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Review Article

COVID-19 impact on pre-existing liver pathologies

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ABSTRACT

Liver damage in patients with COVID-19 may be due to multiple factors ranging from direct viral entry into hepatocytes, pneumonia-induced hypoxia, immune-mediated hepatitis, and drug-induced hepatotoxicity. The impact of COVID-19 on the liver is discussed in a wide range of studies. Even though the respiratory system has been identified as the target organ to be involved with this infection, recent reports showed that about 2-11% of patients with COVID-19 had underlying chronic liver disease. This further emphasizes that there is a need for more research on the subject. This article explores how SARS-COV-2 infection has affected the course of hepatocellular carcinoma, autoimmune hepatitis, and hepatitis B and C infection in terms of risk of acquisition of the disease, diagnosis, treatment, and treatment and prevention modalities of these diseases.

Keywords

SARS-CoV-2, COVID-19, hepatitis, hepatotoxicity, hepatocellular carcinoma, autoimmune hepatitis,

Abbreviations

Coronavirus disease-2019 (COVID-19); personal protective equipment (PPE); MERS-CoV (Middle East respiratory syndrome); Angiotensin-Converting Enzyme 2 (ACE-2); Transmembrane Serine Protease 2 (TMPSSR2); DILI (Drug-induced liver injury); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Autoimmune hepatitis (AH); hepatitis B surface antigen (HBsAg); hepatocellular carcinoma (HCC); Primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC); Autoimmune liver disease (AILD); chronic liver diseases (CLD); Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES); AASLD (American Association for the Study of Liver Diseases).

SUMMARY

1. Introduction

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), a virus that originated in Wuhan, China, in December 2019. It has led to widespread infection and the declaration of a global pandemic in March 2020. SARS- CoV-2 is a single stranded RNA virus and as of September 13, 2021, 224,372,380 confirmed COVID-19 cases are recorded with 4,625,006 deaths worldwide; the "test, track, and trace" strategy are the only way to decrease the spread[1]. The United States has recorded more coronavirus infections and deaths than any other country. A broad spectrum of symptoms associated with COVID-19 has been identified, from patients being asymptomatic to experiencing fever, dry cough, sore throat, loss of taste or smell, or developing acute respiratory syndrome[1].

Overall, case fatality rates range between 2-6%; however, the rates are higher in the elderly and those with underlying comorbidities such as diabetes, hypertension, and heart disease. Even though the respiratory system has been identified as the target organ to be involved with this infection, recent reports showed that about 2-11% of patients with COVID-19 had underlying chronic liver disease. This further emphasizes the need for more research on the subject.

Globally, the healthcare system experienced unprecedented challenges, including but not limited to inadequate capacity to handle the acute increase in patient volume with supply shortages of personal protective equipment (PPE). As a result, providers postponed elective care early in the pandemic to reallocate resources for COVID-19 patients[3]. These modifications delayed and interrupted the regular screening programs and treatment regimens of new and previously established patients with chronic diseases, including hepatocellular dysfunction[4].

Most of the research during the early stages of the COVID-19 outbreak focused solely on respiratory pathologies; however, the effect on other organ systems and pathologies is also essential. In patients who tested positive for SARS-CoV-2 and MERS-CoV (Middle East Respiratory Syndrome), hepatic abnormalities were found in more than 60% of cases[5,6]. SARS-COV-2 having a similar genomic sequence has been shown to follow a similar trend. According to the CDC, patients with chronic liver disease or immunocompromised (e.g., liver transplant recipients) might have a higher risk for severe illness from COVID-19. Because of the increasing number of liver pathologies worldwide, a definitive care plan should be evaluated to assess its severity on SARS-CoV-2. According to one study, up to 50% of hospitalized COVID-19 patients could have hepatic manifestations that range from asymptomatic abnormalities in liver enzymes to acute liver failure[7].

