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Coinfection of COVID-19 and viral hepatitis: A Rapid Review

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***Abstract*---**The purpose of this rapid review is to investigate the development of the hepatic manifestations and challenges with SARS-COV-2 and multiple viral hepatitis infections. The literature on the most critical viral, genetic and immunological factors between SARS-CoV-2 and viral hepatitis was reviewed, and the most important interactions that occur with the host were identified in addition to the use of antivirals, another drug, and also the potential of defective viral genomes in antiviral inhibitors. This review specified that some types of viral hepatitis in SARS-COV-2 patients may be reduced reactivation and receive immunosuppressive therapy. We concluded from the current review that it is necessary to consider the special care of persons exposed to infection with SARS-CoV-2 to persons infected with viral hepatitis. In particular, advanced cases of the disease and their stages of treatment as it leads to liver dysfunction and life-threatening patient.

***Keywords*---**SARS-CoV-2, viral hepatitis, acute and chronic liver or respiratory disease.

Introduction

Hepatitis causes worldwide health problems due to liver damage. Although there are different types of hepatitis, viral hepatitis is the more dangerous type.

Hepatitis B and C virus (HBV, HCV) infections can cause acute and chronic hepatitis. Hepatocellular carcinoma (HCC) and liver cirrhosis resulting from progressive chronic HBV and HCV infection are life-threatening viruses worldwide, with high fatality rates (Shackel *et al.,* 2013; Liu *et al.*, 2019). Chronic liver disease (CLD) is associated with a decreased number of functional liver cells. Therefore, it will reduce the effectiveness of drugs that undergo hepatic metabolism in CLD patients (Morgan and McLean, 1995). Most medications are known to be metabolized mainly by the cytochrome P450 (CYP) (Guengerich and Turvy, 1991; Akkaif *et al.,* 2020; Akkaif *et al.,* 2021). Several previous studies have demonstrated this differential effect of liver disease on CYP activity (Lown et al., 1992; George et al., 1995; Akkaif *et al.,* 2021).

Environmental variables, the virus itself (viral load and virus genotype), and immunological (deficiency of the immune response) ethnic distinctions all play a role in the virus's survival and causes for heterogeneity in the pattern and clinical result of HBV and HCV infection (Abdul Amir, 2018). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was a wide range of effects worldwide and had been a significant cause of morbidity and mortality. Thus, due to coronavirus disease 2019 (COVID-19) exhibited a variety of clinical manifestations, the majority of which have been pulmonary indications (Kumar *et al.,* 2021). SARS-CoV-2 with co-infections such as the human immunodeficiency virus (HIV), HBV, and HCV, are widespread in patients. However, the pandemic SARS-CoV-2 on this infection and related liver illnesses is unknown—furthermore, the consequences for individuals who inject drugs are unknown. Therefore, expectations and guidance on difficulties related to viral infections are vital as observations about hepatic symptoms and complications with COVID-19 and chronic active hepatitis symptomatic exacerbation of hepatitis (Reddy, 2020).

Co-infection of hepatitis B patients may be associated with many diseases, including HCV, HDV, HEV, H.I.V., torque teno virus (TTV), human pegivirus HPgV (GBV-C/HGV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), human herpes virus-1 (HSV-1), adenovirus (ADV), and varicella-zoster virus (VZV), has already been reported. However, such co-infections incidence, viral interactions, and clinical significance are not fully elucidated (McArdle *et al.,* 2018; Al-Sadeq *et al.,* 2019), particularly in developing countries, including Iraq. Therefore, this study aims to describe the development of the hepatic manifestations and challenges with SARS-COV-2 and multiple viral hepatitis infections.

Viral hepatitis

Currently, viral hepatitis is a significant health problem worldwide, particularly in Asian countries. Different hepatic viruses cause viral hepatitis and lead to liver-related morbidity (Jefferies *et al.,* 2018). Epstein-Barr virus, Herpes simplex virus, and cytomegalovirus are just a few viruses that can cause liver inflammation. However, hepatotropic viruses, often known as A to E viruses, are the most common cause of liver disease. Although types B, C, and E can become chronic, most hepatotropic viruses are acute and self-limiting (Zarrin and Akhondi, 2022). Viral hepatitis is generally reserved for the hepatic infection caused by a small hepatotropic group of the virus. It has been identified to have the liver as its primary target and produce hepatic disease as its main clinical manifestation. The

incidence of viral hepatitis varies according to geographical areas and immunization (Abdul-Husin, 2013).

