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Editorial board member of *World Journal of Clinical Cases*, Dr. Kvolik is a Professor in the School of Medicine, Osijek University, Croatia. She obtained her MD degree, with specialization in the field of anesthesiology, resuscitation and intensive care from the Zagreb Medical School, Croatia. Afterwards, she undertook postgraduate training in Clinical Pharmacology at the same institution, defending both a Master's thesis and PhD thesis. In 2006, she joined the Osijek University Medical Faculty as a lecturer and was promoted to Professor in 2009. In 2012, she was elected Head of the Department of Anesthesiology, Resuscitation, Intensive Care and Pain Therapy, a position she occupies to this day. She is also the current Head of the Intensive Care Unit at the Osijek University Hospital, Croatia. (L-Editor: Filipodia)

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Liver in the limelight in the corona (COVID-19) time

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Abstract

The novel coronavirus, severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2), is a topic of great interest currently in the medical field due to the significant morbidity and mortality associated with it. There is immense curiosity about this virus as knowledge about it is limited from pathogenesis, host related factors and the variable effect it has on different patient populations. Though it has claimed fame due to its ability to compromise the respiratory system, it possess the capability to infect other organs as well including the liver. It is important for clinicians to recognize that the virus can result in multi-organ dysfunction as well. Presentation with gastrointestinal symptoms and involvement of the liver can be subtle and can be misdiagnosed. Those with pre-existing liver disease may be more susceptible as well as those who are immunosuppressed or have other co-morbidities. This review article provides a brief overview of some of the information that is available so far with regards to how the liver is impacted by the coronavirus.

Key words: Coronavirus; Liver; COVID-19; SARS-CoV-2; Angiotensin converting enzyme 2 enzyme; Gastrointestinal

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Core tip: The severe acute respiratory syndrome-corona virus-2 infection has created turbulence in the medical field. It is widely known to affect the respiratory system but can involve organs such as the liver. In this article, we provide a brief overview of some of the current available information on coronavirus in relation to the liver.

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INTRODUCTION

The emergence of the novel coronavirus, popularly being referred to as corona virus disease-19 (COVID-19) or severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) infection has generated a multitude of challenges across the globe. Not only has it impacted the frail and immunocompromised individuals but also those who are healthy at baseline. It has exerted an effect on the healthcare systems across the world and the providers within them. The challenges being faced are dispersed throughout the community and carry implications for not only those afflicted but those who are struggling to care for them. There is minimal information available on this virus with regards to pathophysiology, virulence factors, host related factors that predispose to the severity of presentation and most importantly treatment. The virus has been shown not only to impact the respiratory system but also other systems such as the gastrointestinal system including the liver. The involvement of the liver can be variable from a mild to modest increase in the liver enzymes to an acute decompensation. Being aware of the impact of this virus on the liver is crucial as not all patients will present with respiratory symptoms. Hence patients with atypical symptomatology may be misdiagnosed and organs such as the liver may be overshadowed by involvement of organs such as the lungs. The focus of this review article is to discuss how the SARS-CoV-2 infection involves the liver. As more data becomes available, there will be further insight to this virus as research is happening fiercely around the world.

PATHOPHYSIOLOGY

The novel coronavirus, SARS-CoV-2, is an enveloped, positive stranded Ribonucleic acid virus, that belongs to the *Coronaviridae* family of *Nidovirales* order^[1,2]. Like SARS-CoV (severe acute respiratory syndrome-CoV) and MERS-CoV (middle east respiratory syndrome-CoV) which were responsible for similar outbreaks, the SARS-CoV-2 is also thought to be zoonotic in origin^[1,2]. There are four human coronaviruses (229E, NL63, OC43, and HKU1-CoVs), which unlike their zoonotic counterparts, are only responsible for a mild respiratory tract infection^[2]. Multiple recombination events and mutational changes in the viral genome, often facilitated by intermediate animal hosts, confers a higher degree of virulence to these newer strains of zoonotic CoVs^[3]. Coronaviruses possess a glycoprotein known as the S (spike) glycoprotein which enables it to attach to a specific host cell-membrane receptor^[4]. This also determines the type of cells the virus can infect⁴. Though the understanding of this novel coronavirus is still somewhat limited, there is some postulation that it shares many similarities with the SARS-CoV. Previously, the angiotensin converting enzyme 2 (ACE2) receptor was identified as the specific receptor used by SARS-CoV to infect the ciliated bronchial epithelial cells and the type 2 pneumocytes^[5-8]. The same receptor is implicated in the pathogenesis of SARS-Cov-2. The interaction of the transmembrane spike glycoprotein receptor-binding domain with the ACE2 receptor is further facilitated by the host transmembrane serine proteases which together mediate the ability to infect a host cells^[9]. Thus, virtually any cell that possess the viral specific receptor is a potential target for it.