Liver damage in patients with COVID-19 may be due to multiple factors ranging from direct viral entry into hepatocytes, pneumonia-induced hypoxia, immune-mediated hepatitis, and drug-induced hepatotoxicity[8]. The impact of COVID-19 on the liver is discussed in a wide range of studies. A retrospective cohort study showed that 15–54% of patients diagnosed with COVID-19 have a hepatic injury, typically manifested by elevated levels of transaminases with a mild degree of hyperbilirubinemia. The systemic inflammatory responses might result in changes in liver biochemistry[9].

Different mechanisms have been proposed to develop liver abnormalities following COVID-19 infection, including direct cytotoxic effects, immune-mediated injury, ischemic hepatitis, and drug-induced lung injury[10]. SARS virus enters the cells using a receptor known as Angiotensin-Converting Enzyme 2 (ACE-2) receptor. This receptor is widely expressed in alveolar epithelial cells, arterial and venous endothelial cells, and smooth muscle cells[11]. Furthermore, this receptor is present in the nasal epithelium but has been widely expressed in the biliary cholangiocytes compared to the hepatocytes in the liver[12]. Further exploration by RNA sequencing has also shown that the Transmembrane Serine Protease 2 (TMPSSR2), used for priming the virion, was found in TROP2+ progenitor cells in the liver[13]. The infection of the cholangiocytes, followed by the inability of the liver to regenerate once the infection wanes, has been proposed as a mechanism of liver injury in the COVID 19 infection[14].

The infection with SARS-COV-2 has been linked with elevated cytokines seen in cytokine syndromes such as IL 1B, IFNγ, and IL-6[10]. Cytokine-mediated tissue injury may be a mechanism of liver injury seen in COVID-19 infection. Furthermore, tocilizumab, an IL-6 inhibitor used to curb the cytokine storm, has been linked with severe hepatotoxicity[15].

It is essential to consider that various potentially hepatotoxic drugs have been used in the clinical trials, including dexamethasone, Lopinavir/ritonavir, remdesivir, and even Chinese herbal medications during the early days of the pandemic. Furthermore, severely ill patients are subject to polypharmacy, and hepatotoxicity may result from the drugs' additive side effects. A recent meta-analysis showed that the pooled incidence of DILI (Drug-induced liver injury) in the patients treated for COVID-19 was 25.4%[16]. The incidence of liver injury associated with remdesivir was found to be 15.2%, while that of lopinavir/ritonavir was found to be much higher at 37.2%[17]. This can be one of the important mechanisms responsible for the injury to the hepatocytes. In addition, hypoxia from respiratory infection leading to ischemic hepatitis may be the cause of injury to the hepatocytes. These mechanisms collectively explain the liver abnormalities seen in the disease.

Hepatocellular carcinoma is the sixth most common cancer with an incidence of 6 %[18]. Patients with malignancies under treatment are susceptible to infections due to immunosuppression. Furthermore, patients with malignancies have been found to have treatment delays and suffer worse outcomes of the COVID-19 infection[19].

The causes of developing HCC coincide with initial manifestations of cirrhosis. The lifetime risk among chronic Hepatitis B virus (HBV) carriers is 10-25%, with cofactors affecting the incidence rate including coinfection with Hepatitis C virus (HCV), HBV genotype, and other environmental exposure factors such as alcohol use, aflatoxin, obesity[20]. Therefore, the implementation of effective HBV vaccination programs can play a crucial role in reducing the incidence of HCC. The ongoing COVID-19 infection has resulted in a halt or slow-down in the continuing effort to eliminate viral hepatitis with projections of an increase in 44,800 liver malignancies and 72,300 deaths from HCV till the year 2030[21].

Autoimmune hepatitis (AH), an idiopathic chronic liver inflammation, is more common in females than males with Type I AH 4:1 and Type II 10:1[22]. The worldwide incidence is 1-2 per 100,000 population per year, with 80% of the cases diagnosed as Type I AH[23]. Steroids are the mainstay of treatment of autoimmune hepatitis in combination with other drugs like azathioprine [24].

