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DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Care of the Hepatology Patient in the COVID-19 Era

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Abstract

Background and Purpose of Review The COVID-19 pandemic has resulted in over 800,000 deaths worldwide and resulted in fundamental changes in practice in nearly every aspect of medicine. The majority of symptomatic patients experience liver-associated enzyme (LAE) elevations which appear to be correlated to disease severity. Furthermore, there are unique considerations of COVID-19 on chronic liver disease. Background, including epidemiology, pathophysiologic mechanisms and therapeutics, as well as the impact of COVID-19 on specific chronic liver disease, is discussed.

Findings Studies suggest that degree of LAE elevation correlates with illness severity, although it is unclear whether this represents true liver injury. Numerous proposed treatments for COVID-19 have been linked with drug induced liver injury and may have clinically significant drug-drug interactions. Others may have unintended consequences on chronic liver disease treatment including reactivation of hepatitis B. The risk of severe COVID-19 in patients with chronic liver disease is largely unknown; metabolic dysfunction-associated fatty liver disease may be linked to higher risk for severe illness. Implications for cirrhosis of other etiologies, autoimmune hepatitis, and viral hepatitis are less well defined. The treatment of chronic liver disease has been severely impacted by the pandemic. The societal factors created by the pandemic have led to decreased in person visits, evolving access to invasive screening modalities, food and financial insecurity, and likely increased alcohol use.

Conclusions The impacts of COVID-19 on the liver range from a potential increased risk of severe infection in chronic liver disease patients, to hepatotoxic effects of proposed treatments, to second and third order impacts on the care of patients with chronic liver disease.

Keywords Severe acute respiratory syndrome coronavirus 2/SARS-CoV-2 · COVID-19 · Chronic liver disease · Cirrhosis · Chemical and drug-induced liver injury

Introduction and Epidemiology

As of 31 August 2020, nearly 25 million cases of COVID-19—caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—have been reported globally, including more than 800,000 deaths. Cases have been reported in more than 180 countries, including all 50 states in the USA.

Among World Health Organization (WHO) regions, the Americas have seen over 13 million cases with more than 450,000 deaths accounting for 55% of the world's total. South-East Asia has seen an overall rise in deaths to more than 75,000 with more than 4 million cumulative cases while Europe has experienced more than 200,000 deaths and over 4 million cases. The Western Pacific, which includes China, has had approximately 10,500 deaths with nearly 500,000 cases. The African region has reported over 1 million cumulative cases with over 21,000 deaths [1–3].

This article is part of the Topical Collection on *Drug-Induced Liver Injury*

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While all ages and health conditions are at risk of contracting the virus, risk factors for severe disease and mortality have been identified. These include advanced age, comorbid chronic health conditions such as diabetes, cancer, obesity, cardiopulmonary disease and chronic renal diseases, and living conditions (i.e., residents of long term care facilities [4]). In the majority of patients, the disease course is mild or even asymptomatic; however in one series of over 1.3 million USA cases, 16% of patients were hospitalized (2% to intensive care) and 5% of infections were fatal [5].

Data regarding risk of severe COVID-19 infection in patients with chronic liver disease are mixed and confounded by the heterogeneity of diseases and comorbidities. In one study of patients with a variety of chronic liver diseases, patients had higher mortality rates than those without liver disease (without cirrhosis: *RR* 2.8, 95% *CI* 1.9–4.0, p-value < 0.001, with cirrhosis: *RR* 4.6, 95% *CI* 2.6–8.3, p-value < 0.001). Notably, these patients were also more likely to have chronic lower respiratory tract and chronic kidney diseases ($p = 0.01$ in both cases) [6].