Historical previous viral hepatitis

The history of viral hepatitis is intriguing and spans thousands of years. When such organisms initially infected humans, a repeated natural cycle began with the ability to infect billions of people, resulting in population extinction; there are tales of jaundice epidemics in China 5,000 years ago while Babylon more than 2,500 years ago. Great jaundice epidemics and pandemics have a long and dreadful history, and they are frequently linked to major wars (Fonseca and Ferrazda, 2010). Hepatitis was communicable due to outbreaks often occurring in overcrowded and unclean conditions, and it was a significant problem throughout World War I. Furthermore, hepatitis in the blood was a major problem throughout World War II, when large numbers of injured combatants were infected by pooled plasma administered to save lives threatened by blood loss. Although, after blood or plasma transfusions, it was believed to be transmitted through water contaminated with feces in the 1950s, serum hepatitis had to be distinguished from the more general global infectious hepatitis thought to be transmitted by feces-contaminated water in the 1960s (Feinstone, 2019).

HDV was discovered in the mid-1970s when a new nuclear antigen was found in patients with severe chronic HBV. The first report from the delta antigen was published in 1977, and the official designation of HDV was given to the virus in 1983. Even though 'delta' is still used, HDV is now favored. After cloning and sequencing the virus's genome in 1986, it confirmed the virus's uniqueness. After that, HDV was given "the delta virus" as its genus (Pascarella and Negro, 2011; Botelho-Souza *et al.,* 2017). In the mid-1970s, an unidentified agent contaminated the world's blood supply, causing non-A, non-B hepatitis post-transfusion. As a result, the first sequences of the hepatitis C virus were not reported until 1989. Hepatitis E was originally identified in the Kashmir Valley in 1978 during a hepatitis epidemic. There were an estimated 52,000 cases of hepatitis in the epidemic, with 1700 deaths (Khuroo, 2011; Webb and Dalton, 2019).

Immunopathogenesis of viral hepatitis

The most prevalent cause of liver cancer is a viral infection, and HBV and HCV infection are the most common causes of chronic liver disease in several parts of the world. Both viruses cause chronic hepatitis, leading to cirrhosis and eventually progressing to hepatocellular carcinoma (Zhang *et al.,* 2021). Immunologically mediated events are important in the pathogenesis and consequence of HBV and HCV infections. The adaptive immune response mediates virtually all viral hepatitis-related liver disorders. However, chronic hepatitis is defined by an insufficient T cell response that cannot eliminate HBV or HCV from the liver, resulting in low-level cell destruction cycles. As a result, cirrhosis and HCC are caused by recurrent immune-mediated liver damage over time (Tang *et al.,* 2018; Zhang *et al.,* 2021).

Immune-mediated pathways are usually blamed for liver damage in chronic HCV and HBV infections. HBV and HCV proteins interfere with the host's immune response in various ways, including disrupting pathogen-associated pattern recognition pathways, interfering with cellular immunoregulation via CD81 binding, and subverting the activity of natural killer (NK) cells, CD4+ and CD8+ T-cells. Finally, T-cells that are specific for HBV and HCV become progressively unresponsive. They disappear due to various factors, including alterations in important viral epitopes, a lack of adequate assistance, clonal anergy, or regulatory T-cell proliferation. Although it is still potential that humoral immunity contributes to bystander damage of virally coated cells via antibody-dependent cellular cytotoxicity, the role of neutralizing antibodies is unknown. Using the perforin/granzyme pathway, cytotoxic lymphocytes kill infected cells and release Fas ligand and inflammatory cytokines like IFN (interferon). The release of soluble effector molecules controls HCV infection. Still, it has the potential to kill uninfected liver cells and entice lymphocytes that aren't HBV or HCV specific to infiltrate the liver. Bystander injury to these non-specific inflammatory cells will amplify the tissue damage caused by HCV infection, triggering fibrogenesis (Cella *et al.,* 2014; Belizário *et al.,* 2018; Zhang *et al.,* 2021).

Unlike hepatitis E, there is no clear information on the effects of HAV infection during pregnancy. However, some evidence suggests a higher risk of pregnancy problems and early birth. Furthermore, even though HAV RNA is negative in blood and stool, the virus might survive in the liver for a long time (Abdul Amir, 2018). In human hepatocytes, HDV is not immediately harmful. On the other hand, HDV RNA decreased during the chronic period. Furthermore, the late-stage reactivation of HBV was described by the advance of cirrhosis and HCC due to replication of HDV/HBV or reduction with clearance of together viruses (Farci and Niro, 2018).

