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COVID-19 vaccination and liver disease

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Abstract

Various vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed in response to the coronavirus disease 2019 (COVID-19) global pandemic, several of which are highly effective in preventing COVID-19 in the general population. Patients with chronic liver diseases, particularly those with liver cirrhosis, are considered to be at a high risk for severe COVID-19 and death. Given the increased rates of disease severity and mortality in patients with liver disease, there is an urgent need to understand the efficacy of vaccination in this population. However, the data regarding efficacy and safety of COVID-19 vaccination in patients with chronic liver diseases is limited. Indeed, several organ-specific or systemic immune-mediated side effects following COVID-19 vaccination, including liver injury similar to autoimmune hepatitis, have been recently reported. Although the number of cases of vaccine-related liver injury is increasing, its frequency, clinical course, and mechanism remain unclear. Here, we review the current findings on COVID-19 vaccination and liver disease, focusing on (1) The impact of COVID-19 in patients with chronic liver disease, (2) The efficacy, safety, and risk-benefit profiles of COVID-19 vaccines in patients with chronic liver disease, and (3) Liver injury following COVID-19 vaccination.+ADw-/p+AD4APA-/html+AD4-

Key Words: Coronavirus disease 2019 vaccine; Liver disease; Side effect; Liver injury; Immune-related hepatitis; Autoimmune hepatitis.

Ozaka S, Kobayashi T, Mizukami K, Murakami K. COVID-19 vaccination and liver disease. *World J Gastroenterol* 2022; In press

Core Tip: Patients with chronic liver disease (CLD), including cirrhosis, are a high-risk group for severe coronavirus disease 2019 (COVID-19). Presently, the results of several clinical trials for measuring the efficacy and safety of the available COVID-19 vaccines in patients with CLD have been reported. Given the increased rates of severity and

mortality of COVID-19 in patients with CLD, the importance of aggressive vaccination in the effective management of severe acute respiratory syndrome coronavirus 2 infection should be emphasized. Although liver injury following COVID-19 vaccination has also been reported, it is infrequent and is not a factor in vaccine hesitancy.

INTRODUCTION

The December 2019 outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread worldwide and became a global health threat[1,2]. COVID-19 is a respiratory disease caused by SARS-CoV-2, which can damage not only the lungs, but also other organs, including the cardiovascular system, liver, and gastrointestinal tract[3-5]. Vaccines are the most effective prophylaxis against COVID-19, and several vaccines against SARS-CoV-2 have been developed in response to the COVID-19 pandemic, among which vaccines produced mainly by Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca are now widely used[6]. These vaccines are of great importance in controlling severe COVID-19 not only in healthy individuals, but also in high-risk populations, including those with chronic diseases. Chronic liver disease (CLD) is characterized by the gradual destruction of liver tissue over time, and includes liver diseases that are caused by chronic inflammation (chronic viral hepatitis, non-alcoholic fatty liver disease [NAFLD], alcoholic liver disease, and autoimmune hepatitis [AIH]) with or without cirrhosis and hepatocellular carcinoma (HCC). Patients with CLD, particularly those with cirrhosis, and liver transplantation (LT) recipients infected with SARS-CoV-2 have been reported to have a higher risk of adverse outcomes than the general population. For example, among 2780 individuals with COVID-19 in the United States, comparison between 250 individuals with liver diseases *vs* the rest of the cases indicated a significantly higher mortality rate in those with liver disease (hazard ratio [HR], 2.8; 95% confidence interval [CI]; 1.9 to 4.0) and a higher mortality risk in those with cirrhosis (HR, 3.0; 95%CI; 1.5 to 6.0)[7]. In a recent study, the mortality rate of cirrhotic patients with COVID-19 was significantly higher than that of non-cirrhotic patients (HR, 2.38; 95%CI,

2.18 to 2.59), and was also increased in cirrhotic patients with underlying CLD (HR, 3.31; 95%CI, 2.91 to 3.77)[8]. Therefore, patients with CLD are considered to be at an increased risk of SARS-CoV-2 infection and worse outcomes. Given the increased rates of severity and mortality in patients with liver disease, there is an urgent need to understand the efficacy and safety of vaccination, as well as the importance of aggressive vaccination in this population. However, since most of the phase 2/3 trials of COVID-19 vaccines mainly recruited healthy individuals, data regarding the efficacy and safety in patients with liver diseases is limited. Presently, the results of several clinical trials for measuring the efficacy and safety of the available COVID-19 vaccines in patients with CLD have been reported.

The safety profiles of each vaccine have also been extensively studied. Common side effects of COVID-19 vaccines include injection site pain, transient fever, headache and fatigue[9,10]. Recently, however, several organ specific or systemic immune-mediated side effects following COVID-19 vaccination have also been reported[11]. These side effects include immune-mediated liver injury resembling AIH.