Pathophysiology

The primary proposed mechanism of SARS-CoV-2 infectivity is the spike protein, one of four structural proteins. Cell entry is facilitated through the angiotensin-converting enzyme 2 (ACE2) receptor along with other host cell receptors and endosomes, similar to other corona viruses [7, 8]. The virus likely gains access to the luminal GI tract through these receptors (expressed in all human epithelial cells) leading to prominent GI symptoms [9–11]. Furthermore, expression of the ACE2 receptor is also abundant in cholangiocytes and to a lesser extent in hepatocytes, providing a theoretical mechanism for biliary and hepatic involvement [12, 13]. The most common hepatic manifestation of SARS-CoV-2 infection is elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with cholestatic liver injury (alkaline phosphatase, bilirubin) occurring less commonly. The degree of elevations generally correlates to disease severity and clinical outcomes [14–19].

Proposed mechanisms of transaminase elevations include direct viral cytopathic effect, microthrombotic ischemic liver injury, cytokine mediated, and cardiomyopathy associated hepatic congestion. Liver enzyme elevations are likely multifactorial and likely represent true hepatic injury [17].

Direct viral cytopathic effects have been demonstrated in post-mortem biopsies noting massive hepatic apoptosis and binuclear hepatocytes on histology as well as viral particles in hepatocyte cytoplasm, mitochondrial swelling, and endoplasmic reticulum dilatation on transmission electron microscopy [16]. In a systematic review, Polak et al. reported pathologic findings including patchy necrosis, Kupffer cell hyperplasia, and mild zone 3 sinusoidal dilatation [20]. The latter of these is likely the result of COVID-19-related cardiomyopathy [21]. Proinflammatory cytokines, such as interleukin-6 (IL-6), have also been implicated in liver damage [22]. Finally, several of the therapeutics used to treat COVID-19 are associated with drug-induced liver injury (DILI) and may contribute to hepatic manifestations in COVID-19 infected patients [23, 24].

Clinical Presentation and Natural History

On initial presentation, 37.2–69% of COVID-19 positive patients without diagnosed chronic liver disease have liver-associated enzyme (LAE) derangements [17, 25, 26]. In hospitalized patients, prevalence rises to 76.3–93% [15, 17]. The majority are low level elevations slightly above the upper limit of normal. Even at low levels, enzyme elevations appear to correlate with increased length of hospitalization and risk of severe disease [15, 25]. A minority of patients experience higher elevations in AST and ALT, with 10.4% of cases being > 3 times the upper limit of normal (ULN) in one study [15] and 17% of cases being > 5 times ULN in another [17]. Transaminase elevations to this degree are associated with increased risk of ICU admission, death, and intubation [15, 17]. Acute liver failure is rare and reported in only 2 of 417 patients in one study [15], and zero in others [17, 25, 26]. While these cases have been reported, most patients have likely alternate explanations for this presentation [27–30].

Treatment

As of the writing of this manuscript, no treatments are Food and Drug Administration (FDA) approved for COVID-19. All treatments discussed herein are considered investigational or off-label although several therapies listed have been given emergency use authorization (EUA) by the FDA. For a current list of therapies under investigation please access https://www.covid19treatmentguidelines.nih.gov/ for additional data and recommendations.

Many of the therapies discussed are associated with liver injury and clinicians must be aware of potential hepatotoxicities. Furthermore, many interact with other drugs commonly used in patients with chronic liver diseases (Table 1). Consultation with a multi-disciplinary team, including clinical pharmacy, may mitigate associated problems with their use. Helpful internet-based resources are also available [31].

Table 1 COVID-19 therapies and potential hepatic implications: recognized potential current and relevant historical treatments. Potential associations with drug-induced liver injury, chronic liver disease, and potential for interactions with medications commonly used in liver disease are also listed. *AST*, aspartate aminotransferase. *ALP*, alkaline phosphatase. *ALT*, alanine aminotransferase. *ALF*, acute liver failure. *CYP450*, Cytochrome P450. *DAA*, direct acting antivirals. *HBV*, hepatitis B virus. *HCV*, hepatitis C virus. *HIV*, human immunodeficiency virus. *IL*, interleukin. *mTOR*, mammalian target of rapamycin. *OATP*, organic anion transporting polypeptides. *P-gp*, permeability glycoprotein. *SJS*, Stevens Johnson syndrome. *TACO*, transfusion-associated circulatory overload. *TEN*, toxic epidermal necrolysis. *TNF*, tumor necrosis factor. *TRALI*, transfusion-related acute lung injury. *ULN*, upper limit of normal