SARS-CoV-2 induced HBV reactivation

SARS-CoV-2 has a considerable affinity for the angiotensin-converting enzyme-2 (ACE2) receptor, located on various cell types, including hepatocytes and cholangiocytes. Overexpression of ACE2 receptors in the liver may have a role in the aberrant liver enzyme activity seen in COVID-19 patients. Furthermore, Aldhaleei *et al.* (2020) reported in their study the first case of hepatitis B virus reactivation caused by COVID-19. During a liver workup, HB surface Ag positivity, HB core Ab positivity (IgM), HB envelops (HBe) Ag negativity, and HBe Ab positivity was discovered, indicating that an HBV infection had reactivated. In addition, his hepatitis B DNA showed a viral load of 2,490 IU/mL (reference: 1000 IU/mL), confirming his diagnosis of acute HBV infection. Also positive was his COVID-19 polymerase chain reaction (PCR) results (Aldhaleei *et al.,* 2020).

SARS-CoV-2-caused Coronavirus Disease 2019 (COVID-19) has been linked to various clinical symptoms, most of which have been pulmonary. Hepatic symptoms have been seen in up to 50% of people who have been infected. Asymptomatic anomalies in liver biochemical tests to a rare case of acute liver failure are all part of the spectrum (Bangash *et al.,* 2020; Zhang *et al.,* 2020; Reddy, 2020). At this time, the etiology of hepatic symptoms is unknown.

However, it could be caused by a variety of factors, including a symptom of an ischemic liver injury, immune-mediated liver injury, systemic illness, drug-induced liver injury, or a virus's direct cytopathic effect (Cano *et al.,* 2017; Xu *et al.,* 2020; Reddy, 2020; Premkumar and Kedarisetty, 2021).
Patients are frequently infected with other viruses, such as HBV, and the influence of SARS-CoV-2 on these infections and induced liver disorders is unknown (Reddy, 2020). SARS-CoV can also infect the liver, causing mild to moderate lobular inflammatory response and apoptosis. Hepatocytes with significant mitoses, perhaps due to hyperproliferative condition and cell cycle arrest, are a key characteristic of SARS liver disease. As a result, it might be used to target SARS-CoV potential viral replication in hepatocytes and specific therapy to reduce viral replication and change the disease's clinical course (Chau *et al.,* 2004). Also, one of the clinical results accompanying this case is that infected patients with SARS-CoV-2 and HBV showed more severe thrombocytopenia and monocytopenia and more disturbed hepatic function in lipid metabolism and albumin production. Therefore, caution needs to be taken to manage infected patients with SARS-CoV-2 and HBV (Liu *et al.,* 2021).

SARS-CoV-2 and HBV-infected patients had dysregulation of immune cells in the blood, with COVID-19 patients having fewer white blood cells (WBC). Low lymphocyte numbers mainly caused low WBC counts. In addition to decreased monocyte levels and increased CD8 T cell levels in SARS-CoV-2, and HBV patients, inflammatory cytokine levels (IFN-, TNF-, IL-2, IL-4, IL-6, and IL-10) were shown to be higher in infected patients with SARS-CoV-2 and HBV or SARS-CoV-2 alone or HBV alone (Liu *et al.,* 2021). Lactate dehydrogenase (LDH) and creatine kinase (CK) were revealed to be risk factors for severe COVID-19 in a previous study (Zhang *et al.,* 2020; Zhou et al., 2020), and Liu *et al.* (2021) showed that higher levels of creatine kinase indicated a higher risk of illness development in SARS-CoV-2 and HBV patients (disease severity).

In SARS-CoV-2 and HBV-infected patients, increased lymphocyte, monocyte, eosinophil, basophil, NK, T, and B cell counts and AST decrease and ALB production were found after COVID-19 recovery. However, at the time, there was no difference in red blood cell and platelet counts in both groups (HBV infected with SARS-CoV-2 and SARS-CoV-2 alone) (Liu *et al.,* 2021). Entecavir or Lamivudine are utilized as anti-HBV treatments. Individuals with HBV and SARS-CoV-2 do not display hepatotoxicity due to combined therapy, as evidenced by the before and after ALT, AST, and ALB readings (Liu *et al.,* 2021). To determine the problem or impacts of the SARS-CoV-2 infection in HBV patients, researchers evaluated several complete blood count parameters, serum biochemistry indicators, and immune responses in people with and without HBV or SARS-CoV-2. They discovered that COVID-19 individuals have leukopenia, erythropenia, thrombocytopenia, and significant liver damage and inflammation. The presence of SARS-CoV-2 and HBV infection did not affect the result of COVID-19. SARS-CoV-2 and HBV coinfected patients, on the other hand, had more severe monocytopenia and thrombocytopenia at the initiation of COVID-19, as well as more impaired hepatic function in albumin synthesis and lipid metabolism. In addition, patients with SARS who had previously had HBV infections developed acute respiratory distress syndrome (Liu *et al.,* 2021).