In this review, we summarized the current knowledge, focusing on the impact of COVID-19 in patients with liver disease, as well as the efficacy and safety of COVID-19 vaccination in these patients. In addition, we analyzed case reports of acute liver injury following COVID-19 vaccination.

OVERVIEW OF COVID-19 VACCINES

Vaccines against SARS-CoV-2 can be categorized based on the platform they are developed on into mRNA, viral vector, inactivated virus, attenuated virus, protein subunit, and recombinant DNA vaccines. The major COVID-19 vaccines currently used worldwide include the vaccines produced by Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca[6]. These, plus the CoronaVac vaccine (Sinovac Biotech) and Janssen-Ad26.COV2.S vaccine (Johnson & Johnson), are the five vaccines registered in the WHO Emergency Use Listing (EUL) of Qualified Vaccines (Table 1)[12]. Various COVID-19 vaccines have been proven to be highly effective and have good safety profiles in

healthy populations. The efficacy of vaccines is evaluated based on their (1) immunogenicity, (2) efficacy rate in clinical trials, and (3) real-world efficacy rate.

mRNA vaccines

The BNT162b2 mRNA (Pfizer-BioNTech) and mRNA-1273 mRNA (Moderna) vaccines are based on mRNA encoding SARS-CoV-2 spike proteins[13]. The injected mRNA is internalized into local host cells and translated, resulting in the production of antigen proteins and antigen-specific immune responses[14,15]. mRNA based vaccines have been shown to be safe and well tolerated in clinical trials. The BNT162b2 mRNA vaccine was administered to healthy adults (18-55 and 65-85 years old) at doses of 10 μg, 30 μg, or 100 μg in a phase 1/2 trial and showed immunogenicity, tolerability, and safety profiles consistent with these doses[16,17]. A phase 3 study of 43,548 individuals also showed an efficacy rate of 95% (95%CI, 90.3 to 97.6; 8 cases of COVID-19 [0.04%] of 21720 in the BNT162b2 group *vs* 162 cases of COVID-19 [0.75%] of 21,728 in the placebo group)[18], and a 6-month follow-up of 44,616 adults aged 16 years and older and 2,264 participants aged 12 to 15 years showed an efficacy rate of 91.3% (95%CI, 89.0 to 93.2)[19]. The mRNA-1273 vaccine also showed an efficacy of 94.1% (95%CI, 89.3 to 96.8; 11 cases of COVID-19 [0.07%] of 15210 in the mRNA-1273 group *vs* 185 cases of COVID-19 [1.22%] of 15210 in the placebo group) in a phase 3 study of 30,420 healthy individuals aged 18 or above[20]. It should be noted, however, that the efficacy against the recent epidemic Omicron strain is reduced for both these mRNA vaccines. Neutralizing antibody titers 3 wk after two doses of the BNT162b2 vaccine were significantly lower for the Omicron strain compared with the Wuhan strain[21], and even with the mRNA-1273 vaccine, neutralizing antibody titers against the Omicron strain after two doses of the vaccine were 1/41 to 1/84 of those against the European strain[22]. On the other hand, it was also shown that the neutralizing antibody titer against the Omicron strain increased significantly after the third dose of both vaccines and was almost equivalent to that after two doses[21,22], and the booster dose of mRNA vaccines was also effective against the Omicron strain, with a good efficacy rate of 60 to 70%[23].

Viral vector vaccines

The ChAdOx1 nCoV-19 vaccine (AZD1222), which was developed by Oxford-AstraZeneca, is a viral vector vaccine. Immunity to the spike protein is induced by administration of a chimpanzee adenovirus vector containing the SARS-CoV-2 spike protein gene[24]. A clinical trial of ChAdOx1 nCoV-19 reported an efficacy of 62.1% (95%CI, 41.0 to 75.7; 27 cases of COVID-19 [0.6%] of 4440 in the ChAdOx1 nCoV-19 group *vs* 71 cases of COVID-19 [1.6%] of 4455 in the control group)[25]. The efficacy of Ad26.COV2.S, a single-dose viral vector vaccine produced by Johnson & Johnson, has also been reported. In a phase 3 study, vaccine efficacy after 28 days was 52.9% (95%CI, 47.1 to 58.1; 433 cases of COVID-19 of 19113 [2.3%] in the Ad26.COV2.S group vs. 883 cases of COVID-19 of 18924 [4.7%] in the placebo group)[26,27]. Inactivated vaccines

Sinovac-CoronaVac is an inactivated vaccine developed by Sinovac Life Sciences and is being used in several countries. Its efficacy and safety were demonstrated in a phase 1/2 study by Zhang *et al* and the phase 3 study of Tanriover *et al*[28,29]. In a population aged 18-59 years, CoronaVac was shown to be highly effective in preventing symptomatic COVID-19 (83.5% vs. placebo) and COVID-19-related hospitalizations (100%) at least 14 days after the second dose[29].