These receptors are not only expressed in the cytoplasm of the gastrointestinal glandular epithelial cells such as those of the stomach, duodenum and rectum^[10], but are also expressed in the liver^[11]. According to some recent data, a predominant expression is seen in the cholangiocytes, which can suggest a direct viral induced toxicity to the intrahepatic bile ducts^[11].

Liver biopsies of SARS patients had previously not only detected viral nucleic acid in hepatocytes and but had also demonstrated apoptosis and ballooning, presence of acidophilic bodies and mild to moderate lobular lymphocytic infiltration with lack of fibrosis^[9,12]; all of which pointed towards direct hepatic involvement. Although, the SARS-CoV-2 viral particles have not yet been identified in hepatocytes, the autopsy of COVID-19 patients have demonstrated microvesicular steatosis and portal inflammation^[13], pointing towards hepatic involvement in SARS-CoV-2 infection as well.

Various hypotheses have been put forward to explain the mechanism of hepatotoxicity seen with SARS-CoV-2 infection. Direct hepatocyte damage as a result of viral hepatitis is one of them^[9]. Indirect hepatic damage from an overwhelming systemic immune response or various experimental drugs currently used is also a possibility^[9].

Many of the currently approved or experimental therapeutic agents including antivirals, antibiotics, immunomodulators and steroids have a well-known adverse effect of hepatotoxicity^[14].

Both the innate and adaptive immune pathways have been implicated in the pathogenesis of SAR-CoV-2 infection. Innate immune cells of the pulmonary system include antigen presenting cells which make the first contact with the virus^[15]. They activate the adaptive CD4+ and CD8+ T-cells, which in turn activates the humoral and cytotoxic immune responses, respectively^[15]. This causes T-cell mediated destruction of viral infected cells which in turn leads to further inflammation creating a vicious inflammatory cascade^[16]. In severe cases, this leads to an overwhelming release of inflammatory cytokines, such as IL-6, IL-10, TNF and T-Cell exhaustion^[15,16]. This aberrant systemic inflammatory response also called cytokine storm is not only implicated in ARDS and respiratory failure, but also in shock and multi-organ failure seen in severe cases^[16,17]. Severe hypotension and hypoxemia that follows can lead to hepatic ischemia and hypoxia-reperfusion injury resulting in hepatocellular injury and death^[16]. Levels of reactive oxygen species become elevated and through a cascade of events cause more generation of mediators that can enhance the pro-inflammatory state and cause further liver injury^[16,18]. **Table 1** below summarizes some of the suggested mechanisms that may contribute to liver dysfunction due to the coronavirus.

Exacerbation of chronic liver diseases, either from the overall inflammatory stress or consequence of experimental pharmacotherapies is also a possibility. Furthermore, therapeutic interruptions due to fear of contracting the infection is also common which can cause a relapse of these conditions. Due to these reasons, some have suggested that liver damage seen in SARS-CoV-2 infection can be partially attributed to presence of an underlying chronic liver diseases^[19].

CLINICAL MANIFESTATIONS

The typical signs and symptoms of the novel coronavirus infection stem mainly from the involvement of respiratory system. They can vary in severity from mild, such as dry cough, dyspnea to severe resulting in respiratory failure requiring mechanical ventilation^[9]. The most commonly reported symptoms are fever, cough and fatigue^[17], however non-specific gastrointestinal symptoms, such as nausea, vomiting, diarrhea, abdominal pain are also often reported^[9]. These symptoms can result from any liver injury irrespective of the etiology. Varying degrees of liver function abnormalities including aminotransferase elevation and mild hyperbilirubinemia are reported as well^[20]. Hypo-albuminemia and coagulopathy can be seen in more severe cases^[9,21].

Severe cases have an overall greater likelihood of developing liver injuries^[17,21,22]. Such cases also show significantly higher elevations in markers of hepatic function, such as aminotransferases, alkaline phosphatase and glutamyl transferase^[23]. This pattern is observed not only on initial presentation but also during the course of the illness^[23]. However, most of the available literature suggests that the liver injury associated with COVID-19 tends to be transient only mild elevations in serum aminotransferases^[24,25]. Although uncommon, acute liver failure and intrahepatic cholestasis have also been reported, which mostly tends to occur in the more fulminant cases^[25].

DISCUSSION

The mechanism of hepatotoxicity due to the novel coronavirus is not yet clear and various theories have been proposed. Whether it is a direct injury to the intrahepatic bile ducts or to the hepatocytes themselves or an indirect mechanism is still a matter of debate and a multifactorial etiology for COVID-19 related liver injury remains the best possible explanation^[9].