Treatment	Hepatic monitoring	Adverse effects/extrahepatic side effects	Potential liver related drug-drug interactions [31]	Comments
Chloroquine/hydroxychloroquine	No clear association with hepatotoxic side effects	Cardiac dysrhythmia, ↑QTc/Torsade de Pointes, ↑ mortality	No clear associations reported	Not recommended in COVID-19
Azithromycin (with chloroquine or hydroxychloroquine)	Well-described association with drug-induced liver injury. Recommend baseline liver enzymes and regular monitoring while on therapy	Symptoms associated with drug-induced liver injury may include fatigue, jaundice, abdominal pain, pruritus	May interact with calcineurin and mTOR inhibitors. May interact with certain HCV DAA	Low rates (1–2%) of acute, transient, asymptomatic elevations in AST/ALT. Self-limited cholestatic hepatitis reported within 1–3 weeks of initiation. Can induce hepatocellular injury with jaundice. Rare cases of ALF and SJS/TEN
Lopinavir	Possible, rare cause of clinically apparent liver injury		Avoid coadministration with mTOR inhibitors. May interact with anti-metabolites and calcineurin inhibitors	Severity of injury ranges from mild to ALF. Lopinavir-based antiretroviral therapy can exacerbate HBV or HCV in HIV coinfected patients
Ritonavir	Probable rare cause of clinically apparent liver injury		May interact with certain HCV DAA. Avoid coadministration with mTOR inhibitors. May interact with anti-metabolites and calcineurin inhibitors	Moderate-severe elevations in AST/ALT (> 5 × ULN) reported in up to 15% of patients. Ritonavir-based antiretroviral therapy can exacerbate HBV or HCV in HIV coinfected patients
Remdesivir (Veklury ®)	Obtain baseline liver tests prior to initiation and daily while on treatment	Gastrointestinal side effects (e.g., nausea/vomiting). Hypersensitivity/anaphylactic reactions	Avoid coadministration with: (a) strong inducers of CYP450, OATP, or P-gp (e.g., rifampin). (b) Chloroquine or hydroxychloroqine due to risk of reduced antiviral activity [32]	Should not be initiated in patients with baseline ALT ≥ 5 × ULN. Should be discontinued if ALT ≥ 5 × ULN or if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing bilirubin, ALP, or INR during treatment
Convalescent plasma	N/A	Rare (< 1%) incidence of TACO/TRALI		Theoretical risk for antibody-dependent enhancement of infection
Corticosteroids	Increased risk for hepatitis B reactivation with prolonged use	May be associated with hyperglycemia, secondary infections, psychiatric effects, avascular necrosis	Moderate CYP450 3A4 inducer. Potential interactions with calcineurin and MTOR inhibitors	Cases of hepatoxicity associated with high dose IV corticosteroids (methylprednisolone) have been associated with acute liver injury/failure [33]. Follow guidelines for hepatitis B reactivation when using long term corticosteroids [34]

Table 1 (continued)

Treatment	Hepatic monitoring	Adverse effects/extrahepatic side effects	Potential liver related drug-drug interactions [31]	Comments
IL-1 inhibitors (anakinra)	Probable rare cause of clinically apparent liver injury	Increased rates of infection reported with long term co-administration with anti-TNF	May interact with anti-metabolites, mTOR and calcineurin inhibitors. Avoid coadministration with IL-2 inhibitors (e.g., basiliximab)	Rare cases of acute, self-limited liver injury have been reported
IL-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab)	Associated with dose dependent, elevations in liver enzymes	Rash	May interact with anti-metabolites, mTOR and calcineurin inhibitors. Avoid coadministration with IL-2 inhibitors (e.g., basiliximab)	
Interferons (alpha, beta)	Associated with elevations in liver enzymes	Flu-like symptoms, nausea, fatigue, weight loss, hematologic toxicity, psychiatric problems	Potential for increased toxicities when administered with immunomodulators	

Direct Antiviral Therapies

The following medications have previously demonstrated, direct acting, antiviral effects making them appealing candidates for use against SARS-CoV2.