IMPORTANCE OF COVID-19 VACCINATION IN PATIENTS WITH LIVER DISEASES

During the COVID-19 pandemic, many cases have been accumulated and the clinical course of COVID-19 in patients with CLD has been characterized. Patients with CLD, including those with cirrhosis or HCC, and LT recipients, are a high-risk group for severe COVID-19[30]. In a large cohort study using electronic health record data from more than 17 million patients in the United Kingdom, which included more than 0.1 million patients with CLD, CLD was a risk factor for death from COVID-19 (HR: 2.39; 95%CI, 2.06 to 2.77)[31]. A particularly high mortality rate due to COVID-19 has been reported in patients with cirrhosis[7,8,32], and recent prospective data from a multicenter study reported a high mortality rate of 32% among 729 patients with CLD from 29

countries. In particular, patients with decompensated cirrhosis were found to be at a higher risk of hospitalization, mechanical ventilation and death (overall mortality: Child-Pugh-A: 19%, Child-Pugh-B: 32%, Child-Pugh-C: 51%, non-cirrhosis: 8%)[33]. Similarly, in a North American multicenter cohort study, compensated cirrhosis had no effect on mortality in COVID-19, while mortality was increased in patients with decompensated cirrhosis[34]. Furthermore, cirrhotic patients with COVID-19 had a significantly higher mortality rate than patients with COVID-19 alone (30% vs. 13%, *P* = 0.03) in a multicenter cohort study in the US and Canada[35]. Patients with CLD, particularly those with cirrhosis, have multiple mechanisms of immune dysfunction that can lead to increased susceptibility to SARS-CoV-2 infection and an abnormal inflammatory response during infection. Thus, it has become clear that liver cirrhosis patients are at an increased risk of adverse COVID-19 outcomes, including death, as has been established by large observational cohorts and population-level data and international registry findings.

In addition to cirrhosis, NAFLD, alcoholic liver injury, and HCC are known to be factors affecting COVID-19 severity. Several observational cohort studies revealed a significant increase in the risk of severe COVID-19 in patients with NAFLD. In a Chinese study analyzing 202 COVID-19 cases, NAFLD complications were significantly more frequent in 39 patients whose disease progressed after hospitalization than in non-progressors (87.2% vs. 25.8%), and the rate of severe disease was significantly higher in patients with NAFLD than in those without NAFLD (44.7% vs. 6.6%)[36]. A meta-analysis by Pan *et al* showed that NAFLD was associated with more severe COVID-19 (odds ratio [OR], 2.93; 95%CI, 1.87 to 4.60)[37]. Two other meta-analyses have also been reported, both of which showed that NAFLD is a severity factor for COVID-19[38,39]. Patients with NAFLD have decreased hepatic innate immunity with skewed M1/M2 macrophage polarization, as well as increased levels of inflammatory mediators and cytokines. This underlying inflammatory status associated with NAFLD might lead to further exacerbation of the SARS-CoV-2 infection and can lead to a cytokine storm, which greatly increases the mortality rate[37]. Furthermore, it should be noted that

diabetes mellitus, obesity, and cardiovascular diseases are also frequently present in the background of NAFLD, and these metabolic disorders might also be factors related to the increased mortality of COVID-19. Regarding alcoholic liver disease, Marjot *et al* reported that it is an independent risk factor for COVID-19 related death (OR, 1.79; 95%CI, 1.03 to 3.13)[33], and Kim *et al* also reported a 2.4-fold increase in COVID-19 mortality (HR, 2.42; 95%CI, 1.29 to 4.55) in these patients[34]. Their report also showed that HCC is a risk factor for death from COVID-19 (HR, 3.96; 95%CI. 1.74 to 8.98)[34]. Since HCC often occurs secondary to cirrhosis, the greater severity of COVID-19 in this patient group is thought to be a result of reduced immunity. Since LT recipients are required to use immunosuppressive agents for a long period of time, they are also considered to be a high-risk group for severe COVID-19. However, many reports from actual cohort studies concluded that liver transplantation is not an independent risk factor for COVID-19 related death[40-42]. Webb *et al* compared mortality in 151 COVID-19 patients who underwent LT with 627 healthy subjects without LT, and reported no difference in overall mortality between the two groups (absolute risk difference 1.4%; 95%CI, 7.7 to 10.4)[43]. On the other hand, their study also reported that gastrointestinal symptoms, such as diarrhea, but not respiratory symptoms, were significantly increased in post-LT patients affected by COVID-19 (30% *vs* 12%, P < 0.0001)[43]. In addition, a report from the European Liver Transplant Association (ELITA) of 103 LT recipients affected by COVID-19 showed a significantly higher mortality rate in recipients older than 60 years[44]. Thus, since patients with CLD, especially those with cirrhosis, are a high-risk group for severe COVID-19, aggressive vaccination of this patient group is most important for the effective management of SARS-CoV-2 infection.

EFFICACY AND SAFETY OF COVID-19 VACCINES IN PATIENTS WITH LIVER DISEASES

Given the increased severity and mortality rates of COVID-19 in patients with liver disease, we need to understand the efficacy and safety of vaccination in this population.