The management of COVID-19 infection requires a balancing act of use of various kinds of drugs. The use of steroids and antivirals, particularly in patients with autoimmune liver disease, can be confusing. Patients with cirrhosis are found to have immune dysregulation with either immunodeficiency or systemic inflammation[19] and hence are found to have greater severity of covid-19 infection as well[25].

The overall global prevalence of chronic HBV infection, described as the prevalence of hepatitis B surface antigen (HBsAg), is 3.5%[26]. The primary cause of mortality in chronic HBV carriers is HCC (43%), followed by complications from cirrhosis (40%). The global prevalence of chronic HCV infection, described as HCV-RNA-positive, is 1%, highest in the Eastern Mediterranean region[27]. In the United States, the reported rates have increased among young adults over the past decade, most likely due to the opioid epidemic and heavy injection drug use.

It has been found that coinfection with SARS-COV-2 in patients with co-morbid HBV develops a more severe disease and has increased mortality rates[28]. Furthermore, delayed clearance of SARS-COV-2 has also been observed in patients with comorbid HBV infection[29]. In addition, medications like tocilizumab and steroids used in case of COVID-19 infection have increased concerns regarding reactivation of HBV infection.

This article aims to explore how SARS-COV-2 infection has affected the course of hepatocellular carcinoma, autoimmune hepatitis, and hepatitis B and C infection in terms of risk of acquisition of the disease, diagnosis, treatment, and prevention modalities of these diseases.

2. Liver Malignancy

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. The significant risk factors for HCC are chronic HBV and HCV and alcohol-induced cirrhosis, among others, with Hepatitis B(HBV) being the most common cause. Patients with HBV have a 5-to-15-fold higher risk of developing liver cancer. Men are two to four times more likely to be affected by HCC than women[30]. Liver cancer itself and anticancer treatment place patients at higher risk of acquiring infection, including COVID-19, caused by SARS-CoV-2, a novel virus capable of affecting and damaging multiple organs.

In most currently available studies on cancer patients with COVID-19 infection, hepatocellular carcinoma is relatively underrepresented. A retrospective cohort study was done by Zhang et al. in which cancer patients with confirmed COVID-19 from 3 hospitals in Wuhan, China, were included. The data were collected from medical records from January 13, 2020, to February 26, 2020. There were 28 COVID-19 infected cancer patients with a median age of 65. The patients presented with the following clinical results after the COVID-19 infection: 23 had a fever, 22 with dry cough, 14 had dyspnea, 23 had lymphopenia, and 21 had anemia. The mortality rate was 28.6%. If the patient had an antitumor treatment in the last 14 days, the patient was at significantly increased risk for adverse outcomes. The study results depicted that COVID-19 has harmful effects on cancer patients.

Furthermore, this retrospective study portrayed that cancer patients receiving antitumor treatments should be readily screened for COVID-19 infection. In addition, the dosages of antitumor treatments for COVID-19 cancer patients should be decreased to mitigate the immunosuppressant effects of the treatment. It also brought emphasis to the relationship between patients receiving antitumor treatments and COVID-19. The weakening of the immune system due to antitumor treatments places cancer patients in a susceptible situation, allowing for SARS- CoV-2 infection. Furthermore, it brings to light the vitality of modifying antitumor therapies in cancer patients to reduce the risk of COVID-19 infection. It is recommended that cancer patients treated with antitumor agents should have effective screening for COVID-19 infection and should avoid medications causing immunosuppression[31].