Chloroquine and hydroxychloroquine with and without azithromycin were initially used based on in vitro antiviral activity against SARS-CoV2 [35]. A small, nonrandomized series [36] received early attention and helped gain an FDA EUA. Larger, well-designed studies not only failed to demonstrate benefit [37] but also found harmful side effects including increased mortality [38–40]. The EUA was withdrawn and the FDA now recommends against the use of all three of these medications in COVID-19 patients outside a clinical trial [41]. While chloroquine and hydroxychloroquine are not strongly associated with liver injury, azithromycin is commonly implicated in both cholestatic and hepatotoxic liver injuries [24]. Additionally, these medications have drug-drug interactions with commonly used medications in liver patients [31].

Despite early enthusiasm, a randomized, controlled trial of the HIV protease inhibitor, lopinavir/ritonavir, demonstrated no benefit [42] leading to recommendations against these medications for the treatment of COVID-19. Both lopinavir and ritonavir are known to be hepatotoxic agents [43, 44]. Additionally, ritonavir is a known CYP3A4 inhibitor and may impact the metabolism of mTOR inhibitors (e.g., sirolimus and everolimus) and calcineurin inhibitors (e.g., tacrolimus).

Finally, the viral RNA polymerase inhibitor remdesivir is, perhaps, the most promising antiviral therapy in the treatment of COVID-19. A large, randomized trial of patients receiving remdesivir demonstrated improvement in both time to recovery and mortality [45] leading to an EUA for hospitalized patients with severe COVID-19. No specific guidance exists for the use of remdesivir in the treatment of mild or moderate COVID-19 patients. Transaminase elevations were similarly noted in both groups leading to recommendations for monitoring of liver enzymes prior to and during treatment [32].

Immune-Based Therapies

While not specifically targeting the virus, immune-based therapies, including human blood-derived products such as convalescent plasma (CP), have a long history of use in a variety of infections. CP appears to be safe in COVID-19 patients with severe or life-threatening disease [46] though efficacy is not as well established [47]. In this setting, an EUA was issued for CP in hospitalized patients

[48]. In contrast, other plasma derived therapies such as IVIG derived from either non-SARS-CoV-2 or SARS-CoV-2 donors and mesenchymal stem cells are not recommended. Although report cases of viral hepatitis transmission through CP exist [49], there are no well-described hepatic side effects with the use of CP.

Immunomodulatory agents are also being considered in the treatment of COVID-19 given its robust systemic inflammatory response. Corticosteroids have previously demonstrated benefit with other corona viruses but are associated with extended viral shedding [50, 51]. Of all classes of corticosteroids, dexamethasone appears most promising [52] while trials studying alternate corticosteroids (e.g., methylprednisolone and prednisone) demonstrate conflicting results [53, 54]. Dexamethasone is recommended in mechanically vented patients and those requiring oxygen but not for patients breathing room air. Alternative glucocorticoids can be considered if dexamethasone is not available [55].

Inhibitors of IL-1 and IL-6 such as anakinra, tocilizumab, sarilumab, and siltuximab are FDA approved for a variety of rheumatologic and hematologic conditions. Owing to the associated cytokine storm, these are naturally appealing targets. Unfortunately, limited data in COVID-19 are available [55]; therefore, these agents are neither recommended for or against. Hepatotoxicities are well described with many of these agents (Table 1) and liver enzymes should be monitored carefully when used.