Patients infected with SARS-CoV-2 or chronic HBV developed liver disease, and the proportion of patients with severe COVID-19 was higher in those with liver disease (Zou *et al.,* 2020). COVID-19 was not shown to be more severe in patients with HBV infection. In COVID-19 individuals with persistent HBV infection, reactivation of the hepatitis B virus is a major problem (Liu *et al.,* 2020). In patients with current or previous HBV exposure this is primarily connected with COVID-19 management because of immune-suppressive corticosteroid medication or biological therapies such as IL-6 receptor antagonists (Rodriguez-Tajes *et al.,* 2021). To lower viral load and hepatitis B flares, such patients require HBV DNA load monitoring and therapy with antivirals such as Tenofovir or Entecavir (Mehta *et al.,* 2020).

The recovery rate and fatality rate are recognized between infected patients with SARS-CoV-2 alone and SARS-CoV-2 with HBV coinfected patients, remaining similar between the two groups (Liu *et al.,* 2020). Although medication hepatotoxicity or immune-mediated inflammation can induce liver damage in COVID-19 patients, thus, SARS-CoV-2 infection of liver cells cannot be excluded (Chai et al., 2019). SARS patients who were infected with HBV died after being reactivated. Due to the importance of cytokine imbalance in the pathogenesis of SARS-CoV and SARS-CoV-2, non-steroidal or steroid anti-inflammatory treatments have been employed as first-line therapy. Immunosuppression is likely to help manage cytokine storms, but it may also make HBV reactivation easier. Therefore, in COVID-19 individuals with chronic hepatitis B, HBV antivirals such as Tenofovir or Entecavir should be used before immunosuppressive therapy. Furthermore, lowering the viral load may reduce the risk of hepatitis B flare-ups (Mehta *et al.,* 2020).

COVID-19 patients with HBV may be at an increased risk of morbidity and mortality. Therefore, liver enzyme abnormalities and acute hepatic injuries may be shared among COVID-19 patients with HBV (Mirzaei *et al.,* 2021). Chronic HBV infection, for example, could be reactivated, contributing to COVID-19's increased liver enzyme abnormalities. Case studies of the interaction between preexisting liver conditions and COVID-19, on the other hand, require accurate assessment. Digestive problems and elevated liver enzymes may be important in many COVID-19 patients, especially those with unusual symptoms. More research is needed to understand better the source of liver damage in COVID-19 patients who already have a history of liver disease. A significant number of patients with COVID-19 have elevated liver-related enzymes (Agarwal *et al.,* 2020; Aldhaleei *et al.,* 2020).

Our patient's liver aminotransferases, such as AST, ALT, and gamma-glutamyl transferase (GGT), were high during the subclinical period. In severe cases of COVID-19, however, there is a higher frequency of abnormal liver aminotransferase levels, elevated AST levels, and liver damage. Furthermore, patients with abnormal liver test findings, particularly men, were more likely to have a moderate to high fever. On the other hand, our patient was hypothermic at admission and had extremely high levels of liver enzymes, total bilirubin, ammonia, and international normalized ratio (Fan *et al.,* 2020; Aldhaleei *et al.,* 2020). The diagnostic indicators for cholangiocyte damage are serum ALP and GGT. While COVID-19 cases with HBV co-infection exhibited more significant

percentages of abnormal GGT than COVID-19 subjects without HBV infection, most COVID-19 subjects had normal ALP. Furthermore, during the entire 3-week period, there have been no significant differences in serum ALP and GGT levels between the two groups. As a result, these findings suggest that hepatic cholangiocyte cytotoxicity is not the major cause of liver injury. However, inactive HBV carriers with SARS-CoV-2 co-infection are at a greater risk of hepatocyte-type liver damage when combined (Cai *et al.,* 2020; Lin *et al.,* 2021).