A multicenter, retrospective, cross-sectional study was held in 6 referral centers of Paris, France, by Amaddeo G et al. In this study, a comparison was conducted amongst two groups. Exposed groups (The first 6 weeks of the COVID-19 outbreak from March 6, 2020 to April 17, 2020) and the unexposed group (from 6th March 2019 to 17 April 2019) to determine the outcome of the COVID-19 on the treatment of patients with HCC. Patients more than age 18 diagnosed with HCC were included. After screening, the results were, n = 670 patients were included (n = 293 exposed to COVID-19, n = 377 unexposed to COVID-19). 21.5% vs. 9.5% of patients had a treatment delay longer than 1 month in 2020 relative to 2019 ($p < 0.001$). In 2020, 7.1% (21/293) of patients had a confirmation of COVID-19 infection: 11 (52.4%) patients hospitalized, and 4 (19.1%) patients died. It was concluded that in the pandemic, limited patients with (HCC) presented to the multidisciplinary tumor board, especially with the first diagnosis of HCC. Patients with HCC had a prolonged treatment that was extended in the COVID-19 era than in 2019. This was a snapshot study (6 weeks), suggesting that physicians should be aware that pandemic impacts the management of patients with HCC in terms of delaying the treatment[32].

COVID-19 pandemic has driven resources away from cancer management, and hospitals have reduced cancer care services to deal with the abundance of COVID-19 cases. Furthermore, anticancer treatment places patients with HCC at increased risk of acquiring SARS due to immunosuppression. SARS infection can lead to poor outcomes; therefore, physicians must be careful and take specific measures to aid these patients. According to ICLA (International Liver Cancer) Guidelines, patients with HCC should be treated in COVID-19 free institute to reduce their risk of acquiring infection and lower subsequent mortality[33]. The guideline also recommends that Early-stage HCC be given trans-arterial therapies to substitute for curative resection or ablation. Those with late-stage HCC can continue receiving tyrosine kinase inhibitors[33]. In Addition, the American Association for the Liver Disease (AASLD) suggests HCC surveillance should be delayed by 2-3 months to avoid exposure to medical staff and hospitals. However, physicians should make this decision based on the discussion with patients about the risk[33,34]. Our knowledge of COVID-19 is limited, and as we continue to understand its effect in patients with HCC, in this literature review, we have provided a general approach to managing HCC in the presence of COVID-19.

3. Autoimmune Hepatitis

According to the National Institutes of Health, autoimmune diseases are a leading cause of chronic illness in the U.S. Over 23 million Americans have autoimmune diseases. Primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC) are chronic liver diseases that likely have an autoimmune basis to their pathogenesis. Patients with cirrhosis or portal

hypertension resulting from their Autoimmune liver disease (AILD) are at a higher risk of severe COVID-19 illness and developing more complications from their existing liver disease with prolonged hospitalization and increased mortality.

In a research article entitled "SARS-CoV-2 infection in patients with Autoimmune Hepatitis," published on January 25, 2021, patients with AIH had higher rates of hospitalization than patients without liver disease but no increased risk of Intensive care Unit (ICU) admission or death[35]. This study combines data from 3 large registries to describe the course of COVID-19 in this patient group. Between March 25 and October 24, 2020, data were collected from 932 patients with CLD and SARS-CoV-2 infection, including 70 patients with AIH. Fifty-eight (83%) patients with AIH were taking at least one immunosuppressive drug. In this patient group, age and baseline liver disease severity remained the most important determinant of an outcome in contrast to the use of immunosuppression, for which no negative impact was detected[35]. This should reassure patients and clinicians and lend weight to recommendations that immunosuppressive medication should not routinely be modified or discontinued during COVID-19.

Another case series published by Gerussi A et al. reported 10 patients with a history of AIH and positive COVID-19 infection and immunosuppressive therapy[36]. This series consisted of 70% of female patients aged between 27-73. The study showed that liver enzymes were within normal limits in all cases except two, which showed improvement. Those two cases were treated with high-dose steroids. It was further emphasizing the point of not stopping immunosuppression therapy in AIH who are already on it.