However, data regarding the efficacy and safety of COVID-19 vaccination in patients with CLD is limited. Previous studies on vaccine efficacy and safety in patients with liver disease that have been reported to date are shown in Table 2[45-65]. It should be noted that most of the reports in Table 2 do not take into account the influence of the omicron variant, which is a limitation of using previous data in the current clinical environment of omicron variant predominance.

Response to vaccination in liver cirrhosis patients

Given the higher COVID-19 related mortality in individuals with decompensated cirrhosis, it is important to prioritize vaccination in this group. Patients with cirrhosis have previously shown hyporesponsiveness to hepatitis B virus and pneumococcal vaccines[66,67], and were also considered to be less responsive to COVID-19 vaccines[68]. Indeed, cirrhosis has been reported to be a high-risk factor (3.0-fold) for COVID-19 related deaths after COVID-19 mRNA vaccination in a large UK cohort study. A defect in acquired immunity in patients with cirrhosis probably predicts a low response to vaccination in this patient population[69]. However, a recent study in the United States found that 75% of CLD patients without cirrhosis and 77% of those with cirrhosis had adequate antibody responses to COVID-19 vaccination[46]. In that study, antibody responses to the BNT162b2 mRNA vaccine and mRNA-1273 mRNA vaccine were favorable (64.4% and 76.4%, respectively), whereas those to the Ad26.COV2.S vaccine (Johnson & Johnson) were low (15.8%). In a study analyzing the immune response of 110 patients with cirrhosis after two doses of the BNT162b2 mRNA vaccine, while the antibody initial acquisition rate was 96%, which was not significantly different from that in the control group (99%) ($P = 0.04$), the antibody titer showed a rapid and significant reduction in patients with cirrhosis[48]. This suggests that although the initial results after vaccination with the COVID-19 BNT162b2 vaccine are favorable in patients with cirrhosis, it should be noted that the antibody response deteriorates rapidly over time, and, hence, the timing of the booster shot needs to be addressed in the near future. The immunogenicity of COVID-19 vaccines in patients with cirrhosis appears to be inferior to that in healthy individuals, although real-world cohort studies showed that

BNT162b2 mRNA and mRNA-1273 vaccines reduce the development of COVID-19 infection by 64.8% after the first dose and 78.6% after the second dose[45]. Furthermore, a recent report on BNT162b2 mRNA, mRNA-1273, and Ad26.COV2.S vaccines has shown significantly reduced COVID-19-related mortality in vaccinated patients with cirrhosis (HR, 0.21; 95%CI, 0.11 to 0.42)[70]. In the report on the Sinovac-CoronaVac vaccine, the immunogenicity in patients with CLD was lower (77.3%) compared to that in healthy controls (90.3%), although the presence or absence of cirrhosis in CLD patients did not affect the antibody retention rate (non-cirrhotic CLD [76.8%], compensated cirrhosis [78.9%], and decompensated cirrhosis [76.7%]). The safety in each group was as good as in healthy controls in that report (healthy controls [16.0%], non-cirrhotic CLD [15.5%], compensated cirrhosis [16.3%], and decompensated cirrhosis [20.0%])[50]. In a study examining the efficacy of the Ad26.COV2.S vaccine, the vaccine efficacy in patients with cirrhosis was 64% (OR 0.36; 95%CI, 0.20 to 0.62, P = 0.005), which was non-inferior to the results of a phase 3 trial[71]. Regarding safety, Cao et al reported that of 85 patients with decompensated cirrhosis who received at least one dose of a SARS-CoV-2 vaccine, only one patient (1.2%) had an adverse reaction requiring hospitalization[72]. Bakasis et al also reported that there was no significant difference in the safety of mRNA vaccines given to 87 patients with liver diseases including cirrhosis, and 40 controls[73]. The limitations of these studies[50,71-73], however, include a relatively small sample size of participants who received the vaccines and a short follow-up period. Research with larger sample sizes is, thus, required in the future. Hence, although each vaccine is slightly inferior in immunogenicity in patients with cirrhosis compared with healthy individuals, they can be safely used with adequate efficacy in patients with cirrhosis. However, there is insufficient data to allow recommendation of one vaccine over another. Liver Transplantation (LT) COVID-19 outcomes in LT recipients are not necessarily worse than those in the general population, although they have a higher rate of admission to the intensive care unit.