Presenting symptoms, such as fever and fatigue can be nonspecific and unreliable, hence it is imperative to obtain serum markers, including hepatic function tests to identify liver involvement. A thorough history (including exposures and contacts) and physical exam is also important. Furthermore, hepatic function derangements, if seen, should be followed up by tests for other common viral hepatitis as well as routine testing per guidelines, especially when there is a possibility of underlying pre-existent liver disease. Non-invasive imaging modality such abdominal ultrasound can be used to evaluate liver parenchyma, assess for any biliary dilation and patency of the hepatic

Table 1 Mechanisms of injury

Angiotensin-converting enzyme 2 receptor	Expression on cholangiocytes (predominantly), hepatocytes
Immune mediated	Activation of system inflammatory response syndrome. Generation of a cytokine storm and pro-inflammatory state with multi-organ dysfunction. Stimulation of innate and cellular immunity. Activation of T killer lymphocytes
Medications	Acetaminophen. Antivirals (Remdesivir, lopinavir/Ritonavir, Oseltamavir). Antibiotics (macrolides). Janus kinase inhibitors. Methotrexate. Tocilizumab
Hypoxia-reperfusion injury	Hypotension and hypoxemia leading to hepatic ischemia

and portal veins. Clinicians should also be mindful of potential exposure to hepatotoxic medications which are increasingly being used to treat COVID-19 patients. Medications as common as acetaminophen, which used as antipyretic and analgesic can inadvertently contribute to liver injury especially in those with chronic liver disease. Other experimental medications such as antivirals (*e.g.* Remdesivir, Lopinavir/Ritonavir, Oseltamavir *etc.*), immunomodulators (Tocilizumab) and commonly prescribed (*e.g.* Azithromycin) have been reported to have hepatotoxicity^[14,17].

Decompensation of any underlying pre-existing liver disease should also be kept in mind. Effect of COVID-19 on chronic liver diseases, such as alcoholic liver disease, non-alcoholic fatty liver disease or chronic viral hepatitis is unclear at this time^[24]. Some reports have indicated a higher disease severity in patients with chronic hepatitis B^[22]. A multi-center study including 2780 patients observed that those with pre-existing liver disease were at a significantly higher risk for mortality when compared to those without prior liver disease^[26].

Non-alcoholic fatty liver disease patients, not only demonstrate a significantly higher disease severity but due to poorly understood mechanisms also show a prolonged shedding of SARS-CoV-2 virus^[27]. In patients with primary biliary cholangitis, there may be an elevation in alkaline phosphatase and γ -GT or worsening of intrahepatic cholestasis (as increased expression of ACE2 receptor on cholangiocytes)^[24]. Immunocompromised patients including those with cirrhosis, hepatocellular carcinoma may be at higher risk as well^[24]. Patients who are on medications that suppress the immune system such as those with liver transplants or autoimmune liver disease are also hypothesized to be more prone. A case series from an area with a high SARS-CoV-2 infection rates from Northern Italy, reported good outcome for majority of autoimmune liver disease cases and suggested against the tapering of immunosuppressive therapies as previously thought^[28]. A recently published case report described a post liver transplant hepatocellular carcinoma patient on immunosuppressive therapy (tacrolimus and mycophenolate), who succumbed to COVID-19^[29]. Though the etiology of his demise was considered to be multifactorial, it was initially proposed that immunosuppressive therapy might be contributory^[29]. This emphasized the challenges that hepatologists are faced with. Withholding immunosuppressants may cause graft rejection while continuation may increase susceptible to infection. Even the etiology of liver function derangements in such patients may be difficult to accurately determine. This dilemma has recently been addressed by multiple liver disease societies (AASLD, APASL and EASL), who have recommended against the reduction of immunosuppressive therapy in patients with mild COVID-19^[30].

Autoimmune Liver Disease Overall, based on the currently available data, it appears that liver involvement in most cases tends to be transient in the form of mild to moderate elevations of liver. Severe cases tend to more often have liver involvement which can often be more pronounced^[25]. Experimental treatment strategies are quickly being rolled out. Work on a possible vaccination is currently underway as well. As we continue to discover more about the novel coronavirus and better understand the pathophysiology, the treatment strategies will also evolve.

CONCLUSION

The SARS-CoV-2 infection has swept humanity into peril and research is being conducted worldwide to decipher this virus. The hallmark of this infection is recognized as the involvement of the respiratory system. However, it affects other systems as well such as the heart, nervous system and among others the liver as well.

It is important for clinicians to be aware of the potential for liver injury associated with this virus. Varying degrees of involvement can occur though it tends to more often be mild based on data that is seen thus far. Being wary of those with underlying liver disease and the possible implications from the virus itself and associated experimental treatments. A thorough investigation should be carried out when a derangement of liver enzymes occurs as performed in general practice. Clinicians should be cognizant of the potential for liver involvement and have a high index of suspicion in those with gastrointestinal symptoms and even atypical symptoms presenting with abnormal liver enzymes.

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