Interestingly, one patient in the study stopped taking the steroids by themselves and had a relapse of AIH, which was eventually treated with steroids. This suggests that there may be potential harm in holding the immunosuppression in such patients. Being a case series with small sample size, short follow-up periods, and other limitations, a more extensive study is required to better understand the outcomes in AIH patients and the effects of immunosuppression[36].

A retrospective study was performed from March 11 to November 12, 2020, on AIH patients with COVID-19 from 34 centers in Europe and the US[37]. This study analyzed factors associated with severe COVID-19 outcomes in patients with AIH. The outcome factors were defined as the need for mechanical ventilation, intensive care admission, and death. Thirty-two (29.1%) patients with AIH had features of cirrhosis.102 (92.7%) were on various immunosuppressive therapy before COVID-19 infection, 87.3% were symptomatic during COVID-19 infection, and for 30 % of patients, the dose or type of immunosuppression was modified. The outcome of patients with AIH has then been compared to a propensity-score matched cohort of non-AIH patients with chronic liver diseases (CLD) and COVID-19. The frequency and clinical significance of new-onset liver injury (alanine aminotransferase >2xupper limit of normal) during COVID-19 was also evaluated. They included 110 AIH patients (80% female) with a median age of 49 (range:18–85) years at COVID-19 diagnosis. New-onset liver injury was observed in 37.1% (33/89) of the patients. Use of antivirals was associated with liver injury (p=0.041while continued immunosuppression during COVID-19 was associated with a lower rate of liver injury (p=0.009. Cirrhosis was an independent predictor of severe COVID-19 in patients with AIH (p<0.001). This study reveals that patients with AIH were not at risk for worse outcomes with COVID-19 than other causes of CLD. Cirrhosis was the strongest predictor for severe COVID-19 in AIH patients[30]. Maintenance of immunosuppression during COVID-19 was not associated with increased risk for severe COVID-19 but did lower the risk for new-onset liver injury. However, the significant limitations of this study were that it was a retrospective study, the possibility of selection bias, different management, and therapeutic strategies used[37].

The management plan in a known case of AIH with SARS-CoV-2 infection is to strike a balance between the infection-induced organ damage following inflammation and autoimmune flare-induced hepatitis[38]. As per the treatment protocol, in an asymptomatic patient with mild COVID-19 infection, it is advisable to continue their baseline treatment. For moderate to severe infection, assess the risk of relapse and add immunosuppressants such as Azathioprine at a lower dose (25-50%). Suppose patients are being treated in a hospitalized setting; in that case, it is vital to monitor their Liver enzymes daily compared to weekly or biweekly in patients treated in an outpatient setting. In case if patients develop SARS-CoV-2 associated neutropenia and

lymphopenia, bacterial/fungal, or superadded infection, then reduce the dose of Azathioprine or Mycophenolate, whichever immunosuppressant the patient is on, and monitor labs weekly. Dexamethasone should be used in patients requiring hospitalization and respiratory support[38].

As for prevention, In AIH patients of low risk, provide general information about their condition, delay hospital-based follow-up if not emergency; use web-based consultation; and arrange for local pharmacy drug dispensation. In patients with cirrhosis, provide separate access to emergency, limit invasive procedures, avoid screening, start standard therapy for treatment, provide adequate care in case of hepatic failure, and decrease immunosuppressant dose in infection. Avoid unnecessary hospital visits in non-cirrhotic patients with acute onset of symptoms and chronic management of decompensated cirrhotic patients. In non-cirrhotic, clinically stable patients, defer invasive diagnostic procedures; start web-based empiric therapy and follow up[39]. Vaccination of cirrhotic patients against Streptococcus pneumonia, seasonal flu, and COVID-19 is recommended.

In summary, the above studies suggest that there is no data showing evidence of modifying immunosuppressants in previously diagnosed AIH patients affected by COVID-19. Further, it also supports no changes in severity, hospitalization, ICU admissions, and mortality in patients with and without AIH. Particularly, cirrhosis is associated with increased severity of COVID infections in such patients.