Treatment/Management of Chronic Liver Disease

Viral Hepatitis

The interactions between COVID-19 and chronic viral hepatitis, specifically hepatitis B (HBV) and C (HCV), are not well understood. Interestingly, early reports point to a possible inverse association between chronic viral hepatitis and COVID-19. An early case report of an HIV/HCV coinfected patient demonstrated a delayed SARS-CoV2 antibody response with early virus clearance. The authors implicate immune dysfunction delaying antibody formation as the explanation for the findings [56]. Stemming from this case, a review of over 2000 patients hospitalized with COVID-19 found a lower percentage with HBV compared to an age-matched, geographically similar population. Similarly, authors suggest "immune exhaustion" in which HBV-stimulated T-cells do not mount as robust a cytokine response to SARS-COV2 infection leading to a less severe course [57]. On the other hand, a small observational study suggests that chronic hepatitis B (CHB) patients have significantly higher levels of total bilirubin, the significance of which is unknown [58]. We agree with currently published guidance regarding management of HBV and HCV medications in COVID-19 negative patients and COVID-19 positive patients already on treatment (see Table 2) [59–61]. We recommend that management of risk for HBVr and treatment of reactivation be informed by previously published guidelines [34]. Prior guidelines also recommend HBV screening for at risk patients prior to initiation of immunosuppression [34].

Autoimmune Hepatitis

Patients with AIH are typically managed with long term immunosuppression, only coming off therapy after carefully observing them over a number of years [63]. Despite this, an early cross-sectional report from Italy during a high incidence period did not find that AIH patients on various immunosuppressive regimens were at increased risk of developing COVID-19 beyond that of the general population [64]. Due to this, multiple societies support the continuation of immunosuppression among non-infected patients, with reduction (but not cessation) in patients with COVID-19 [59–61]. The decision to reduce immunosuppression is a balance of risks and benefits, individualized to each patient. Factors to consider include the severity of COVID-19, as well as a patient's personal history of AIH flares/relapse after prior withdrawal attempts as well as their degree of underlying fibrosis as a potential way to gauge the likelihood of decompensation should a flare occur. The duration of their biochemical remission can also play a role in the decision to reduce therapy [65]. Notably, should a flare or relapse occur after the decision to lower or withdraw, more intensive immunosuppressive therapy would likely be necessary, at least in the short term.

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)

MAFLD (previously known as non-alcoholic fatty liver disease or NAFLD) may predispose patients to higher mortality and increased severity of disease in COVID-19 [6, 66], particularly in patients with intermediate (1.3–2.67) or high (> 2.67) fibrosis-4 (FIB-4) scores (adjusted OR of severe disease as compared to patients without MAFLD 2.59, 95% *CI* 1.09 to 6.13 and 4.04 95% *CI* 1.22–13.3 respectively) [67]. However, comparison between groups with and without MAFLD while successfully eliminating confounding comorbidities is difficult in this population, given the well-established increase in COVID-19-related disease severity in diabetes mellitus and obesity [68, 69] and the strong association between all three of these disease entities. The COVID-19 pandemic may also indirectly lead to increasing rates of MAFLD in the coming years. The social conditions created by the pandemic (increasing unemployment rates, financial

Table 2 Summary of considerations and international societal guidance regarding management of chronic liver disease during COVID-19 pandemic. *AASLD*, American Association for the Study of Liver Disease. *EASL*, European Association for the Study of Liver Diseases. Similar recommendations for these conditions are made by the Asian-Pacific Association of the Study of Liver Diseases (APASL) [61]. *AFP*, alpha-fetoprotein. *AH*, alcoholic hepatitis. *ALD*, alcoholic liver disease. *HCV*, hepatitis C virus. *LT*, liver transplantation. *NAFLD*, non-alcoholic fatty liver disease. *MAFLD*, metabolic-associated fatty liver disease

