunocompromised and susceptible people, such as those with chronic liver disease, from being infected with SARS-CoV-2, thus avoiding the increase in mortality in this category of patients. The aim of this analysis was to examine the liver damage caused by SARS-CoV-2 infection and the clinical-biological implications during the pandemic on the range of morbidity and mortality and, therefore, the possibility of developing preventive measures in patients with chronic liver pathology.

Keywords: Liver; Hepatic Disorders; SARS-COV 2 Infections; COVID-19

Abbreviations: WHO: World Health Organization; ACE2: Angiotensin-Converting Enzyme 2; CLD: Chronic Liver Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome

Introduction

According to current data and studies, in December 2019, an initial outbreak of pneumonia began in Wuhan, Hubei Province, Republic of China. Its causative agent was identified as a previously unknown coronavirus and given the provisional name 2019 coronavirus (2019-nCoV). In February 2020, after an important increase in cases of viral infection worldwide, the World Health Organization (WHO), based on taxonomy and phylogeny, renamed 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), while the resulting disease was designated coronavirus disease 2019 (COVID-19). From a microbiological point of view, SARS-CoV-2 is a single-stranded RNA virus with a positive sense, with a length of 27-32 KB from the Orthocoronavirinae subfamily [1]. The virus can be transmitted from one person to another through flügge respiratory droplets and close contact. Clinical manifestations of COVID-19 include fever, dry cough, and diarrhea, to which is added liver dysfunction, which has also been reported in subsequent studies [2]. Thus, SARS-CoV was identified in the liver of infected individuals and approximately 60% of SARS patients showed symptoms of liver damage [3]. Therefore, during infection, SARS-CoV-2 can be contained in human liver tissue. The prevalence of liver lesions in SARS-CoV-2 virus infection is 14-53% and is recurrent. Drugs used to treat SARS-CoV-2, such as lopinavir/ritonavir, remdesivir, chloroquine, and tocilizumab, are also believed to have destructive and toxic effects on the liver.

However, despite the significant prevalence of hepatic steatosis and fibrosis reported in autopsies, liver lesions in COVID-19 are subclinical [4]. A study by Fan et al. showed that liver disorders are more common in men, and another study found that the angiotensin-converting enzyme 2 (ACE2) receptor is significantly increased in the liver tissue of women, implying a better prognosis compared to men [5]. Liver injury associated with COVID-19 pathology is defined as any liver injury during the course and treatment of SARS-COV 2 infection in patients with or without underlying liver disease [6]. Liver damage may also be due to direct or indirect effects of SARS-CoV-2, such as septic shock, ischemia, multiorgan dysfunction, drug-related toxicity, and hepatitis due to the inflammatory response of the immune system following the cytokine storm that leads to directly to the evolution towards COVID-19 [7,8]. This study aimed to understand the evolutionary mechanisms and clinico-biological correlations involved in the development and worsening of liver disease caused by SARS-CoV-2, in order to reduce the incidence of clinical symptoms and complications after post-COVID-19 recovery. From the point of view of therapy in patients who associate SARS-COV-2 infection with chronic liver pathology, the anti-aging gene Sirtuin 1 (S1RT 1) is important to the treatment of liver damage caused by SARS-CoV-2 infection [9]. Activators of Sirtuin 1 may need to be consumed to treat liver disease and stabilize the effects of the COVID-19 virus.

Chronic Liver Disease and SARS-COV-2 Infection

COVID-19 can cause significant liver damage; approximately 23% of patients have pre-existing chronic liver disease (CLD). Chronic liver disease (CLD) includes non-alcoholic fatty liver disease (NAFLD), alcohol-related disease, and chronic viral hepatitis [10]. CLD patients had significant levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) at the time of admission [10]. However, the elevated levels of liver enzymes AST and ALT by various factors are not different in patients with or without CLD [11]. As previously mentioned, these factors include drug hepatotoxicity (anti-inflammatory and antiviral drugs used during hospitalization), pro-inflammatory cytokines of the immune system, ischemia and congestion associated with positive pressure ventilation, which in turn lead to liver disorders [8,10]. In addition, length of hospital stays, length of intensive care unit (ICU) stay, and increased ventilatory requirement have been reported to be longer in patients with CLD than in patients without CLD [10]. On the other hand, it was found that the risk of mortality is significantly higher in patients with liver diseases, especially decompensated cirrhosis [12]. Cirrhosis-related immune system dysfunction has been reported in patients with advanced chronic liver disease predisposed to SARS-CoV-2 infection [13].