Thus, COVID-19 vaccination should be prioritized for these patients, since the benefits far outweigh the potential risks. Vaccination for LT recipients is an interesting area of research, with a series of reports on its efficacy and safety. Several reports of low humoral and cellular responses after COVID-19 vaccination in LT recipients suggest that vaccine-induced immunity in this patient subgroup is lower than in the general population. As shown in Table 2, LT recipients exhibit significantly attenuated humoral and cellular immunity 2 wk after mRNA vaccination compared to healthy individuals[56,58], lower seroconversion rates[59] and significantly lower immunogenicity[51]. Indeed, combination immunosuppressive therapy, including mofetil mycophenolate, is reportedly a predictor of reduced responsiveness to vaccination[55,58,59]. The results of such vaccine responses in LT recipients were similar to the results of other studies in kidney transplant recipients[74], lung transplant recipients[75], and allogeneic hematopoietic stem-cell transplant recipients[76]. On the other hand, a recent multicenter cohort study showed that mRNA vaccines reduce SARS-CoV-2 infection rate, occurrence of symptomatic COVID-19, and mortality in LT recipients as well as in patients with cirrhosis[70]. While the immunogenicity of mRNA vaccines in LT recipients appears to be attenuated compared with that in healthy individuals, the disease status of COVID-19 is greatly attenuated in vaccinated LT recipients compared to unvaccinated recipients. Additionally, the value and safety of routine immunization in liver transplant recipients has been well established, and current guidelines recommend pre-transplant vaccination whenever possible[77]. However, since LT recipients also show a rapid decrease in antibody titers after mRNA vaccination[59], and because booster doses are reportedly extremely safe in post-organ transplant patients [78], it is recommended that all LT recipients receive a third or fourth booster dose if they have low or insufficient antibody titers[47].

Hepatocellular Carcinoma (HCC)

HCC patients are considered a high risk group for severe COVID-19[34]. Nevertheless, there are no cohort studies investigating the immunogenicity and safety of COVID-19 vaccines in patients with HCC. According to the American Association for the Study of

Liver Diseases (AASLD), patients with HCC receiving locoregional or systemic therapy should also be considered for vaccination without interruption of treatment[79]. Most patients treated for solid tumors, including HCC, show an adequate humoral response against SARS-CoV-2 after two vaccine doses. However, vaccination during chemotherapy tends to be associated with lower antibody levels, resulting in a suboptimal response in a small percentage of patients[80,81]. Furthermore, the concentration of neutralizing antibodies decreases over time, further reducing immunity[82]. Based on these reports, many countries are prioritizing a third vaccine dose in patients with solid tumors.

Viral Hepatitis and NAFLD

With regard to viral hepatitis and NAFLD, several cohort studies evaluating the efficacy of inactivated vaccines have been reported from China. Xiang T *et al* analyzed the seroprevalence of anti-spike protein antibodies and neutralizing antibodies in chronic hepatitis B (CHB) patients who received two doses of inactivated vaccines, and reported high seropositivity rates of 87.2% and 74.5%, respectively[61]. This report showed that nucleotide analog therapy has no effect on vaccine-induced immune responses, suggesting that vaccination should be performed even during treatment of CHB. He *et al* also reported that seroconversion rates of SARS-CoV-2 antibodies after 1, 2, and 3 mo in patients with CHB who received an inactivated vaccine were comparable to those in healthy controls[62]. No serious adverse reactions were reported in either study. Next, in a multicenter study of the safety and immunogenicity of inactivated vaccines in 381 individuals with NAFLD, the incidence of adverse reactions within 7 days and 28 days after vaccination was 24.9% and 29.4%, respectively. Neutralizing antibodies were detectable in 364 (95.5%) patients, and titers of neutralizing antibodies were shown to persist for a long time[63]. Given that NAFLD is a risk factor for severe COVID-19[37-39], active vaccination of this patient population would be ideal.

Autoimmune Hepatitis (AIH)

There have been two reports on the immunogenicity of COVID-19 vaccines in patients with AIH. Duengelhoef *et al* reported that 91 of 94 (97%) AIH patients who received the

second dose of a vaccine achieved seroconversion, although AIH patients showed impaired spike-specific T-cell responses and lower antibody levels at 7 mo compared with healthy individuals or patients with primary biliary cholangitis (PBC)/ primary sclerosing cholangitis (PSC) (641 vs. 1020 vs. 1200 BAU/mL, respectively). These results were not related to the use of immunosuppressive medications, suggesting that the underlying immune abnormality of AIH might be involved in this diminished response[64]. In addition, a study that followed the antibody responses after mRNA vaccination in patients with AIH and healthy controls showed that anti-SARS-CoV-2 antibodies were sufficiently produced after the second and third vaccinations in both groups[65]. Therefore, early booster doses of vaccines should be considered in patients with AIH. Although none of the patients in these reports had serious adverse reactions, it is noteworthy that several case reports have been published reporting an increased risk of developing AIH-like syndromes after SARS-CoV-2 vaccination.

