Hepatic Medicine: Evidence and Research

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COMMENTARY

COVID-19 and the Liver: A Complex and Evolving Picture

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Abstract: Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily attacks the respiratory system, other organs, such as the liver, are also affected. In this overview, the effects of SARS-CoV-2 infection on the liver in both healthy people and in those with pre-existing liver disease are documented; the relationship between coronavirus disease 19 (COVID-19) vaccination and liver injury is examined; the mechanism of SARS-CoV-2-associated liver injury is explored; and the long-term consequences of COVID-19 are delineated, both in people with and without pre-existing liver disease.

Keywords: COVID-19, COVID-19 liver disease, pathophysiology, SARS-CoV-2

Introduction

Human infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared at the end of 2019 in China. The World Health Organization (WHO) declared coronavirus disease 19 (COVID-19) to be a "disease of public health importance" on 30 January 2020, and on 11 March 2020 confirmed that the world was facing a pandemic. Over 3 years later, on 5 May 2023, the WHO declared "with great hope" an end to the COVID-19 public health emergency. The ultimate toll of the pandemic in terms of morbidity and mortality and the magnitude of the longer-term health consequences can only be imagined at this time.

Infection with SARS-CoV-2, and the resultant COVID-19, primarily affects the respiratory system.[1] However, infection has widespread effects on many organs systems, including the liver.[2] Whether SARS-CoV-2 is directly hepatotropic has been a subject of debate[3,4] but infection does, nevertheless, result in disturbed liver function in previously healthy people and exacerbation of liver injury, with detrimental effects on outcomes in those with established liver disease.[5,6] Public health measures intended to control the spread of the global pandemic often led to significant increases in alcohol consumption, adoption of a carbohydrate-rich diet and reduced levels of physical activity, further affecting the liver.[4,7–10] COVID vaccination has been associated with the development of an autoimmune hepatitis,[11–13] while the longer-term effects of infection include the development of secondary sclerosing cholangitis.[14–16]

Difficulties arise, however, in appraising the current literature, particularly epidemiological and clinical studies, because of the evolving therapeutic landscape over the past 3 years. Thus, some studies were undertaken pre-vaccination and pre-effective treatment regimens, whilst others were undertaken when some or all of these available options were available and accessible. Ongoing review of existing datasets continues in light of the identification of additional risk factors, and new studies are underway. Thus, understanding of the COVID-19 pandemic and its effects on the liver are far from complete. This "commentary" reflects understanding of the situation at the time of publication.

Received: 1 August 2023
Accepted: 28 October 2023
Published: 7 November 2023

Effects of the Pandemic on the General Population

In early 2020 lockdown initiatives were adopted, by many world governments, in response to the sweeping COVID-19 pandemic. These measures, which included "stay at home" policies, travel restrictions, job losses, and banning of any kind of gathering, led to physical separation from family and friends and widespread social isolation.[17] This had a major impact on peoples' mental health, which, in many instances, was further aggravated by the adoption of unhealthy behaviours, including increased alcohol consumption, consumption of carbohydrate-rich foods, and reduced physical activity.[5,7–10]

In a survey involving >50,000 people from 11 countries 43% reported an increase in the frequency of drinking during lock-down, while 36% reported an increase in the amount of alcohol they drank on a typical day.[18,19] The factors associated with an increase in alcohol use included older age, employment as an essential worker, parents with children, those with a personal relationship with someone severely ill with COVID-19, and those with higher depression, anxiety, or positive urgency impulsivity.[18]

People with an underlying alcohol use disorder (AUD), and those who were otherwise socioeconomically disadvantaged, were more likely to increase their drinking during lockdown, particularly as they were not able to access the psychosocial support that might otherwise have been available.[6,20] In addition, they were more at risk of contracting COVID-19 infection because their adherence to lockdown policies was generally poor; they were also more likely to develop severe infection because of the depressant effects of alcohol on their immune systems.[21]

In a systematic review investigating the effects of pandemic confinement, involving almost 500,000 participants, 7.2% to 72.4% of the population reported weight gain ranging from 0·6 kg to 3·0 kg, mainly in those who were already overweight or obese.[9] The key factors were increased consumption of unhealthy food and a reduction in physical activity.[9] A population survey in a well-characterised northern Italian community[10] identified an overall increase in the intake of most categories of food, but with a worsening of the quality of the diet. Furthermore, both the quantitative and qualitative dietary changes adopted during quarantine appear to have persisted following relaxation of lockdown restrictions.[10]

Liver Injury

Abnormalities in 'liver function tests' (LFTs) were observed in 15% to 65% of SARS-CoV-2 infected individuals with no pre-existing liver disease.[3] The biochemical picture is generally hepatocellular, rather than cholestatic, with elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities, typically 1–2 times the upper limit of the reference range; hyperbilirubinaemia and hepatic synthetic dysfunction are rare.[3] In most instances, these abnormalities resolve in the post-acute phase.