Among the chronic liver pathologies preexisting the infection with SARS-COV-2, studies have shown an increased prevalence of liver cirrhosis and chronic viral hepatitis (virus B present). As a result of cirrhosis-related immune disturbances, severe acute respiratory syndrome caused by SARS-CoV-2 increased in patients with liver cirrhosis, leading to a severe evolution of COVID-19. In addition, acute or chronic liver dysfunction in people with decompensated liver cirrhosis may occur due to stress or viral sepsis. Also, cirrhotic patients are more susceptible to influenza virus than non-cirrhotic patients [14]. As noted, cirrhosis leads to increased mortality in patients with acute respiratory distress syndrome (ARDS), while the effect of cirrhosis on COVID-19 is controversial. However, COVID-19 patients with pre-existing liver disease have been shown to require special clinical intervention due to impaired immune function [15]. In this sense, the monitoring of patients with compensated cirrhosis and the care of patients with severe evolution represented challenges with multiple therapeutic approaches during the SARS-CoV-2 epidemic [16]. From the point of view of chronic liver viral damage (HBV), studies and experiments have demonstrated that the severity of COVID-19 may not be affected by chronic HBV infection, but there are a number of differences of opinion [17]. It is assumed that the symptoms and severe forms of the disease are most frequently induced by hyperactive macrophages and the cytokine cascade, leading to the dysfunction of several organs and systems [18].

There is also evidence of transient increases in liver transaminase levels following systemic viral infections. Elevated transaminase levels indicate immune system activity and inflammation caused by the cytokine cascade, leading to "bystander hepatitis" without liver dysfunction [15]. Patients with COVID-19 associated with HBV infection have been shown to have an increased risk of liver injury and disease, as well as mortality [16]. An analysis of 15 patients with chronic hepatitis B infection and COVID-19 showed a substantial increase in total bilirubin levels and a higher mortality rate than patients with COVID-19 without HBV infection. In addition, Chen et al. found that people with chronic hepatitis B were more likely to develop COVID-19 [19]. Another pathology with increased prevalence in Romania was alcoholic steatohepatitis (AFLD) and non-alcoholic steatohepatitis (NAFLD), which were accompanied by forms with increased severity in association with SARS-COV-2 infection, with significant morbidity and mortality. In people with NAFLD, the progression of COVID-19 and the rate of viral clearance are considerably higher. Patients with persistent liver abnormalities have been shown to have NAFLD and a BMI over 35 kg/m2 [5]. A study of 202 patients in China reported that risk factors such as obesity and NAFLD increased the progression of COVID-19 and consequently further affected liver function [5]. In addition, data show that NAFLD has a significantly greater impact on disease severity and the occurrence of pulmonary complications, respiratory dysfunction, hypoxemia, progressive systemic inflammatory reaction, and ARDS in patients with COVID-19.

Material and Method

A study group consisting of 173 patients was evaluated from a clinical and functional (biological) point of view, the distribution by gender and the environment of origin being shown in (Figure 1). A preponderance of the male sex is observed (M/F ratio 1.27), respectively of patients from the urban environment compared to the rural one, an explanation being the increased addressability related to the medical services of the patients in the first category. The biological parameters evaluated dynamically (at admission - T0, 3 months - T+3M and 6 months - T+6M) were liver enzymes (AST, ALT, GGT), respectively the inflammatory factors frequently used in current practice: C-reactive protein (hsCRP) and ferritin. The explorations carried out in the dynamics of the evaluated parameters showed a statistically significant decrease ($p<0.05$), respectively a clinical and functional improvement of the symptoms and the quality of life of the patients in the study group after 3 months (T+3M), respectively 6 months (T+6M) (Figure 2). 12 patients showed increased values of liver enzymes at 6 months, comparable to those at the time of hospitalization, the average being 80 IU/L (±5 IU/L), and the inflammatory factors remained at a high level - hsCRP 30 mg /dl (±7 mg/dl), respectively ferritin with increased values of more than 30% compared to normal ones, our conclusion being the presence of a long-term infection with the SARS-COV 2 virus associated with previous liver pathology. These cases required clinical and functional monitoring for a longer period, respectively the periodic review of the therapeutic indications.