LIVER INJURY AFTER COVID-19 VACCINATION

Adverse effects of COVID-19 vaccines Vaccination in patients with liver diseases is generally considered safe and effective and should be strongly recommended. The common side effects of COVID-19 vaccination include injection site pain, fever, headaches, and fatigue. All these side effects are mild and typically resolve 1-3 days after vaccination. However, recent worldwide dissemination of COVID-19 vaccines and post-marketing surveillance have led to an increasing number of reports of several organ-specific immune-related diseases, including myocarditis, immune thrombotic thrombocytopenia, Guillain-Barré syndrome, and pancreatitis, among others[11,83-85]. It is speculated that an abnormal immune response following vaccination is involved in the development of such diseases. Acute liver injury was not previously reported in clinical trials on COVID-19 vaccination because the sample size was insufficient to detect rare adverse events after vaccination. Recently, a large-scale population-based study on acute liver injury occurring after COVID-19 vaccination was reported from Hong Kong. In that study,

among 2,343,288 COVID-19 vaccine recipients, acute liver injury within 56 days after the first and second vaccine dose occurred in 307 and 521 (335 and 334 per 100,000 person-years) individuals vaccinated with BNT162b2, and 304 and 474 (358 and 403 per 100,000 person-years) of those who received CoronaVac. The incidence of acute liver injury within 56 days of SARS-CoV-2 infection, on the other hand, was 32,997 cases per 100,000 person-years, indicating that the incidence of acute liver injury after COVID-19 vaccination was much lower than that after SARS-CoV-2 infection. It was also concluded that compared to the non-exposure period, no increased risk of acute liver injury was observed in the 56-day risk period following the first (IRR = 0.800; 95%CI, 0.680 to 0.942) and second (IRR = 0.944; 95%CI: 0.816-1.091) BNT162b2 dose, and the first (IRR = 0.689; 95%CI, 0.588 to 0.807) and second (IRR = 0.905, 95%CI; 0.781 to 1.048) CoronaVac dose. Thus, COVID-19 vaccines do not seem to increase the risk of acute liver injury[86]. However, since there have been case reports of acute liver injury requiring hospitalization after COVID-19 vaccination, this is an adverse effect that should not be overlooked. The current review aimed to increase awareness of this rare adverse effect to promote its early recognition. Review of case reports on liver injury after COVID-19 vaccination Since the summer of 2021, several case reports of liver injury after COVID-19 vaccination have been reported. The clinical and histological findings of most patients resembled AIH and the reported cases responded well to corticosteroid therapy. Previous cases of AIH-like acute liver injury after COVID-19 vaccinations are shown in Table 3[87-109]. Twenty-three reports (28 cases) of acute liver injury secondary to COVID-19 vaccines have been published in the PubMed database as of July 2022 (Table 3). The median age at the time of diagnosis was 61 (range 27-80) years, with a predominance of women (79%, females: 22, males: 6). Eight patients (29%) had no underlying disease, whereas nine patients (32%) had been diagnosed with other immune disorders (Hashimoto's disease: 5, primary sclerosing cholangitis: 2, primary biliary cholangitis: 1, sarcoidosis: 1). One patient was three months postpartum, and another patient was taking hormonal therapy due to menstrual irregularities. Liver injury occurred after

vaccination following the BNT162b2 vaccine in 11 (39%) of the cases, mRNA-1273 vaccine in nine (32%), ChAdOx1 nCoV-19 vaccine in seven (25%), and CoronaVac vaccine in one case (4%). Seventeen patients (61%) developed liver injury after the first dose, 10 patients (36%) after the second dose, and two patients (7%) after the booster shot. The median time from vaccination to the onset of acute liver injury was 11 (range 3-35) days. The most common symptom was jaundice, while other symptoms, such as fatigue and anorexia, were also frequently observed. The most common pattern of liver injury was hepatocellular injury, with transaminase levels exceeding 1000 U/L in many cases. The mean alanine aminotransferase (ALT) level was 848.2 (±465.0) U/L, mean aspartate aminotransferase (AST) level was 1031.5 (±578.3) U/L, and mean total bilirubin level was 9.08 (±5.76) mg/dL. Serum immunoglobulin G (IgG) levels were measured in 25 patients and were elevated in 22 patients (88%). Anti-nuclear antibodies (ANA) were positive in 22 (82%) of 27 patients, while anti-smooth muscle antibodies (ASMA) and anti-mitochondrial antibodies (AMA) were elevated in some cases. Liver biopsy was performed in all cases. According to the simplified international diagnostic criteria published by the International AIH-group (IAIHG), seven cases were "typical" of AIH and 20 cases were "compatible with" AIH. Only one patient had poor findings of typical AIH and was diagnosed with drug-induced liver injury. Steroids as first-line treatment were used in 26 of the patients (93%), of whom 10 received prednisone, 14 received prednisolone, one received budesonide, and one was given methyl-prednisolone intravenously. Azathioprine was concomitantly used in five patients. The overall outcomes with corticosteroid therapy were favorable, and improvement was seen in 27 patients (96%). Only one male patient reported from India progressed to liver failure and died despite five cycles of plasma exchange[99]. All of the patients developed acute liver injury soon after COVID-19 vaccination, with findings consistent with AIH on liver biopsy, and responded well to corticosteroids. These case reports strongly suggest that the association between vaccination and the onset of AIH-like liver injury might be more than coincidental. However, it is difficult to establish a causal relationship between vaccination and liver injury with certainty.