Greater and more prevalent abnormalities in LFTs are observed in people with severe COVID-19 requiring hospitalisation; on admission, 57% to 63% have increased serum AST and 30% to 37% increased serum ALT activities.[22] Two weeks following admission 81% and 67% show increased serum AST and ALT activities respectively.[22]

While the transaminitis may reflect direct liver injury other factors might also contribute including an associated immune-related inflammatory response, congestive hepatopathy, hepatic ischaemia, venous and arterial thrombosis, muscle breakdown, and drug-induced liver injury, including use of specific experimental COVID-19 treatments, such as lopinavir–ritonavir and tocilizumab, and complementary or alternative medicines.[3,22–25]

Mortality

The mortality rate associated with SARS-CoV-2 infections in the general population is around 6.4%;[26] rates tend to be higher in men than women and increase with age and with the presence of underlying medical conditions. Thus, in people with no underlying health issues the mortality rate is 3.0%, but it increases to 12.0% in those with diabetes, systemic hypertension, obesity and, more particularly, chronic obstructive pulmonary disease and chronic kidney disease.[26] In hospitalized patients, without pre-existing liver disease, abnormal LFTs on admission and during the first 2 weeks of hospitalization are associated with increased mortality.[22]

Effects of the Pandemic on Patients with Liver Disease

The diversion of healthcare resources and manpower to the pandemic frontline in 2020 and 2021 meant that people with pre-existing liver disease, known to services, did not receive the level of care and follow-up they needed.[27] In some instances, video or telephone consultations were offered, but for many these were poor substitutes for outpatient visits,[28] although for some people avoidance of hospital visits and hence the risk of contracting COVID-19 was welcomed. The difficulties of arranging blood tests and imaging, and the postponement of health interventions, particularly in those with established cirrhosis, often resulted in the need for crisis management, rather than the use of assured, preventative algorithms.

It is also clear that people with pre-existing liver disease, who were not known to services, were more likely to have escaped detection, as family practitioners, primary healthcare services and hospital services were diverted to deal with those directly affected by the COVID-19 pandemic.[29] There was also likely to have been a reluctance to come forward because of the awareness that services were stretched, but also because of the perception that clinical settings were "not safe".[30]

Alcohol-Related Liver Disease

Patients with alcohol-related liver disease were amongst those most impacted by the pandemic,[31] mainly because the lockdown and the relative lack of medical and psychosocial support made a return to hazardous drinking more likely.[32] Those aware that they should seek help were deterred through fear of the risk of COVID-19 infection and loss of their previous contacts within support services through closures or redeployment. Community alcohol detoxification schemes were halted or significantly reduced, whilst valuable non-statutory face-to-face support groups were transferred to online platforms. Thus, the overall support for this particularly vulnerable group was significantly reduced.[32]

Considerable attention has been paid to the effects of the pandemic on admissions and outcomes in patients with acute alcoholic hepatitis (AAH).[7] Hospitalizations for AAH increased by 50% during the COVID-19 era;[32] increases were seen particularly among younger adults,[7,33] women,[7,33] and ethnic minority groups.[33,34] Rehospitalization rates increased by 94% suggesting premature discharge or inadequate post-discharge support.[33] Most studies found that the numbers of patients with AAH, admitted to the intensive care unit (ICU), remained stable during the pandemic. However, one centre in the United Kingdom reported an increase in the proportion of patients with AAH requiring high dependency or critical care from 10.7% in June 2019 to 23.9% in June 2020.[32] A German group also reported that the proportion of patients admitted to the ICU with acute-on-chronic liver failure, precipitated by severe AAH, increase significantly from 24% to 27% in pre-pandemic years to 57% in 2020.[35] Overall mortality rates from AAH during the pandemic were generally similar to previous years,[7] although data continue to be collected and analysed.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