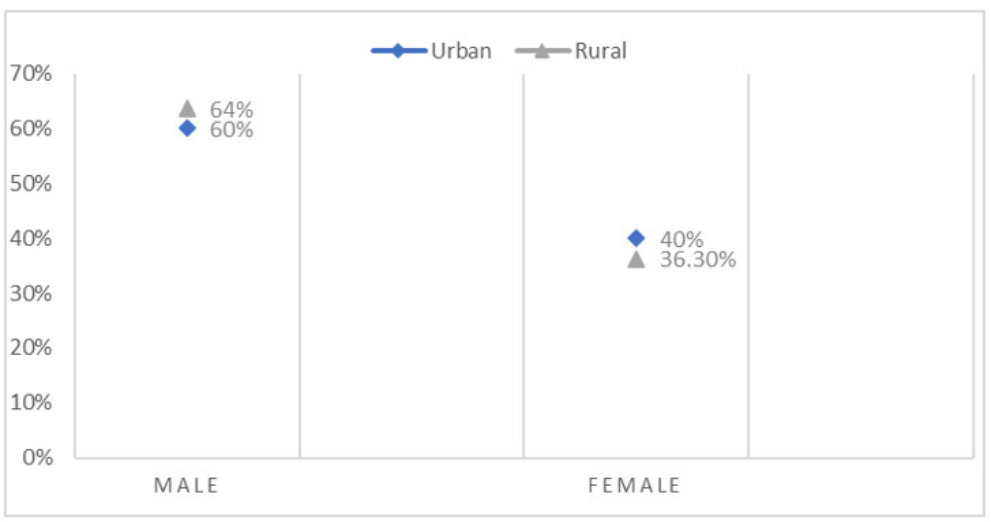

Figure 1: The distribution of patients in the studied group according to gender and place of origin.

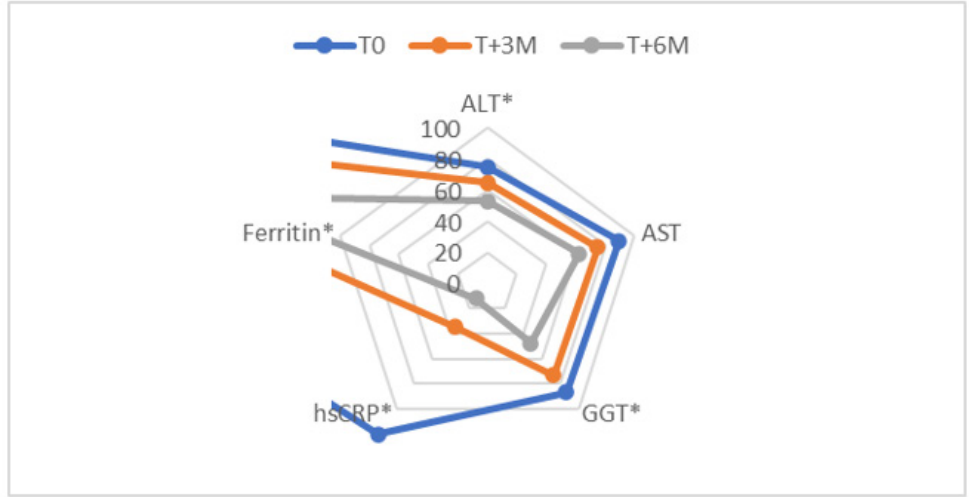

Figure 2: Evolution of biological parameters in the studied group.

Results and Conclusions

The wide range of symptoms associated with COVID-19 may be related to the tropism of the virus for angiotensin-converting enzyme 2 (ACE2), expressed on various human cells [20]. Liver damage in patients with SARS-CoV-2 infection could be directly caused by viral infection of liver cells, as ACE2 is expressed in both liver cells and bile duct cells [5] and pathological studies in patients infected with SARS. identified in 2003 reveal the presence of the virus in the liver tissue. Liver enzyme abnormalities could also be explained by the effect of antibiotics and antiviral drugs administered to patients and the cytokine storm associated with the infection [4,21]. Moreover, pre-existing underlying liver diseases could contribute to hepatic ALT/AST/GGT elevation. Therefore, current treatments for COVID-19, including the use of steroids, may promote reactivation of chronic latent hepatitis B infection, which is a major cause of liver disease.

Thus, all these factors should be considered by doctors to properly manage the infection. Therefore, monitoring and providing preventive measures to inhibit and control infection in high-risk patients and those susceptible to severe COVID-19 are essential, such as in people with pre-existing liver disease, HCC, liver transplant patients, and in patients taking antiviral drugs [22]. In addition, the death rate is higher in the elderly and in people with pre-existing diseases. The conclusion of the study would be the fact that SARS-COV 2 infection causes the aggravation of previously existing liver pathologies, with a slow but progressive improvement of biological parameters and clinical symptoms under specialized treatment. However, information on the effect of pre-existing chronic liver disease on the severity of COVID-19, as well as the effect of this disease on liver function and the quality of life of patients, is insufficient and requires more extensive and detailed research in subsequent studies [23-30].

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008375

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