4. Hepatitis B and C

Hepatitis B virus (HBV) infection is another widely spread virus that is a global public health problem. According to the World Health Organization survey, there were 257 million HBV carriers worldwide in 2015, with 887,000 people dying due to HBV-related liver dysfunction[40]. Globally, there were approximately 100 million people with serologic evidence of HCV exposure and 71 million people with chronic HCV infection (prevalence of 1%)[41]. COVID-19 patients with HBV and HCV face a significant risk of morbidity and mortality; even the ICU admissions increased by 14.1% and 21.4%, respectively, in patients with hepatitis B and C[42].

A research article entitled "Effect of SARS-CoV-2 coinfection was not apparent on the dynamics of chronic hepatitis B infection" published on January 15, 2021, no significant variations in any laboratory or clinical markers for hepatitis B between the cohorts were observed[43]. Data were collected from 67 patients with COVID-19. Among 67 enrolled, 7 patients were also suffering from HBV infection. Clinical and laboratory data were collected on days 1, 4, 7, 14, 18, 21, 28. Firstly, no apparent changes in the serum levels of HBsAg/Ab, HBeAg/Ab, or HBV-DNA viral load were observed during acute SARS-CoV-2 infection. Secondly, there was no difference in serum levels of ALT and Total bilirubin in hepatitis B patients before and after hospitalization either. Finally, the results showed that the administration of antiviral drugs like lopinavir/ritonavir, arbidol, and interferon-α 1b, which were prescribed by clinicians attempting to inhibit SARS-CoV-2 in the initial stage, seemed to have no affection on the HBV replication[43].

On the other hand, the pre-existing HBV in the host body also appeared not to affect COVID-19 progression, anti-NP antibody formation, the intensity of anti-NP response, and even the liver injury after acute SARS-CoV-2 infection[43]. More extensive studies are required to determine the exact interactions between SARS-CoV-2 and HBV coinfection because of the limited sample size. More attention should be paid to viral control, immune modulation, and appropriate medication in patients' therapy coinfected with HBV and SARS-CoV-2.

A retrospective study entitled "Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection" was done to see the effect of hepatitis C virus infection upon the severity of SARS-CoV-2 infection. The primary outcome was to measure the all-cause mortality and hospitalization (defined as any admission to an acute care facility that happened within 14 days after a positive SARS-CoV-2 test). Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) was used for the study. Data from 975 patients were collected with HCV and SARS-CoV-19 patients and compared with 975 patients without HCV (control). The study found that a higher proportion of patients with HCV required hospitalization. However, there was no difference in the proportion of patients requiring admission or transfer to the ICU. However, during subgroup analysis, hospitalization was significantly higher in patients with fibrosis (measured with FIB-4 score). This was the only study we found that studied the direct impact of

HCV on SARS-CoV-19 patients. From this study, we now know that close observation is needed to screen for fibrosis in HCV patients, which, if present, can alter the mortality and ICU admission rates[44].

Another case series study was published in December 2020 in the U.S to interpret the risk associated with Chronic Liver Diseases (CLD) in patients with SARS-COV-2. The study included electronic medical records of 62.2 million patients (age>18years), of which 16,530 were positive for COVID-19, and 820 patients were found to have both SARS-CoV-2 infection and CLD. Outcomes of 6 major CLD's were assessed and compared to the patients without CLD's. Results showed an adjusted odds ratio [AOR]- 8.93 in chronic hepatitis C and [AOR]=4.37 for chronic hepatitis B infection. However, the critical thing that the study found was that African Americans with CLD's were twice more likely at risk of developing SARS-CoV-2 compared to Caucasians. However, we could not find more information explaining the course of CLD, especially HBV/HCV, in these populations[45].