It is likely that the increase in population alcohol consumption levels during the pandemic also impacted on individuals with MASLD (previously termed non-alcoholic fatty liver disease—NAFLD). There is evidence, for example, that moderate alcohol consumption has a significant harmful effect on the development of advanced fibrosis in patients with this condition.[36]

Additional harm is likely to have followed the changes in diet and exercise activity reported during lockdown. Thus, in a prospective study involving >6000 healthy Spanish individuals, significant differences were observed in anthropometric and clinical variables before and after lockdown.[37] MASLD scales worsened with increased insulin resistance, body weight, body mass index, plasma LDL cholesterol and blood glucose and reduced plasma HDL cholesterol.[37]

There is currently no consensus on the effects of COVID-19 in people with MASLD.[37] Although several studies have highlighted the role of MASLD in the progression of COVID-19, there is still no evidence that MASLD will affect its prognosis.[38]

The situation is further complicated by the fact that people with MASLD are likely to have significant co-morbidities, for example diabetes and cardiovascular disease, which might themselves adversely affect the outcome of COVID-19. Furthermore, other mechanisms such as an increased susceptibility to infections, impaired immune responses, and an increased risk of coagulation could enhance the risk of severe COVID-19 in people with MASLD.[39]

Prospective and larger retrospective studies are needed to better understand the behaviour of the virus and its interaction with MASLD.

Chronic Hepatitis B and C-Related Liver Disease

The effects of infection with SARS CoV-2 in people with pre-existing chronic hepatitis B (HBV) and C (HCV) is unclear. Several issues confuse the clinical picture, such as whether infection is active; whether antiviral agents are in use; whether prophylaxis against reactivation is provided; the presence and number of co-morbidities; the severity of the SARS-CoV-2 infection; vaccination status; the need for immunosuppressant treatment, and, perhaps most importantly, the severity of any pre-existing liver disease. Guidelines on the use of viral prophylaxis and treatment in these already immunocompromised people varied frequently during the pandemic and the number of studies available remains small. Thus, firm conclusions cannot be made.[3,4]

HBV Infection

The evidence for the influence of SARS-CoV-2 and HBV co-infection and HBV-related liver disease is limited.

In a large study from Hong Kong, neither current nor past HBV infections were risk factors for mortality following SARS-CoV-2 infection.[40] The presence of cirrhosis was independently associated with a higher risk of mortality but only 6.5% of patients with current HBV and 3.6% with past HBV infection had this degree of liver injury.

In a small Spanish study, the risk of HBV reactivation in patients with severe COVID-19 and resolved HBV infection (HBsAg negative/anti-HBc positive), taking immunosuppressants, was low whether entecavir prophylaxis (62%) was provided or not.[41]

The associations between chronic HBV infection, HBV antiviral treatment, and COVID-19 outcomes were explored in a complex Korean nationwide cohort study.[42] The presence of chronic HBV decreased the risk for developing SARS-CoV-2 infection; as did the use of the antiviral agents, tenofovir and entecavir. The presence of chronic HBV was not associated with an increase in the risks of developing severe COVID-19 or of dying. Likewise, the risks of severe COVID-19 and mortality did not differ in patients taking antiviral agents and those who did not. However, no information was provided in this study on the use and consequences of immunosuppressant therapy.

HCV Infection

The impact of SARS-CoV-2 infection on outcomes in people with HCV infection was explored in almost 1000 infected persons, identified using the HCV Infected Veterans (ERCHIVES) database, and the same number of propensity score matched HCV-negative controls.[43] The mean FIB-4 score was significantly higher in cases than controls (1.9% vs 1.2%), as was the proportion of cases with advanced fibrosis or cirrhosis, based on a FIB-4 score of >3.25 (8.1% vs 1.4%). Small numbers of cases and controls received remdesivir, systemic corticosteroids or both.