Etiology	Considerations	Guidance statements/recommendations
Viral hepatitis	- Initiation and continuation of antiviral treatment - Risk of reactivation of hepatitis B	**AASLD**[59]**:** - Initiation of hepatitis B/C treatment in patients without COVID-19 is not contraindicated - Initiation of chronic hepatitis B treatment for patients with COVID-19 is not contraindicated and should be considered particularly when starting immunosuppression **EASLD**[60, 62]**:** - Continue therapy through mailed prescriptions and initiate therapy as recommended by established guidelines
NAFLD/MAFLD	- Risks factors for severe COVID-19 - Lifestyle alterations	**AASLD**[59]**:** - Educate patients that they may be at increased risk given metabolic comorbidities **EASL**[60, 62]**:** - Educate patients regarding increased risk of severe COVID-19 with metabolic comorbidities - Continue intensive lifestyle interventions, nutritional guidance, and weight loss advice, treat hypertension per guidelines
ALD	- Reduced psychosocial support - Potential for more severe COVID-19 - Use of steroids, LT	**AASLD**[59]**:** - Use steroids with caution in patients with COVID-19 (when potential benefit may outweigh risk) **EASL**[60, 62]**:** - Pre-emptive outreach via telephone with alcohol liaison and cessation services - Educate against disinformation regarding alcohol use reducing COVID-19 risk - Careful use of corticosteroids for severe AH
Hepatocellular carcinoma	- Missed screening/surveillance - Locoregional therapy - Chemotherapy/immunotherapy	**AASLD**[59]**:** - Continue monitoring for HCC as close to on-time as possible but an arbitrary delay of 2 months is reasonable, after informed consent - Proceed with treatments or surgical resections when able rather than delaying **EASL**[60, 62]**:** - Multidisciplinary tumor boards should continue to function and provide recommendations - Prioritize patients for screening through published HCC risk stratification tools (including patients with elevated AFP, chronic hepatitis B, HCV-related cirrhosis, or NASH)
Autoimmune liver disease	- Alterations to immunosuppression - Management of flares	**AASLD**[59]**:** - Do not make anticipatory adjustments to immunosuppression in patients without COVID-19 - Start immunosuppressive therapy in patients who have strong indications for treatment - Consider reduction in level of immunosuppression in patients with AIH who have COVID-19 (individualized to patient circumstances) **EASL**[60, 62]**:** - Reduction of immunosuppression only under special circumstances (lymphopenia, bacterial/fungal superinfection) - Emphasis on utilization of vaccinations - Addition of or conversion to dexamethasone if hospitalized for COVID-19

Table 2 (continued)

Etiology	Considerations	Guidance statements/recommendations
Compensated cirrhosis	- Screening for varices - Vaccinations - Nutrition/frailty	**AASLD**[59]**:** Consider primary prophylaxis with non-selective beta-blockers with patients with clinically significant portal hypertension or high risk of decompensation - Continue secondary prophylaxis with endoscopy/band ligation **EASL**[60, 62]**:** - Education regarding risks for worsening hepatic decompensation, severe COVID-19 and death - Every effort should be made to resume the guideline-directed care - Test all patients prior to screening endoscopy and in areas of low prevalence, resume screening endoscopy as appropriate

instability, and outright food shortages) are likely to lead to significant increases in food insecurity worldwide according to United Nations estimates [70]. This has been associated with increased risk of development of MAFLD [71].

Alcohol-Associated Liver Disease (ALD)

Patients with alcohol use disorder as well as ALD are vulnerable to relapse as a result of the social isolation inherent to the response to the pandemic, as well as the stressors brought on by the financial insecurity and reduced availability of medical and psychological resources [72–74]. Furthermore, there may be a bidirectionality between COVID-19 severity and AUD/ALD given the effects of chronic alcohol consumption at the molecular level, including changes in pulmonary ACE2 receptor expression [75]. While no definitive evidence exists demonstrating an increase in alcohol-related hepatitis during this time as of yet, anecdotally, our hospital wards and those of colleagues across the country have seen a consistent influx of alcohol-associated hepatitis (AH) and newly decompensated alcohol-related cirrhosis.