Indeed, post-pregnancy status, use of statins, and concomitant history of autoimmune diseases included in the reported cases are likely major confounding factors. It should be noted that almost all the reported cases lacked pre-vaccination laboratory data, and hence, the presence of pre-existing hepatitis cannot be ruled out. Indeed, Cao *et al* reported that a patient with vaccine-induced AIH had advanced fibrosis on liver biopsy, suggesting the presence of chronic liver disease prior to vaccination[110]. Furthermore, a large international case series that provided evidence for the hepatotoxic potential of COVID-19 vaccines has recently been reported[111]. In that study, data from 18 countries on 87 patients who developed liver injury after COVID-19 vaccination were retrospectively collected. The median age at diagnosis was 48 (range 18-79) years and 63% were female. The median time from vaccination to the onset of liver injury was 15 (range 3-65) days. Liver injury occurred after vaccination with BNT162b2 in 59% of the cases, mRNA-1273 in 18% and ChAdOx1 nCoV-19 in 23%. When elevated IgG and autoantibody positivity were used to define immune-mediated hepatitis, 57% of the patients had immune-mediated hepatitis. Corticosteroids were mainly used in cases of severe liver injury and immune-mediated hepatitis (53%). In this study, there was one case of liver failure requiring liver transplantation, while the remaining cases had a good prognosis. There were no differences in the severity of liver injury, the rate of immune-mediated hepatitis, or the rate of steroid usage depending on the type of vaccine. Responses to treatment and outcomes were favorable in all groups. These results were generally consistent with the characteristics of the previous case reports shown in Table 3. There is also a concern that hepatitis might be exacerbated by vaccination of patients originally diagnosed with AIH. Shroff *et al* reported that six of 16 patients who developed vaccine-induced liver injury previously had AIH. They concluded that hepatotoxicity could be induced after vaccination by autoimmune induction[112]. However, the number of patients described in previous reports[87-109] (Table 3) is extremely small compared with the overall vaccinated population worldwide. The current review, thus, aimed to increase awareness about this rare adverse effect in order

to promote its early recognition.

Mechanism of liver injury after COVID-19 vaccination

The mechanisms underlying the development of liver injury following COVID-19 vaccination remain unclear. As shown in Table 3, liver injury following COVID-19 vaccination is clinically and pathologically similar to AIH, suggesting that immune abnormalities associated with vaccination contribute to its development. However, the association between vaccines and the development of autoimmune diseases is controversial and most studies related to this have been inconclusive[113]. Molecular mimicry and bystander activation have been hypothesized as possible mechanisms by which vaccines can trigger autoimmune reactions. In the antigen-specific mechanism of molecular mimicry, it is hypothesized that similarities between certain pathogenic elements contained in the vaccine and specific human proteins cause cross-reactions. It is believed that the injurious antibodies produced by this mechanism destroy human proteins and cause organ damage[114]. In support of this hypothesis, it has been reported that antibodies against the spike protein of SARS-CoV-2 have cross-reactivity against many human tissue antigens[115]. Although the target antigen of the autoimmune response in hepatocytes and specific autoantibodies in AIH have not yet been identified, Vojdani *et al* reported that anti-SARS-CoV-2 protein antibodies cross-react with liver microsomal antigen, pyruvate dehydrogenase peptide E2 (PDC-E2), and mitochondrial M2 antigen[115]. It has also been shown that anti-SARS-CoV-2 spike protein antibodies cross-react with human tissue antigens, resulting in a marked increase in autoimmune markers such as ANA and AMA[116]. This suggests that COVID-19 vaccination might induce autoimmune reactions based on molecular mimicry in liver tissues, resulting in AIH-like liver injury (Figure 1). Bystander activation, on the other hand, is an antigen non-specific mechanism, in which self-antigens are released extracellularly by vaccination and are taken up by antigen-presenting cells. Then, autoreactive T cells are activated by type I interferon (IFN) and recognize the presented self-antigen, which is hypothesized to attack normal cells[117]. Bystander activation has also been proposed as one of the mechanisms of autoimmune