A higher proportion of cases were hospitalised compared to controls (24% vs 18%); hospitalisation rates were significantly higher in the cases with more advanced fibrosis.[43] Overall ICU admission rates were similar between the two cohorts (13.0% vs 12.5%), as were the all-cause mortality rates (6.6% vs 6.5%); cases with fibrosis were more likely to be admitted to ICU than were controls, although mortality rates were similar; the number of events was, however, too small to make meaningful comparisons.[43]

In a single centre study in New York, 4.1% of 1000 patients with COVID-19 had a history of HCV infection.[44] All HCV patients received anti-viral treatment; approximately 50% had a sustained viral response. The patients with HCV infection were more likely to have severe COVID-19 requiring mechanical ventilation than those without HCV (63% *cf.* 8%) and had a higher-hospital mortality rate (63% *cf.* 15%), irrespective of baseline comorbidities, or the additional presence of COVID-19-associated liver injury.[44]

In an Egyptian study involving 125 patients with chronic HCV and COVID-19 co-infection,[45] patients with HCV-related cirrhosis (51%) were significantly more likely to develop severe COVID-19 than those without cirrhosis (45.3% vs 18.0%), and were significantly more likely to die (51.6% vs 14.8%). Previous attainment of a sustained virological response, following treatment with direct acting antiviral agents, did not impact on COVID-19 disease severity or outcome; HCV-related cirrhosis was an independent predictor of mortality.[45]

Autoimmune Hepatitis

There is a general agreement that patients with pre-existing autoimmune hepatitis (AIH) who contract SARS-CoV-2 infection, including those taking immunosuppressants, have similar outcomes to patients with other forms of chronic liver disease (CLD).[46]

Thus, no differences were observed between patients with AIH and those with other types of CLD in the rates of hospitalization, ICU admission, or death.[46] In addition, there were no differences in outcomes between patients with AIH taking immunosuppressants and those who were not.

Hepatocellular Carcinoma

Cancer diagnoses were delayed throughout the COVID-19 era,[47] and the diagnosis of hepatocellular carcinoma (HCC), in the context of cirrhosis, was no exception.[48] The decrease in the rates of diagnosis of HCC during the pandemic, was likely the result of delays in or discontinuity of regular surveillance programmes.[49] Delays in the start of treatment, once the diagnosis of HCC had been made, were also recorded.[50]

Liver Transplantation

There was significant uncertainty about the continuity of liver transplantation programs at the beginning of the COVID-19 pandemic, primarily for fear that immunosuppressed patients would be more vulnerable to severe infection and adverse outcomes, although in most instances these fears were not realized.[51,52] Transplant units responded differently: some stopped all activity; others limited their transplant activity favouring the "sickest first", while others continued as normal. In addition, despite the absence of supporting data, many statutory and non-statutory organisations produced "pragmatic" guidelines, particularly in relation to the use of donor organs.[51]

The results of studies undertaken over the last 3 years are often contradictory, but they are not strictly comparable as their timeframes, particularly in relation to the availability of vaccines and effective medications, differ significantly. These uncertainties may also have affected organ procurement activity.

There is, however, a consensus that liver transplant programmes were severely impacted as a result of the pandemic.[51,53–55] Overall, transplant activity decreased, at least initially. The number of new patients accepted on to waiting lists was stable or reduced. The number of living and deceased donor organs decreased. The hazard of death or delisting increased, reflecting the lack of donor organs, as only a very small proportion of waiting list deaths or delistings occurred in patients with COVID-19. The transplant rates overall were lower.[53–55]

Some differences in activity were reported in relation to disease aetiology.[7,56,57] Thus, there was a significant rise in the number of waiting list registrations for AAH during the pandemic. There was also an increase in the proportion of listed patients with alcohol-related liver disease–not limited to AAH–which exceeded the combined listings for chronic hepatitis C and metabolic dysfunction-associated steatohepatitis (MASH; previously termed non-alcoholic steatohepatitis - NASH). Patients with alcohol-related liver disease also had a 50% greater chance of receiving a donor liver than those with liver disease of other aetiologies.[7] It is not clear whether the increase in liver transplantation for AAH is attributable solely to the general increase in the levels of alcohol consumption during the pandemic or at least, in part, attributable to recent changes in organ allocation policy. However, the concurrent increase in waiting list registrations for AAH during the pandemic suggests an overall increase in numbers.[7]

Access to transplantation also decreased in patients with HCC, primarily because of a reduction in the number of donor organs and the subsequent delays in the procedure. The outlook in people with HCC is adversely affected with time, increasing the risk of delisting as well as death. While early postoperative outcomes of liver transplantation for HCC were similar to those recorded pre-pandemic, overall survival and graft survival beyond 180 days were significantly inferior.[57]

Symptomatic SAR-CoV-2 infection is associated with a high risk of early death in liver transplant candidates although outcomes are modulated by both the severity of the infection and of the underlying liver disease.[58] Respiratory failure frequently results in candidates becoming ineligible for transplantation and is the most frequent cause of death. Laboratory Model for End-Stage Liver Disease (Lab-MELD) scores of ≥20 and dyspnoea on presentation are both

independent negative predictors of survival. A short-term survival rate of 96% was reported in the candidates who were transplanted; SARS-CoV-2 reinfection was not observed.