For severe AH, uncertainty regarding optimal management strategies, including the use of corticosteroids (prednisolone) and liver transplantation (LT), have continued during the global pandemic. While abstinence is the only proven intervention, nutritional therapy and corticosteroids are commonly utilized and are currently guideline recommended [76]. However, it is important to recognize that the use of steroids should only be undertaken once several contraindications, such as GI bleeding, active infection, or renal failure have been ruled out. Whether infection with SARS-CoV-2 itself is a contraindication to steroids is unclear, as is how a course of prednisolone changes the risk of contracting the virus. Recent data have suggested a benefit of dexamethasone in hospitalized patients with COVID-19 [52] prompting the NIH to issue guidance in support of its use for patients requiring supplemental oxygen or mechanical ventilation [55].

The utilization of LT as a definitive treatment option for severe AH is likely to become a focal point. A recent consensus statement suggested that patients with severe AH presenting for the first time in the absence of uncontrolled medical or psychiatric comorbidity who are nonresponsive to medical therapy, should be considered for LT evaluation, and provided they meet criteria related to their underlying AUD [77]. There is no available evidence to suggest that these policies or recommendations should be altered specifically due to the pandemic, though adopting a standardized multi-disciplinary approach to the LT evaluation for these patients across centers would likely help prevent overwhelming any one program. The management of LT recipients in the era of COVID-19 is discussed in another article in this issue.

Hepatocellular Carcinoma (HCC)

The major impacts of COVID-19 on HCC include delays in diagnostic testing and the delivery of therapy. Surveillance for HCC is a core component of healthcare maintenance in patients with cirrhosis and chronic hepatitis B, typically performed by imaging (ultrasound or MRI) with or without alpha fetoprotein measurement [78, 79]. Broader use of surveillance has been proposed for patients with NAFLD [80]. Best practice guidelines recommend weighing the risks of healthcare exposure during times of reduced radiologic capacity for at-risk patients against the benefits of on-time surveillance and suggest that a delay of 2 months is reasonable, albeit arbitrary [59]. It is estimated that approximately 98% of at-risk patients would not develop HCC during any one surveillance interval, based on an annual incidence of 2–3% [81]. There are growing data demonstrating heterogeneity among the HCC tumor growth patterns [82]. Rich et al. retrospectively assessed cirrhotic patients with HCC, demonstrating that over a quarter of patients demonstrated rapid growth (tumor doubling time < 90 days) [82]. This being the case, some experts recommend continued surveillance

on a case-by-case basis [83]. Non-radiographic means of testing such as the blood-based GALAD score have been reported recently in light of growing needs for screening the NAFLD population [84] and could be a means of risk stratifying patients. Locoregional and systemic therapies for advanced HCC should be chosen by a multidisciplinary team based on local availability and expertise, though oral therapy (e.g., sorafenib and lenvatinib) may reduce health care exposure as compared to regimens requiring infusion like atezolizumab/bevacizumab [81, 85].

Compensated Cirrhosis

In chronic liver disease patients with advanced fibrosis/cirrhosis but without decompensations (variceal hemorrhage, encephalopathy, or ascites), the goal is the prevention of these complications given the precipitous decline in long term survival [86–89]. Recently published recommendations for quality cirrhosis care include many process and outcome measures which are relevant to the patient with compensated disease and have been complicated by the pandemic [90]. These include ensuring variceal and cancer screening, delivering appropriate vaccinations, managing the underlying etiology for cirrhosis, as well as assessing for frailty or nutritional concerns.