disease development after vaccination. Furthermore, there is a rapid increase in type I IFN expression and oxidative stress coupled with effective anti-SARS-CoV-2 neutralizing antibody production after vaccination in healthy individuals[118]. Therefore, the side effects of COVID-19 vaccines are thought to be only a by-product of a transient burst of type I IFN generation with induction of an effective immune response[119]. It has also recently been hypothesized that the COVID-19 vaccine triggers autoimmune diseases *via* induction of age-associated B cells (ABCs)[120]. The number of ABCs, a rare subset of B cells that express CD11c and T-bet, increases with age in healthy individuals, and is increased early in patients with infectious diseases and autoimmune disorders[121]. In the pathogenesis of autoimmune diseases, ABCs are implicated in generating immunoglobulin G, in increasing antigen presentation to T cells, and in germinal center formation. Moreover, ABCs are hyper-responsive to Toll-like receptor (TLR) 7 signaling, and are capable of generating autoreactive antibody-secreting plasmablasts. COVID-19 vaccines use TLR7/8 agonists as adjuvants, which might stimulate ABCs, leading to the triggering of post-vaccination autoimmune syndromes[122]. Activation of TLR7 can lead to the production of type I IFN, which is an important cytokine in the development of autoimmune disorders, such as rheumatic diseases and systemic lupus erythematosus[123]. It was previously shown in a mouse model that lipid nanoparticles (LNPs), which are one of the potent adjuvants of mRNA vaccines, could trigger inflammatory responses. This is characterized by activation of diverse inflammatory pathways, massive neutrophil infiltration, and production of various inflammatory cytokines, including the secretion of IL-1β and IL-6[11,124]. Hence, although several hypotheses have been considered for the mechanism of vaccine-induced autoimmune disease, the exact mechanism remains to be elucidated. In any event, only a very small percentage of vaccinated subjects subsequently developed autoimmune phenomena, suggesting a genetic predisposition to vaccine-induced autoimmune disorders. Further research into the direct associations between vaccines and autoimmune diseases, as well as the biological mechanisms behind them, is warranted.

DISCUSSION

+ADw-html+AD4APA-p+AD4-Since COVID-19 is an infectious disease with a high burden of morbidity and mortality, and that has resulted in a global pandemic, vaccination against COVID-19 is our best strategy for its control. For this, highly effective and safe vaccines are desperately needed. Although various COVID-19 vaccines have been proven to be highly effective and have good safety profiles in healthy populations, data regarding the efficacy and safety of vaccination in special population groups is limited. Thus, we believe it is worthwhile to summarize the efficacy and safety of the COVID-19 vaccines in patients with CLD. Based on the evidence from real-world studies, this review shows that vaccination in patients with CLD is effective and safe, and should be strongly recommended.+ADw-br /+AD4-As shown in Table 3, although a number of case reports of acute liver injury after COVID-19 vaccination have been reported, their frequency is extremely low. Thus, given the serious health sequalae from COVID-19 in patients with liver disease, the potential benefits of vaccination appear to outweigh the risk of vaccine-related liver injury. However, it is important to remember that most of the studies referred to in this review were conducted in the era before the emergence of new viral variants. Since new SARS-CoV-2 variants are still emerging all over the world, COVID-19 remains a global public health problem. In addition, since vaccines against the mutant viruses are still being developed, it will be necessary to continue evaluating the efficacy and safety of these new vaccines.+ADw-/p+AD4APA-/html+AD4-

CONCLUSION

+ADw-html+AD4APA-p+AD4-Given the increased rates of severity and mortality of COVID-19 in patients with CLD, especially those with cirrhosis, the importance of aggressive vaccination in the effective management of SARS-CoV-2 infection should be emphasized. However, there is insufficient evidence about the immunogenicity and safety of COVID-19 vaccines in patients with CLD. According to the accumulated real-

world data on each vaccine, the safety of COVID-19 vaccines in patients with CLD appears to be comparable to that in healthy individuals. Regarding efficacy, the disease behavior of COVID-19 is known to be attenuated in vaccinated compared with unvaccinated patients, including in those with CLD+ADs- however, vaccine-induced immunity seems lower in CLD patients as compared with the general population. Since a rapid decrease in acquired antibodies has also been observed in this patient population, an effective booster shot is desirable, particularly in patients with cirrhosis, LT recipients, and those with HCC.+ADw-/p+AD4-

+ADw-p+AD4-On the other hand, acute liver injury following COVID-19 vaccination has also been frequently reported. However, recent large cohort studies found no increased risk of liver injury after COVID-19 vaccines. Since acute liver injury after SARS-CoV-2 infection is much more common than after COVID-19 vaccination, the benefits of vaccination might outweigh the risk of liver injury during this pandemic. The reported rare immune-mediated liver injury after COVID-19 vaccination is clinically and pathologically similar to AIH. Although the involvement of abnormalities in the immune system, including molecular mimicry, bystander activation, and induction of ABCs in the pathogenesis of this condition have been pointed out, the relationship between vaccination and acute liver injury is an issue that remains to be clarified in the future. Finally, clinicians should consider the possibility of AIH-like liver injury in patients who present with elevated liver enzymes following COVID-19 vaccination, and treat it with corticosteroids.+ADw-/p+AD4APA-/html+AD4-

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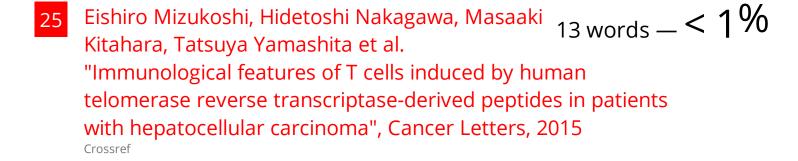Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease", Hepatology, 2021
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