Immunosuppression

Patients with cirrhosis are frequently immunocompromised, particularly transplant candidates and recipients, making them more susceptible to SARS-COV-2 infection. However, it has been suggested that immunosuppressive regimens that include calcineurin inhibitors or everolimus may be protective in this patient population, either because their T-cell response is modulated or because of a direct antiviral effect on SARS-CoV-2 itself. In a study exploring the effects of reducing/stopping immunosuppressant drugs in post-transplantation patients, discontinuation of tacrolimus was associated with an increase in the number of deaths; dose reduction of the agents reviewed did not affect outcomes.[59]

Mortality

Results from large multicentre or registry studies have show that the mortality rates associated with SARS-Cov-2 infection, in patients with preexisting liver disease, varying significantly by disease severity and aetiology.[60–62]

In a multicentre study involving 13 Asian countries the mortality rate in patients with known or newly diagnosed CLD and COVID-19 was 2.7% in those with non-cirrhotic disease, but 16.3% in those with cirrhosis.[60] Overall, 43% presented with acute liver injury, whilst 20% of the patients with cirrhosis presented with either acute-on-chronic liver failure or acute decompensation.

Data from combined European and north American registries recorded mortality rates of 8% in patients with non-cirrhotic liver disease with COVID-19, but of 32% in patients with cirrhosis.[61] Mortality rates in the patients with cirrhosis increased with decreasing hepatic reserve: 9% in Child-Pugh Class A, 35% in Class B, and 35% in Class C. Of note, the mortality rate in the patients with non-cirrhotic liver disease increased significantly with increasing age, whereas mortality rates were more evenly distributed across age categories in those with cirrhosis, including a high rate (31%) in those aged under 40.[61] Overall, 71% of deaths were attributed to COVID-19-related lung injury, whilst only 19% of deaths were attributed to liver-related complications.[61] In patients with cirrhosis, factors such as enhanced respiratory compromise due to worsening ascites, venous thromboembolism and coexisting hepato-pulmonary syndrome, porto-pulmonary hypertension, or hepatic hydrothorax may additionally compromise respiratory function.

Information on the influence of liver disease-aetiology on the outcome of SARS-CoV-2 infection is less clear. The large European and North American registry study reported that alcohol-related liver disease was an independent risk factor for death following SARS-CoV-2 infection, even after controlling for liver disease severity.[60] Otherwise, there is little evidence that other liver disease aetiologies for example MASLD, AIH or viral-related liver disease are independent risk factors for outcome in SARs-CoV-2 infected patients with CLD.[63]

Mechanism of SARS-CoV-2-Associated Liver Injury

The mechanism(s) involved in the development of COVID-19 liver injury remain unclear. In particular the question as to whether SARS-CoV-2 displays specific liver tropism, causing liver injury by direct infection, has been a matter of debate. SARS-CoV-2 is known to gains entry into cells via interaction between its spike protein and the angiotensin converting enzyme-2 (ACE-2) receptor, with priming of the spike protein by the transmembrane serine protease 2 (TMPRSS2).[64] However, ACE-2 receptor expression on healthy hepatocytes is much lower than on pneumocytes, although, cholangiocytes and pneumocytes display similar expression levels.[65] There is evidence, however, that hepatocyte ACE-2 receptor expression may be upregulated in the patients with CLD and in the presence of inflammation.[66]

Electron microscopic studies have demonstrated specific viral particles, such as spike proteins, in the cytoplasm of hepatocytes in patients with COVID-19, along with intracellular membrane damage, mitochondrial swelling and apoptosis.[67] However, the most compelling evidence for SARS-CoV-2 liver tropism comes from recent work undertaken on liver sample obtained from patients who had died from COVID-19 infection.[22] SARS-CoV-2 RNA was identified in hepatic parenchymal cells and SARS-CoV-2 replication-competent virus was recovered from the liver samples,[22] suggesting that primary hepatocytes may support SARS-CoV-2 viral replication. Furthermore, transcriptomic and proteomic profiling of these samples confirmed the expression of known SARS-CoV-2 entry receptors and infection

facilitators including ACE-2, TMPRSS2, Procathepsin L, and Ras-related protein Rab-7a. This profiling also showed upregulation of interferon responses, JAK-STAT signalling and liver-specific metabolic modulation, providing a viral activity profile that broadly overlaps with other hepatotropic viral infections such as HCV.[22,68] The identification of a transcriptomic signature of interferon responsiveness provides evidence that SARS-CoV-2 infection may be directly enhancing intrahepatic innate immune responses.