Portal hypertension is the driving force behind multiple cirrhosis complications, including the development of gastroesophageal varices (GEV). Non-invasive risk stratification for high-risk varices has been recommended instead of universally screening all newly diagnosed cirrhotic patients with endoscopy (EGD) [89, 91]. If transient elastography measurement is less than 20 kPa and the platelet count is greater than 150,000/mm^3, EGD could be safely deferred given the low rate of high-risk varices (< 5%). This includes patients with cholestatic liver disease who may have a presinusoidal component of portal hypertension [92, 93]. While this does still require a patient to have a non-invasive study to determine liver stiffness, it could avoid the risk of having low-pretest probability patients undergo an aerosol-generating procedure. During times of reduced endoscopic capacity, this recommendation provides a means of nuanced resource allocation and reduction in unnecessary healthcare exposure.

The question of how to manage a compensated patient with clinically-significant portal hypertension (CSPH) or history of non-bleeding varices is a commonly encountered scenario, with multiple factors to consider during the pandemic. Guideline-directed indications for primary prophylaxis against hemorrhage still require direct endoscopic visualization to assess presence, size, and stigmata of varices, as well as the patient's overall Child-Turcotte-Pugh Class [89, 91]. Neither of these guideline statements recommend the initiation of pharmacologic therapy with non-selective beta-blockage (NSBB) for the prevention of variceal formation. However, recent data from a multi-center study of patients with compensated cirrhosis and CSPH but without high risk varices suggests that the initiation of long-term treatment with NSBB (or carvedilol) could prolong decompensation free survival, mainly through avoiding ascites development [94]. These data support early utilization in high risk patients (e.g., those with continued etiological activity or those with thrombocytopenia). If routine surveillance comes due for a patient, primary prophylaxis has been advocated by the AASLD during the COVID-19 pandemic instead of endoscopic evaluation [59].

Future Directions

Future investigations will help elucidate the long term impacts of COVID-19 on the liver. Prolonged time to symptom resolution has been noted already [95], as has persistence of cardiac inflammation well past negative COVID-19 test results [96]. Data gathered from continued use of COVID-19-associated therapeutics may also aid in differentiating COVID-19-mediated inflammation from drug-induced liver injury. Early evidence suggests pre-existing liver disease, particularly cirrhosis [6] or advanced fibrosis [67] may predispose patients to more severe illness though differentiation between concomitant comorbidities and COVID-19 infection has been challenging. Additionally, the impact of immunosuppression in autoimmune hepatitis and incidence of HBVr with COVID-19 treatment remain unknown.

On a population level, examination of the effects of delayed or missing health care maintenance visits (e.g., variceal and HCC screening) as well as the reduction in procedures such as locoregional therapies require further investigation. These factors are likely to be associated with more severe disease presentations and missed opportunities for early detection and risk mitigation [74]. Finally, research on the impacts of societal factors such as financial strain and food scarcity and its effect on MAFLD [71] and decompensations in those with cirrhosis [74] merit exploration. Hepatologists in a variety of practice settings have begun seeing higher rates of alcoholic hepatitis, potentially because of the mental health burden of the pandemic. The effects of these issues on chronic liver disease deserve attention in future research.

Ongoing, innovative approaches to these complex issues should be shared and analyzed. Many approaches have already been proposed, including increased access to telehealth [60], expanded use of non-invasive screening tools, increased use of home monitoring equipment, and electronic medical record tracking [74]. Continuing to provide the same quality of care will involve a paradigm shift from

care centered around face-to-face interactions to a literal and figurative patient-centered focus.

Conclusion

Liver-associated enzyme abnormalities are common in COVID-19 infections and marked elevations may be associated with severe disease. Whether this represents true hepatic injury or simply a sign of a more severe underlying disease process is unknown, current data suggest COVID-19-associated acute liver failure is rare. Many currently used COVID-19 treatments may be associated with drug-induced liver injury; liver tests should be monitored while on these medications. The effects of the global pandemic on patients with chronic liver diseases are wide ranging with impacts including potentially delayed HCC diagnoses, increased variceal bleeding complications, and a rise in the incidence of alcohol-related liver disease. The full impact of COVID-19 will likely not be appreciated for many years to come.

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