Another case report from China published in January 2020 showed a delayed antibody response for SARS-CoV-2 in a coinfected patient with HIV and Hepatitis C. This report showed that SARS-CoV-2 RNA was persistently negative on many specimen samplings at different times. However, the plasma anti-SARS-CoV-2 antibody was positive. This showed that HBV/HCV infections might have an immunological response to SARS-CoV-2; however, the mechanisms remain unclear[46].

Beyond all the morbidity and mortality associated with direct infection with HCV and HBV, COVID-19 has slowed down various hepatitis elimination programs in different countries. This pictures that further delays in elimination programming are anticipated to heighten already strained national and regional plans for hepatitis elimination[47].

Coronavirus is a single-stranded RNA (ss RNA) virus with overlapping features with other ssRNA viruses such as HCV[48]. Some studies have predicted the efficacy of sofosbuvir, a nucleotide analog that inhibits the HCV polymerase[49]. An RCT with sofosbuvir and daclatasvir published in August 2020 showed the decreased time to discharge, and fewer hospital stays in patients with moderate to severe COVID-19 infection[50]. AASLD (American Association for the Study of Liver Diseases) has recommended not stopping antivirals in HBV but delaying treatment for HCV. We should also keep in mind the use of corticosteroids in COVID-19 patients, leading to reactivation of Hepatitis B infection. Information regarding antivirals in managing HCV and HBV patients with SARS-CoV-2 has been minimal, and more studies explaining its effect are needed.

5. Conclusion

Even though the respiratory system has been identified as the target organ involved with this infection, recent reports have shown that 2-11% of patients with COVID-19 already had underlying chronic liver disease. In this article, we have explored a few key points on how SARS-COV-2 infection has affected the course of hepatocellular carcinoma, autoimmune hepatitis, and hepatitis B and C infection, in terms of risk of acquisition of the disease, diagnosis, treatment, and prevention modalities.

- Weakened immune system due to antitumor treatments places cancer patients in a susceptible situation to acquire SARS-CoV-2 infection. Furthermore, it brings to light the vitality of modifying antitumor therapies in cancer patients to reduce the risk of COVID-19 infection.
- It is recommended that cancer patients treated with antitumor agents should have effective screening for COVID-19 infection and avoid immunosuppressant medications, however, there is no data presenting evidence of modifying immunosuppressants in previously diagnosed AIH patients affected by COVID-19.
- Furthermore, it also supports no changes in severity, hospitalization, ICU admissions, and mortality in patients with and without AIH.
- Beyond all the morbidity and mortality associated with direct infection with HCV and HBV, COVID-19 has slowed down various hepatitis elimination programs in different countries. This pictures that further delays in elimination programming are anticipated to heighten already strained national and regional plans for hepatitis elimination. AASLD has recommended not stopping antivirals in HBV but delaying treatment for HCV (Table 1). We should also keep in mind the use of corticosteroids in COVID-19 patients, as it can lead to reactivation of Hepatitis B infection. Information regarding antivirals in managing HCV and HBV

Table 1. Guidelines and Recommendations

Recommending Body	Disease	Recommendation	Reason
ICLA (International Liver Cancer)	Hepatocellular carcinoma (HCC)	Patients with HCC should be treated in COVID-19 free institute	Reduction of risk of acquiring infection and to lower subsequent mortality
		Early-stage HCC should be treated with trans-arterial therapies as a substitute to curative-resection or ablation	
		Late-stage HCC can continue receiving tyrosine kinase inhibitors	
American Association for the Study of Liver Disease (AASLD)	HCC	HCC surveillance should be delayed by 2-3 months	To avoid the exposure to medical staff and hospitals
American Association for study of Liver disease (AASLD)	Hepatitis B and C	Do not stop antivirals in HBV but delay the initiation of treatment of HCV	

HBV – hepatitis B virus; HCV – hepatitis C virus.

patients with SARS-CoV-2 has been minimal, and more studies explaining its effect are needed.

Conflict of Interest

The authors declare no conflict of interest.

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