Clinical Manifestations and Pathogenesis of Hepatic Damage in SARS-CoV-2 in Comparison to MERS-CoV and SARS-CoV

Jasndeep Kaler[1]*, Elsa Tabrez[2], Azhar Hussain[1,3], Shams SM Tabrez[4], Sundus Nasim[5] and Sohail Kumar[5]

[1]*MD Candidate, Xavier University School of Medicine, Oranjestad, Aruba*

[2]*Medical Student, American University of Integrative Sciences, Barbados*

[3]*Doctoral Candidate of HealthCare Administration, Franklin University, Ohio, USA*

[4]*Assistant Professor of Medicine and Board-Certified Gastroenterology and Hepatology at University of Central Florida, Florida, USA*

[5]*MBBS, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan*

*Corresponding Author: Jasndeep Kaler, MD Candidate, Xavier University School of Medicine, Oranjestad, Aruba.

Abstract

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread globally, its systemic manifestations continue to gain more focus. Recently, an association between n2019-CoV and hepatic damage has emerged. While there is no clear-cut understanding of the viral mechanism causing hepatic and biliary injuries, the involvement of several different mechanisms is likely. Current hypotheses suggest that the liver presents with a high expression of ACE2 receptors, allowing the virus to penetrate the hepatocytes and the bile duct epithelial cells. The hepatic injury in n2019-CoV positive patients could also result from other reasons such as cytokine storm that leads to the systemic inflammatory response syndrome, administration of hepatotoxic drugs, such as acetaminophen and antivirals, and pre-existing liver diseases. Its resemblance to the injury caused by SARS-CoV and MERS-CoV is remarkable which could be attributed to the genetic makeup of these different types of coronaviruses. As research continues, there is a greater need to understand the full extent of the hepatic injury that occurs due to SARS-CoV-2 and the mechanism to minimize the damage. It is necessary to compare the disease at a biochemical and pathological level with both MERS-CoV and SARS-CoV; this article aims to do so.

Keywords: Hepatic Damage; SARS-CoV-2; Coronavirus; MERS-CoV; SARS-CoV

Introduction

Earlier this year, the world was hit by a global pandemic due to the rapidly spreading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With cases prevalent in 213 countries, this outbreak was first reported to the World Health Organization (WHO) nation office in China on December 31, 2019 and was soon after denoted a global pandemic [1]. The first case of novel coronavirus disease-2019 (n2019-CoV) traced back to the wet animal market located in Wuhan City, China. Due to this association, n2019-CoV has both zoonotic and human to human transmission [2]. According to Situation Report-118, prepared by WHO on July 28, 2020, 16,114,449 cases and 646,641 deaths have been globally recorded [3]. The primary mode of transmission of this virus is via respiratory droplets. However, recent studies suggest transmissibility through a faecal-oral route due to evidence of the infection in urinary and stool samples of SARS-CoV-2 positive patients [4].

SARS-CoV-2 is not the only virus from the coronaviruses family to have received international attention. Previous global outbreaks have also been attributed to pathogens that belong to the *Betacoronaviruses* family, namely the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [2]. The overlapping genomic makeup of the said viruses justifies the similarities of respiratory symptoms. Genomic wide phylogenetic analysis amongst the three coronaviruses has reported that SARS-CoV-2 possessed 79.5% and 50% of genomic makeup equivalent to that of SARS-CoV and MERS-CoV, respectively [2,5]. Standard features like fever, dyspnea, dry cough, and bilateral ground-glass opacities on chest CT (computerized tomography) scans have been observed in infection with coronavirus disease 2019 (COVID-19) and other betacoronaviruses [2].