LDH, D-dimer, and IL-6 are examples of immune-mediated liver damage mechanisms. During the three weeks following the start of symptoms, the outlier ratios of serum LDH., D-dimer, and IL-6 levels in COVID-19 patients with HBV who were inactive HBV carriers with COVID-19 were substantially more significant than those in COVID-19 patients without HBV. While there were no significant differences in serum D-dimer and IL-6 levels between the two groups over the three weeks, the mean serum LDH levels in COVID-19 patients with HBV co-infection were significantly higher than those in COVID-19 patients without HBV co-infection at 2-3 weeks after the onset of symptoms. These findings suggested that the inflammatory response after SARS-CoV-2 co-infection could cause immune-mediated liver damage (Lin *et al.,* 2021).

After co-infection with SARS-CoV-2, inactive HBV carriers displayed aberrant liver function measures, indicating a high risk of liver injury as hepatocyte type. As a result, inflammatory causes are most likely responsible for inactive HBV carriers' increased liver injury (Lin *et al.,* 2021). Inactive HBV carriers who also have SARS-CoV-2 co-infection are at a higher risk of liver damage. In addition, following SARS-CoV-2 co-infection, the inflammatory response may play a role in this damage. As a result, patients with chronic HBV infection may face these risks (Lin *et al.,* 2021). Furthermore, antibiotics and antiviral medicines such as lopinavir/ritonavir, arbidol, and interferon, which may cause liver injury, are given. In individuals with HBV, it's important to be aware of the risk of HBV reactivation associated with COVID-19 medicines such as corticosteroids and tocilizumab. HBV reactivation has been reported after treatment with tocilizumab and prednisone; therefore, preventing HBV reactivation should be considered (Reddy *et al.,* 2015; Chen *et al.,* 2017). In addition, according to guidelines, in people with newly diagnosed HBV, chronic HBV therapy can be started and continued independently of COVID-19, if required. Finally, caution should be exercised when starting COVID-19-related treatment in someone with advanced liver disease; thereby, established guidelines on such use should be followed to reduce the risk of hepatic decompensation, despite the reality that the risk/benefit of an intervention is likely to weigh heavily in dealing with the highly lethal situation of COVID-19 (Terrault *et al.,* 2018; Reddy, 2020).

In severe SARS-CoV-2 infected patients, there is a risk of HBV reactivation. HBV reactivation following SARS-CoV-2 infection is caused by a disruption in the balance between the host's immunological state and viral replication. As a result, the duration of immunosuppressive therapy is the main risk factor for HBV reactivation. Immunosuppressive medication such as IL-1 or IL-6 receptor antagonists (anakinra. tocilizumab) and high-dose corticosteroids are frequently related to HBV reactivation in individuals infected with SARS-CoV-2. HBV reactivation has been reported in SARS-CoV-2 infected patients on multiple

occasions. In retrospective research, three out of 21 SARS-CoV-2 and HBV-infected individuals suffered HBV reactivation, two receiving corticosteroid therapy. The probability of HBV reactivation in HBsAg-/anti-HBc+ patients with severe SARS-CoV-2 infection undergoing immunosuppressive medication was investigated in recent prospective research. There were no incidences of HBsAg seroconversion after a year. In patients with severe SARS-CoV-2 and cured HBV infection, two out of sixty-nine had detectable sera HBV DNA, indicating a low probability of HBV reactivation. (Carroll, 2011; Chen *et al.,* 2017; Rodriguez-Tajes *et al.,* 2021; Chang *et al.,* 2022).

SARS-CoV-2 induced HCV reactivation

A study conducted by Lensen *et al.* (2021) on an 82-year-old woman with HCV since 2007 who received the Pfizer COVID-19 vaccine observed HCV reactivation, jaundice, anaphylaxis, and hepatic coma, then death after three weeks of receiving the vaccine. This study also showed a substantial increase in the level of HCV viral load a few days after receiving the vaccine, and the inflammatory response to the vaccine may be sufficient to cause the decay of livers, which leads to the emergence of symptoms and disease severity. Therefore, according to previous studies, the most appropriate explanation for HCV reactivation is that vaccines can cause a reactivation of the virus, especially in patients who are immunosuppressed or recipients of biological therapy. For example, it was seen in a study conducted by Lehmann and Matoba (2018) on a case infected with herpes zoster stromal keratitis. The disease was reactivated due to receiving the herpes zoster subunit vaccine. In addition, SARS-CoV-2 encoded proteins have been found to trigger the reactivation of Kaposi's sarcoma-associated herpesvirus, according to Chen *et al.* (2020). As a result, proteins generated by SARS-CoV-2 could reactivate the hepatitis C virus.