How SARS-CoV-2 enters the liver to infect hepatocytes is unknown. It is unlikely that it is blood borne, as infectious virus is not generally found in the blood of patients with COVID-19.[69] It has been suggested that entry via the portal venous system would be more likely.[70] An alternative would be entry via the biliary endothelium;[71] ACE-2 receptor expression is significantly higher in cholangiocytes than in hepatocytes and a COVID-related secondary sclerosing cholangitis has been reported as a longer-term complication of infection.[14–16] An immune-related mechanism is presumed, although bile duct ischaemia, an augmented systemic inflammatory response and the effects of virally-induced microthrombi have been postulated. It therefore follows that viral entry into the hepatocytes via the biliary tract should be considered.

Once SARS-CoV-2 enters the hepatocyte, it can cause damage in a number of way, including direct toxicity; endothelial cell damage and inflammation leading to microthrombi deposition and microvascular dysfunction; over-activation of the innate immune system leading to an immune-related hepatitis irrespective of the presence of pre-existing liver disease; an enhanced inflammatory response with upregulation of inflammasome pathways including the development of cytokine release syndrome; and dysregulation of the renin-angiotensin-aldosterone system leading to tissue damage from vasoconstriction and vascular permeability.[72–76]

However, sole attribution of the liver injury to the virus is unrealistic, particularly in the critically ill where co-factors such as hypoxia, systemic inflammation and sepsis, and polypharmacy are likely to play a role.[7,24] This is reflected in the diversity of the liver test abnormalities,[77] and histological findings in people infected with SARS-CoV-2, which include microvascular and macrovascular fat, lobular necroinflammation, portal inflammation, and vascular pathology.[74,78]

It follows that a better understanding of the mechanisms responsible for COVID-related liver injury might identify new pathways for therapeutic targeting.

COVID-19 Vaccination and Liver Injury

Most vaccination programmes began in late 2020 or early 2021. By the summer of 2021, case reports began to emerge describing the development of vaccine-associated AIH.[11–13] The largest study[12] provided information on 87 cases of vaccine-associated AIH collected internationally, indicating that the incidence of vaccine-associated AIH is rare.

The majority of affected patients are women over the age of 50 years. Between 30% and 50% had a history of liver disease, had other autoimmune conditions, or had received drugs with the potential to induce AIH. Most patients develop symptoms after receiving the first dose of the vaccine.[11–13] Vaccine-associated AIH presents with clinical symptoms, laboratory abnormalities and liver biopsy findings, similar to those of idiopathic AIH. Overall, the frequency and titres of autoantibodies in vaccine-associated AIH are lower than in idiopathic AIH. Liver biopsy shows lymphocytic or plasma cell infiltration and approximately half have an interface hepatitis.

Steroids are effective in treating vaccine-related AIH, resulting in remission and favourable outcomes in the majority. However, deaths have been reported, but were usually attributed to bacterial infection and sepsis.

The underlying cause of vaccine-associated AIH is unclear. However, SARS-CoV-2 antibodies produce moderate-to-strong responses with a variety of tissue antigens suggesting that molecular mimicry, resulting in the production of homologous self-antigens, likely plays a role.[79]

COVID-19 vaccination has also associated with the development of hepatitis as a result of HBV-reactivation.[80] In a recent study from Taiwan, 25 patients developed hepatitis within 90 days of COVID-19 vaccination, 10 of whom had chronic HBV infection and one resolved HBV; none had cirrhosis or were on antiviral medication.[80] The hepatitis was attributed to HBV reactivation in 10 patients, accounting for 90% of vaccine-associated liver disease in the patients with chronic HBV infection, two of whom died. Vaccine-associated hepatitis secondary to HBV reactivation is a rare but clinically significant complication of SARS-CoV-2 vaccination.