Viral replication primarily occurs in the upper respiratory tract, specifically the nasal cavity and pharynx; however, the involvement of the lower respiratory tract and the gastrointestinal (GI) mucosa is not uncommon [5]. The replication of SARS and SARS-CoV-2 occurs within the respiratory epithelium, specifically the type II pneumocytes. Both viruses utilize the angiotensin-converting enzyme 2 (ACE2) receptor located on pneumocytes to enter the host cell. Once replication occurs within the pneumocyte, the newly replicated viral particles are released from the lung epithelial cell and increase the viral load. The presentation of SARS-CoV-2 occurs with an incubation period comprising of fever, fatigue, and cough, followed by the development of severe symptoms due to a high viral load [6]. Although fever and respiratory symptoms are characteristic of n2019-CoV, variable manifestations like acute hepatic and cardiac injury, renal failure, and gastrointestinal symptoms such as diarrhea have also been noted [2,5]. The mechanism of hepatic injury in coronavirus infection is debatable, albeit moderate microvascular steatosis and mild lobular and portal activity have been visible. Whether this is due to direct invasion of SARS-CoV-2 or hyperactive immune response presenting in the form of cytokine storm syndrome or other conditions such as the use of hepatotoxic drugs remains unclear [5]. In fatal cases of COVID-19, hepatic impairment is reported in approximately 78 % of the patients [6] indicating that close monitoring of liver function tests is needed to avoid future complications.
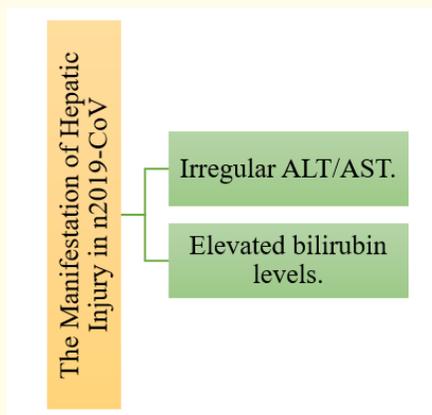

Figure 1: The manifestation of hepatic injury in n2019-CoV.

Xu., *et al.* reported the occurrence of hepatic injury in COVID-19 patients through laboratory testing. As depicted in figure 1, the manifestation of hepatic injury was observable through irregular alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels and mildly elevated bilirubin levels [7]. Previous studies have also noted that hepatic injury was apparent in SARS-CoV and MERS-CoV [7,8]. Under normal physiological conditions, the liver is deemed a vital organ to maintain immune tolerance, filter toxins, and regulate metabolism. Therefore, the possibility of hepatic injury raises concern for hepatologists worldwide. This review aims to summarize the possible mechanisms of SARS-CoV-2 infection-induced hepatic damage and compare it with hepatic injury mechanisms of previous coronaviruses MERS-CoV and SARS-CoV.

MERS-CoV

MERS-CoV was first reported to the WHO from the Arabian Peninsula in September 2012. As of 2014, it has been associated with 699 cases and 209 deaths. Even though a complete picture of this virus is unknown, genomic analysis reveals the possibility of camels being the source of infection. Thus, a camel-to-human transmission might have caused its spread throughout the Middle Eastern regions. MERS patient's median age is 49 years, and the illness may present anywhere from being asymptomatic to causing life-threatening respiratory illness [9].

Clinical manifestation

The characteristic clinical features of MERS-CoV infection are fever, cough, and difficulty breathing. Severe manifestations include respiratory failure, kidney failure and hepatic dysfunction [10]. Figure 2 provides a diagrammatic denotation of the typical and atypical manifestations observed in MERS-CoV positive patients, as explained by Shah., *et al* [11]. Furthermore, a retrospective study by Saad., *et al*. has noted that laboratory testing of MERS-CoV positive patients presented with elevated AST and bilirubin levels and a decrease in the albumin levels. They also demonstrated that reduced serum albumin levels could predict the severity of MERS-CoV associated liver injury [10].
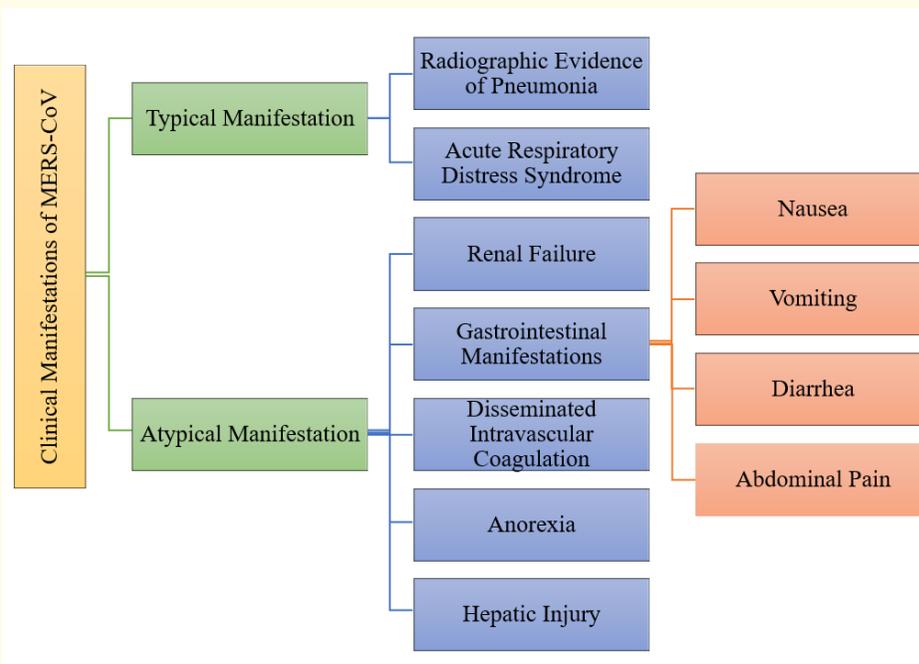