Conclusion

We concluded from the current review that it is necessary to consider the special care of persons exposed to infection with SARS-CoV-2 to persons infected with viral hepatitis. In particular, advanced cases of the disease and their stages of treatment as it leads to liver dysfunction and life-threatening patient. Therefore, we recommended spreading community awareness and providing high-quality services in the health field, especially for people infected with viral hepatitis in shadow spread of COVID-19, which is the most appropriate way to reduce this disease, imposing a compulsory vaccination program for all and conducting periodic examinations for early detection of the disease and prevention to reduce the development of cases to advanced stages. In addition to encouraging researchers to advance sophisticated medical preparation to differing in processing the global problems of viral hepatitis and SARS-CoV-2 infection.

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References

Abdul Amir, Y. F. (2018). Genetic polymorphisms of some interferons associated with chronic viral hepatitis B and C. Ph.D thesis, College of Medicine, Babylon University, Iraqi.

Abdul-Husin, I. F. (2013). Epidemiological Study of Viral Hepatitis Types B and C in Babylon Province. M.Sc thesis, College of Medicine, University of Babylon.

Agarwal, A., Chen, A., Ravindran, N., To, C., & Thuluvath, P.J. (2020). Gastrointestinal and Liver Manifestations of COVID-19. *J Clin Exp Hepatol.*, 10, 263-65.

Akkaif, M.A., Daud, N.A.A., Sha'aban, A., Ng, M.L., Abdul Kader, M.A.S., Noor, D.A.M. & Ibrahim, B. (2021). The Role of Genetic Polymorphism and Other Factors on Clopidogrel Resistance (CR) in an Asian Population with Coronary Heart Disease (CHD). *Molecules*, 26, 1987.

Akkaif, M.A., Ng, M.L., Kader, M.A.S.A., Daud, N.A.A., Sha'aban, A. & Ibrahim, B. (2021). A review of the effects of ticagrelor on adenosine concentration and its clinical significance. *Pharmacological Reports*, 1-14.

Akkaif, M.A., Sha'aban, A., Daud, N.A.A., Ng, M.L. & Ibrahim, B. (2020). Investigate the Strategy of Using Pharmacogenetics and Pharmacometabonomics to the Personalization of Ticagrelor Antiplatelet Therapy. *Syst. Rev. Pharm.*, 11, 1100-07.

Akkaif, M.A., Sha'aban, A., Daud, N.A.A., Yunusa, I., Ng, M.L., SK Abdul Kader, M.A., Noor, D.A.M. & Ibrahim, B. (2021). Coronary Heart Disease (CHD) in Elderly Patients: Which Drug to Choose, Ticagrelor and Clopidogrel? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Cardiovascular Development and Disease*, 8, 123.

Aldhaleei, W.A., Alnuaimi, A., & Bhagavathula, A.S. (2020). COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates. *Cureus*, 12(6), e8645.

Al-Sadeq, D. W., Taleb, S. A., Zaied, R. E., Fahad, S. M., Smatti, M. K., Rizeq, B. R., & Nasrallah, G. K. (2019). Hepatitis B virus molecular epidemiology, host-virus interaction, coinfection, and laboratory diagnosis in the MENA region: An update. *Pathogens*, 8(2).

Bangash, M. N., Patel, J., & Parekh, D. (2020). COVID-19 and the liver: little cause for concern. *The lancet. Gastroenterology & hepatology*, *5*(6), 529.

Belizário, J. E., Neyra, J. M., & Rodrigues, M.F.S.D. (2018). When and how NK cell-induced programmed cell death benefits immunological protection against intracellular pathogen infection. *Innate Immunity*, 24(8), 452-65.

Botelho-Souza, L.F., Vasconcelos, M.P.A., dos Santos, A.d.O., Salcedo, J.M.V. & Vieira, D.S. (2017). Hepatitis delta: virological and clinical aspects. *Virology Journal*, 14:177.

Cai, Q., Huang, D., Yu, H., & *et al.* (2020). COVID-19: abnormal liver function tests. *J Hepatol.*, 73(3):566e574.

Cano, A., Cifuentes, L., & Amariles, P. (2017). Structured Literature Review of Hepatic Toxicity Caused by Medicines. *Revista colombiana de Gastroenterología*, *32*(4), 337-48.

Carroll, M.B. (2011). The impact of biologic response modifiers on hepatitis B virus infection. *Expert Opin Biol Ther.,* 11, 533–44.