Longer Term Outcomes

Pre-Existing Liver Disease

The majority of studies in patients with CLD and COVID-19 have only reported on short-term outcomes. However, there is increasing evidence that the risks of mortality and morbidity in those who survive the acute episode are increased.

A 1-year long follow-up study, involving patients with CLD with a history of COVID-19 and a propensity matched control group without a history, reported a significant increase in all-cause mortality (8.0% vs 2.0%) and higher rates of hospitalisation (34% vs 21%) in the patients who had had COVID.[81] Comparable minorities of the patients had compensated (17.2%) and decompensated (5.5%) cirrhosis at baseline; cirrhosis was, however, an independent predictors of overall survival and hospitalisation. Seventy percent of the patients with a history of COVID-19 had received at least one dose of a COVID-19 vaccine.[81]

People infected with COVID-19 can experience long-lasting debilitating symptoms. The term "long-COVID- 19" is used to describe "physical, medical, and cognitive symptom lasting for at least 2 months following COVID-19 infection, for which there is no other explanation". Between 30% to 67% of COVID-19 survivors in the general population are affected in this way 6 months after recovery, predominantly functional mobility impairments, pulmonary abnormalities, and mental health disorders.[82] A year-long follow-up study of patients with CLD 30% reported symptoms of long-COVID-19.[81]

There is clear evidence of a legacy of adverse behavioural change following the pandemic.[81] Thus, in a long-term follow-up study involving patients with CLD who had COVID-19, a third of whom had been actively drinking prior to the diagnosis of COVID-19, a similar proportion reported active moderate to heavy alcohol use after recovery, whilst 4% reporting increased alcohol use and 1.7% de novo alcohol use. Weight gain was noted in 23% of these patients with a median gain of 10 pounds (4.5 Kg); control data were not available.[81] This is clearly of substantial public health concern.

No Pre-Existing Liver Disease

Abnormalities in liver function tests are observed in 15% to 65% of SARS-CoV-2 infected people with no underlying liver disease. The abnormalities tend to resolve following the acute phase of the illness.

However, reports are emerging of de novo AIH developing as a complication of SARS-CoV-2 infection in people with no prior history of liver disease.[83,84] This is not unexpected as there are already several reports of autoimmune manifestations and autoimmune sequelae of COVID-19 including, but not confined to, acute haemolytic anaemia, Guillain-Barre syndrome, myocarditis and pericarditis.[85,86]

The development of COVID-19-related secondary sclerosing cholangitis (SSC) is also documented.[15,65,87] SSC is known to develop in critically ill patients with no prior history of hepatobiliary disease during or following ICU admission.[15] Ischaemic injury is believed to play a key role in its development, due to severe tissue hypoxia and fibrinogen-associated circulatory disturbances. It follows that SSC could occur in critically-ill patients with COVID-19 requiring prolonged ICU admission.[67] However, the occurrence of SSC in patients critically ill with COVID-19 is higher than in those critically ill patients with influenza (12% vs 0%), although mortality rates were similar (29% vs 35%).[88]

Certain histological features in patients with COVID-19-associated SSC suggest that the primary insult to the biliary tree may be viral rather than ischaemic injury.[89] Recent reports have implicated the use of intravenous ketamine for sedation in the genesis of COVID-associated SCC, but cases have also been described in people who have not required ICU admission and sedation.[90]

Less information is available on the development of COVID-associated SSC in patients with underlying CLD. However, in a study undertaken in patients with predominantly MASLD/MASH, 23% developed cholestatic liver injury while 15% developed SSC;[87] the majority had severe COVID-19, but the development of progressive cholestatic injury was independent of the severity of the underlying liver disease. The occurence of SSC was significantly higher in patients with CLD and COVID-19 than in matched patients with other types of severe chest infections (15.4% vs.4.6%).[87]

Conclusions

Since its first occurrence in Wuhan, China in late 2019, it is apparent that the SARS-CoV-2 virus has a multifaceted effect on those who are infected, resulting in a variable spectrum of disease severity, short and long-term sequalae and outcomes. The long-term hepatobiliary consequences for people with and without pre-existing liver disease could be considerable, particularly given the numbers affected globally.

Funding

STR was supported by a Wellcome Institutional Strategic Support Grant.

Disclosure

The authors report no conflicts of interest in this work.

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