Figure 2: The typical and atypical clinical manifestations of MERS-CoV.

While the above manifestations can be due to the viral invasion's direct damage, the role of inflammatory or drug-induced damage is not to be ignored. Thus, further research must be done on the said subject providing thorough evidence elaborating the pathogenesis to avoid fatal complications.

Pathogenesis of hepatic injury

The hepatic injury noted in MERS-CoV is quite similar to that of SARS-CoV. MERS-CoV, however, differs from SARS-CoV and SARS-CoV-2 in the method of penetrating mucosal epithelium. As explained previously, both SARS-CoV and SARS-CoV-2 utilize the ACE2 receptor to gain entrance into host cells; MERS-CoV utilizes dipeptidyl peptidase-4 (DPP-4) [7,12]. DPP-4 has been acclaimed as being prominent on the surface of cells within human airways and is also present in high levels on the liver [12]. Due to the increased quantity of DPP-4 receptors on the liver, the liver can be a potential target organ of MERS-CoV [7]. Zhao., *et al.* conducted an experiment in which a transgenic mouse was developed that expressed codon-optimized human DPP-4 (hDPP-4) globally; the result revealed that MERS-CoV could penetrate hepatocytes using DPP-4 and cause hepatocyte injury [13].

Furthermore, the transgenic mice presented with mild to moderate hepatic injury succeeding the MERS-CoV infection. The hepatic injury ranged from infiltration of a large quantity of activated Kupffer cells and macrophages to scattered necrosis of hepatocytes, particularly within the sinus region. Fatty changes within the hepatocytes were observed, roughly nine days post-infection with less hepatocyte necrosis [13]. In the acute phases of the viral infection in MERS-CoV positive patients, significant pro-inflammatory cytokine responses were also observed, including the elevation in the serum concentrations of interferon-gamma (IFN-γ), tissue necrosis factor-alpha (TNF-α), interleukin-15 (IL-15) and interleukin-17 (IL-17). However, the mechanism explaining cytokine elevation and its relation with liver injury is yet to be investigated. Histologically, liver injury in MERS patient manifests as mild portal tract and lobular lymphocytic inflammation with mild cellular hydropic degeneration in liver parenchyma [7].

SARS-CoV

SARS-CoV was first denoted as a global pandemic in November 2002 in the province of Guandong in China. With several symptomatic and pathological similarities of SARS-CoV-2, SARS-CoV is responsible for over 8,096 cases and 774 deaths internationally [14].

Clinical manifestations

The SARS-CoV clinical presentation can be associated with non-specific symptoms such as a headache or a febrile state, as shown in figure 3. Figure 3 also depicts other commonly observed manifestations in a SARS-CoV positive patient. Hepatic injury caused by SARS-CoV was noticeable in the early stages of the disease, with a diagnostic mild to moderate increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [7,14].