Cella, M., Miler, H., & Song, C. (2014). Beyond NK cells: the expanding universe of innate lymphoid cells. *Front Immunol.*, 5, 1–11.

Chai, X., Hu, L., Zhang, Y., *et al.* (2019). Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. https://doi.org/10.1101/2020.02.03.931766

Chang, Y., Jeong, S.W., & Jang, J.Y. (2022) Hepatitis B Virus Reactivation Associated With Therapeutic Interventions. *Front. Med.* 8: 770124, 1-9.

Chau, T.N., Lee, K.C., Yao, H., Tsang, T.Y., Chow, T.C., Yeung, Y.C., Choi, K.W., Tso, Y.K., Lau, T., Lai, S.T., & Lai, C.L. (2004). SARS-Associated Viral Hepatitis Caused by a Novel Coronavirus: Report of Three Cases. *Hepatology*, (39)2, 302-10.

Chen, J., Dai, L., Barrett, L., *et al.* (2020). SARS-CoV-2 proteins and anti-COVID-19 drugs induce lytic reactivation of an oncogenic virus. *bioRxiv.*, 4(1), 1-6.

Chen, L.F., Mo, Y.Q., Jing, J., *et al.* (2017). Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis.*, 20:859-69.

Fan, Z., Chen, L., Li, J., & *et al.* (2020). Clinical features of COVID-19-related liver damage. *Clin Gastroenterol and Hepatol.*, 18, 1561-66.

Farci, P. and Niro, G.A. (2018). Current and Future Management of Chronic Hepatitis D. *Gastroenterology & Hepatology*, 14(6), 342-51.

Feinstone, S.M. (2019). History of the Discovery of Hepatitis A Virus. s Cold Spring Harb Perspect Med; 9, a031740.

Fonseca and Ferrazda, J.C. (2010). History of viral Hepatitis. *Review of Society Medicine*. 43(3), 322-30.

George, J., Liddle, C., Murray, M., Byth, K. & Farrell, G.C. (1995). Pre-translational regulation of cytochrome P450 genes is responsible for disease specific changes of individual P450 enzymes among patients with cirrhosis. *Biochem Pharmacol.*, 49, 873-81.

George, J., Murray, M., Byth, K. & Farrell, G.C. (1995). Differential alterations of cytochrome P450 proteins in livers from patients with severe chronic liver disease. *Hepatology.*, 21, 120-28.

Guengerich, F.P. & Turvy, C.G. (1991). Comparison of levels of several human microsomal cytochrome P-450 enzymes and epoxide hydrolase in normal and disease states using immunochemical analysis of surgical liver samples. J *Pharmacol Exp Ther.*, 256, 1189-94.

Jefferies, M., Rauff, B., Rashid, H., Lam, T., & Rafiq, S. (2018). Update on global epidemiology of viral hepatitis and preventive strategies. *World J Clin Cases*, 6(13), 589-99

Khuroo, M.S., (2011). Discovery of hepatitis E: The epidemic non-A, non-B hepatitis 30 years. *Virus Research.*161 (1), 3-14

Kumar, A., Singh, R., Kaur, J., Pandey, S., Sharma, V., Thakur, L., Sati, S., Mani, S., Asthana, S., Sharma, T.K., Chaudhuri, S., Bhattacharyya, S. and Kumar, N. (2021). Wuhan to World: The COVID-19 Pandemic. *Front. Cell. Infect. Microbiol.* 11, 596201.

Lehmann, A., & Matoba, A. (2018). Reactivation of herpes zoster stromal keratitis after HZ/su adjuvanted herpes zoster subunit vaccine. *Ophthalmology*, 125(11), 1682.

Lensen, R., Netea, M.G., and Rosendaa, F.R. (2021). Hepatitis C Virus Reactivation Following COVID19 Vaccination – A Case Report. *International Medical Case Reports Journal,* 14, 573-76.

Lin, Y., Yuan, J., Long, Q., Hu, J., Deng, H., Zhao, Z., Chen, J., Lu, M., & Huang, A. (2021). Patients with SARS-CoV-2 and HBV coinfection are at risk of greater liver injury. *Genes & Diseases,* 8(4), 484-92.

Liu, J., Wang, T., Cai, Q., Sun, L., Huang, D., Zhou ,G., He, Q., Wang, F.S., Liu, L., & Chen, J. (2020). Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res.*, 50, 1211-21.