Pathogenesis of hepatic injury

SARS-CoV positive patients who had severe disease were more likely to present with hepatic injury than the milder cases. Post-mortem autopsy reports conducted on SARS-CoV positive patients concluded that high quantity of viral particles was present in the epithelial cells and vascular endothelium of multiple other organs, such as the liver, in addition to the respiratory system [7]. As previously stated, SARS-CoV utilizes the same receptor for viral entry as SARS-CoV-2: the ACE2 receptor. The ACE2 receptor is present in abundance in the lungs where conversion of inactive angiotensin I to active angiotensin II occurs. However, the receptor is also highly expressed on the hepatic endothelial cells, suggesting hepatic injury in the infected patients [7,15]. Hepatic biopsies conducted in SARS-CoV positive patients also revealed a significant increase in the mitotic cells with eosinophilic bodies and ballooning of the hepatocytes. These findings are suggestive of the hypothesis that SARS-CoV may induce apoptosis of the hepatocytes that can lead to hepatic impairment [7]. These findings were parallel to results by Chau., *et al.* Increased mitosis and apoptosis were observed in patients with hepatic dysfunction. Mild to moderate lobular lymphocytic infiltration with eosinophilia and fibrosis was seen. Immunohistochemical studies revealed that some nuclei were positive for antigen Ki-67 [16]. A study conducted by Tan., *et al.* stated that a SARS-CoV specific protein, protein 7a, can initiate
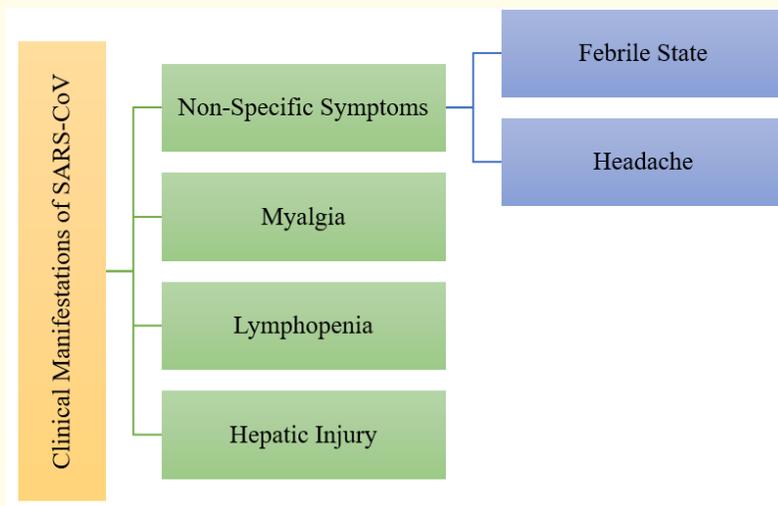
Figure 3: Clinical manifestations of SARS-CoV.

programmed cell death, otherwise known as apoptosis, in multiple different cells within different organs including the liver, kidneys and the lungs; this further confirms the possibility that SARS-CoV can directly attack the hepatic tissue and thus, can cause hepatic injury [17].

SARS-CoV-2

Due to the current issue of the global outbreak of SARS-CoV-2 there is a shortage of adequate information to determine the exact cause of the hepatic injury among positive n2019-CoV patients. However, much like in SARS-CoV positive patients, SARS-CoV-2 utilizes the same ACE2 receptor. Due to this similarity amongst the two viruses, it has been postulated that the pathogenesis of hepatic injury amongst the two viruses may also be similar in presentation [18].
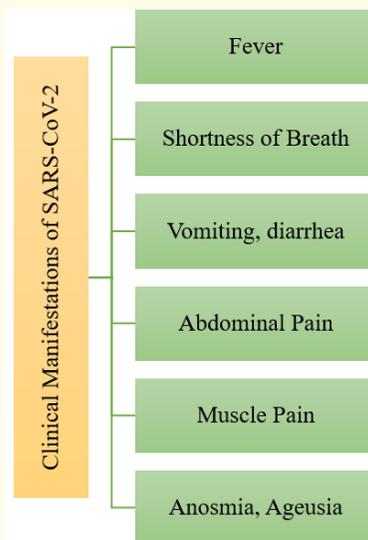
Clinical manifestations

Figure 4: Clinical manifestations of SARS-CoV-2.

Figure 4 reports the most common clinical manifestations that have been associated with SARS-CoV-2. Most of the symptoms are similar to an infection that may be associated with SARS-CoV and MERS-CoV; however, specific presentations such as loss of smell (ageusia) and loss of taste (hypogeusia) are unique to n2019-CoV [18-20].

As the virus primarily affects the respiratory system, the hepatic damage caused by n2019-CoV is considered mostly mild and transient compared to the respiratory system, which has been noted to be extensive. However, approximately 14.8% to 53% of patients with SARS-CoV-2 infection have been reported to have liver damage suggesting that liver injury is relatively common among n2019-CoV patients [7,18]. In a cross-sectional study consisting of 204 confirmed SARS-CoV-2 patients, half of the patients had gastrointestinal symptoms with anorexia and diarrhea as their chief complaints. Six patients had digestive symptoms without any respiratory involvement [21]. Moreover, another study has shown that liver injury was more common in critically ill patients admitted in an intensive care unit (ICU) compared to those admitted in wards [22]. Such evidence indicates that liver function impairment could be a sign of worsening prognosis in patients with n2019-CoV infection.

Pathogenesis of hepatic injury

As mentioned earlier, because of the similarities in the clinical presentation between SARS-CoV and SARS-CoV-2, it has been postulated that the hepatic injury that would be seen in an n2019-CoV positive patient would mirror injury that is noted in a SARS-CoV positive patient. Studies have reported that the incidence of hepatic injury linked to n2019-CoV has been visible in up to 53% of patients [7,18]. This injury presents on a biopsy as increased mitosis, eosinophilic bodies and ballooning of hepatocytes indicating apoptosis [7]. Currently, the underlying mechanism for hepatic injury in patients with n2019-CoV infection is not yet known with certainty; however, it may be attributed to either a direct effect of SARS-CoV-2, or an indirect effect following septic shock, drug-related toxicity, multi-organ dysfunction, immune-related hepatitis, or a systemic inflammatory response (cytokine storm) of the COVID-19 infection.

As stated above, hepatic damage might result from the direct invasion of the liver by the virus. ACE2, the same receptor used by SARS-CoV as the primary source of entry into the alveolar epithelial cells, may also be expressed in hepatocytes and cholangiocytes, suggesting the virus's direct invasion into the liver cells causing injury [23]. Furthermore, as with SARS-CoV, the hepatic injury reported in n2019-CoV was recognized by abnormal levels of ALT/AST with a slightly higher level of bilirubin [18].

Through extensive research, Chai., *et al*. concluded that although both hepatocytes and cholangiocytes express ACE2, ACE2 expression is much higher in the cholangiocytes than in hepatocytes [23]. Cholangiocytes, otherwise known as bile duct epithelial cells, play a crucial role in hepatic regeneration and immune response [18,23]. Chai., *et al*. also propose that the liver injury observed in patients with n2019-CoV infection could be due to viral damage to the cholangiocytes, rather than the hepatocytes [23]. In an autopsy performed on a patient that had developed fatal complications associated with n2019-CoV, hepatic biopsies revealed moderate microvascular steatosis, along with mild lobular and portal activity; such damage is indicative of the notion that the injury may either be the result of the direct invasion of SARS-CoV-2 virus or could be classified as a drug-induced hepatic injury [8,18].

Further research suggests that the hepatic damage in n2019-CoV infected individuals could be due to the summation of stress and systemic inflammation. The immune tolerance of the liver within an n2019-CoV positive patient is quite impaired. The systemic inflammation results from hyperactivated immune responses that lead to the occurrence of a cytokine storm, which ultimately damages multiple organs systems; however, whether this cytokine storm can cause hepatic damage has yet to be determined [8,24]. SARS-CoV-2 has been associated with multiple fatal complications, including multi-system organ failure (MSOF) [25]. MSOF and the other fatal complications witnessed in critically ill infected patients have been attributed to the cytokine storm. The release of cytokines in the respiratory system brings about the characteristic respiratory symptoms and causes systemic inflammation. Research conducted by Prompetchara., *et al*.

indicated the presence of cytokine-induced inflammatory lung injury and viral sepsis. This leads to hepatic damage and can even be fatal [24]. Sepsis is known to be another uncommon but fatal complication in n2019-CoV positive patients that are in critical condition. The pathophysiology of sepsis-related hepatic damage also encloses hypoxic hepatic injury that may be due to ischemia and shock. Cardiac venous return slows down, resulting in sinusoidal dilatation and low blood oxygen saturation in critically ill n2019-CoV patients, leading to liver injury [26].