Liu, R., Zhao, L., Cheng, X., Han, H., Li, C., Li, D., Liu, A., Gao, G., Zhou, F., Liu, F., Jiang, Y., Zhu, C., & Xia, Y. (2021). Clinical characteristics of COVID-19 patients with hepatitis B virus infection - a retrospective study. *Liver Int.*, 41, 720-30.

Liu, S., Zhou, B., Valdes, J. D., Sun, J., & Guo, H. (2019). Serum hepatitis B virus
RNA: a new potential biomarker for chronic hepatitis B virus infection. *Hepatology*, 69(4), 1816-27.

Lown, K., Kolars, J., Turgeon, K., Merion, R., Wrighton, S.A. & Watkins, P.B. (1992). The erythromycin breath test selectively measures P450IIIA in patients with severe liver disease. *Clin Pharmacol Ther.*, 51, 229-38.

McArdle A.J., Turkova A., & Cunnington A.J. (2018). When do coinfections matter? *Curr. Opin. Infect. Dis.* 2018; 31(3): 209–15.

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J.J. (2020). COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression. *Lancet,* 395, 1033–34.

Mirzaei, H., Vahidi, M., Shokoohi, M., Darvishian, M., Sharifi, H., Sharafi, H., & Karamouzian, M. (2021). COVID-19 among patients with hepatitis B or hepatitis C: A systematic review. *Hepat. Mon.*, 20(11): e111617.

Morgan, D.J. & McLean, A.J. (1995). Clinical pharmacokinetic and pharmacodynamic considerations in patients with liver disease: an update. *Clin Pharmacokinet.*, 29: 370-91.

Pascarella, S. & Negro, F. (2011). Hepatitis D virus: an update. *Liver International.* 31(1), 7–21.

Premkumar, M. & Kedarisetty, C.K. (2021). Cytokine storm of COVID-19 and its impact on patients with and without chronic liver disease. *J Clin Transl Hepatol.,* 9(2), 256–64.

Reddy, K.R. (2020). SARS-CoV-2 and the Liver: Considerations in Hepatitis B and Hepatitis C Infections. *Clinical Liver Disease,* 15(5): 191-194.

Reddy, K.R., Beavers, K.L., Hammond, S.P., *et al.* (2015). American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*, 148, 215-19.

Rodriguez-Tajes, S., Miralpeix, A., Costa, J., Lopez-Sune, E, Laguno, M., Pocurull, A., & *et al.* (2021). Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. *J Viral Hepat.,* 28: 89–94.

Shackel, N.A., Patel, K., & McHutchison, J. (2013). Chapter 99 - Viral Hepatitis, Editor(s): Geoffrey S. Ginsburg, Huntington F. Willard, Genomic and Personalized Medicine (Second Edition), Academic Press. P, 1173-90.

Tang, L.S.Y., Covert, E., Wilson, E. & Kottilil, S. (2018). Chronic hepatitis B infection: a review. *JAMA.*, 319:1802–13.

Terrault, N.A., Lok, A.S., McMahon, B.J., *et al.* (2018). Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*, 67, 1560-99.

Webb, G.W. & Dalton, H.R. (2019). Hepatitis E: an underestimated emerging threat. *Therapeutic Advances in Infectious Disease*. 6, 1–18.

Xu, Z., Shi, L., Wang, Y., & *et al.* (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.*, 8, 420-22.

Zarrin A, & Akhondi H (2022). Viral Hepatitis. In: StatPearls [Internet]. Treasure Island (FL).

Zhang, B., Huang, W., & Zhang, S. (2020). Clinical Features and Outcomes of Coronavirus Disease 2019 (COVID-19) Patients With Chronic Hepatitis B Virus Infection. *Clin Gastroenterol Hepatol.*, 18, 2633-37.

Zhang, C., Shi, L., & Wang, F.S. (2020). Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*; 5, 428-30.

Zhang, J., Wang, X., Jia, X., *et al.* (2020). Risk factors for disease severity, improvement, and mortality of COVID-19 patients in Wuhan, China. *Clin Microbiol Infect*; 26(6), 767-72.

Zhang, X., Guan, L., Tian, H., Zeng, Z., Chen, J., Huang, D., Sun, J., Guo, J., Cui, H., & Li, Y. (2021). Risk Factors and Prevention of Viral Hepatitis Related Hepatocellular Carcinoma. *Front. Oncol.* 11, 686962.

Zhou, F., Yu, T., Du, R., *et al.* (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395, 1054-62.

Zou, X., Fang, M., Li, S., *et al.* (2020). Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. *Clin Gastroenterol Hepatol.*, S1542-3565, 30821.