The use of hepatotoxic drugs for n2019-CoV treatment: A silent contributor to hepatic injury

Injuries caused by hepatotoxic medication such as antipyretics (NSAIDs and acetaminophen), antiviral drugs (remdesivir /lopinavir/ ritonavir), antibiotics (macrolides), steroids and many other herbal remedies used to treat SARS-CoV-2 infection could result in increased liver enzymes and hepatic damage. The excessive use of antipyretics to counter COVID associated fever may be linked to hepatic injury as the drug paracetamol is notorious for liver damage [27]. The use of antivirals like ritonavir/lopinavir or arbidol might also cause some hepatic damage. Data from the clinical trial in Shanghai also indicates their possible involvement in hepatic injury [28]. Mild microvascular steatosis and hepatic inflammation in affected patients also support the above facts [29]. Rarely, few cases of fulminant hepatitis have been reported with the use of hydroxychloroquine [30].

n2019-CoV infection with pre-existing liver disease: A challenge for hepatologists

Chronic liver diseases like chronic hepatitis B, non-alcoholic fatty liver disease, and liver cirrhosis are widely prevalent globally, whether the pre-existence of these diseases worsens the manifestations of COVID-19 is yet to be investigated. Patients with COVID-19 and liver cirrhosis may be at a higher risk of getting the most severe disease keeping in mind their immunocompromised status. In COVID patients with autoimmune hepatitis, glucocorticoid administration effects are not entirely understood. Due to the expression of ACE2 receptors in cholangiocytes, the worsening of pre-existing cholestasis in SARS CoV-2 infection should be monitored, and any elevation of liver enzymes should be considered suspicious [31].

Thus, the coexistence of COVID and chronic liver disease has become a challenging situation for hepatologists around the globe. Boettler T., *et al*. recommended guidelines for the treatment care of chronic liver disease patients with COVID-19 [32].

Early admission is advised according to the risk factors involved and to avoid devastating consequences in the future. Acetaminophen (2 - 3 g/day is considered safe in cirrhosis patients without current alcohol consumption), and NSAID overdosing should be avoided in patients with cirrhosis and portal hypertension.

Specific considerations included treating COVID patients with decompensated cirrhosis and associated complications like spontaneous bacterial peritonitis and ascites should be continued. In patients with hepatocellular carcinoma, there must be discontinuation of immune suppressors. Continuation of kinase inhibitors should be decided according to every case. Dose adjustment of calcineurin- and/ or mTOR (mechanistic target of rapamycin)- inhibitors should be done in liver transplant patients. It is essential that treatment regimens be tailored according to infected patients' needs and as to minimize treatment-related adverse effects, keeping the comorbidities and immune-compromised state of patients in mind.

It should be kept in mind that the currently available research also states uncertainty as to whether hepatic damage is directly correlated to an increased viral load of SARS-CoV-2 or secondary to any pharmaceutical regimes. Whether the presence of any prior comorbidity exacerbates the liver manifestations, remains a question of interest.
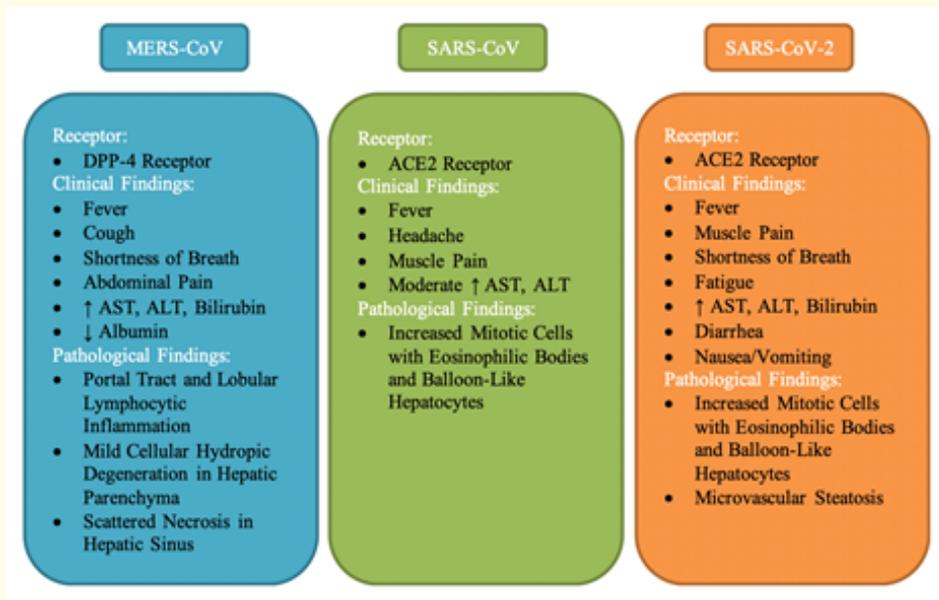
Figure 5: Findings in MERS-CoV, SARS-CoV and SARS-CoV-2.

Comparison of MERS-CoV, SARS-CoV, and SARS-CoV-2

Being from the same *Betacoronaviruses* family, SARS-CoV-2 has a similar structure and clinical presentation to some extent, to that of MERS-CoV and SARS-CoV [33]. Figure 5 aims to highlight the key clinical and pathological findings in a patient infected by each virus. While the clinical manifestations prove to be undeniably indistinguishable, the pathological findings differ at a microscopic level. MERS-CoV induces hepatic injury in the form of necrosis and fatty liver change, while SARS-CoV and SARS-CoV-2 induced hepatic injury, predominantly occurs as a result of hepatocyte apoptosis [7,8,11,13,14,18]. This variance in microscopic injury can most likely be attributed to the different receptors used by the MERS-CoV compared to SARS-CoV and SARS-CoV-2 to gain entry into the host cell. The DPP-4 receptor has an increased expression on hepatocytes, while the ACE2 receptor has an increased expression on cholangiocytes and hepatocytes; hence, the manifestation of injury can be dependent upon the receptor utilized, as well as the type of host cell.

Conclusion

n2019-CoV continues to persist as a global threat, there is a great need to focus on understanding the virus's systemic manifestations. The pathological features and presentation of n2019-CoV resemble significantly to the symptoms and pathological features seen in SARS-CoV and MERS-CoV. The exact mechanism of liver injury with SARS-CoV-2 infection currently remains vague. Several proposed mechanisms of liver injury in n2019-CoV, such as drug-induced, systemic inflammation-related or the injury, could also be attributed to the high expression of ACE2 in the liver and cholangiocytes. While the exact mechanism is unknown, the proposed mechanisms allow for a slight understanding of the role of n2019-CoV in causing hepatic damage. The symptomatic presentation of n2019-CoV has been accredited to cytokine release in the respiratory system, the respiratory system, in response to type II pneumocyte destruction. From a clinical perspective, it is imperative to manage the primary disease caused by SARS-CoV-2 and monitor the changes for evidence of any drug-induced liver injury. Since the liver is being referred to as the most frequently affected organ apart from the respiratory system due

to ACE2 expression, utilization of greater surveillance is essential to ensure that liver function tests are up to par and the risk of liver injury is minimal. In n2019-CoV positive patients with pre-existing conditions that may already be on hepatotoxic pharmaceutical agents, cessation of said medication is crucial to ensure that the progression of hepatic injury is slowed down. Replacement of hepatotoxic medication with one having a lesser hepatic impact can also be presented as an alternative to ensure the hepatic injury can be hindered, if not completely halted. Moreover, special attention should be given to infected patients with chronic liver disease to avoid fatal complications.

Conflicts of Interest

None.

Funding Sources

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