Association between immunosuppressants and antibody responses to SARS-CoV-2 vaccines in patients with autoimmune liver diseases

Hu Li
The Second Affiliated Hospital of Chongqing Medical University
Yuting Wang
The Second Affiliated Hospital of Chongqing Medical University
Ling Ao
The Second Affiliated Hospital of Chongqing Medical University
Mingxia Ke
The Second Affiliated Hospital of Chongqing Medical University
Zhiwei Chen
The Second Affiliated Hospital of Chongqing Medical University
Min Chen
The Second Affiliated Hospital of Chongqing Medical University
Mingli Peng
The Second Affiliated Hospital of Chongqing Medical University
Ning Ling
The Second Affiliated Hospital of Chongqing Medical University
Peng Hu
The Second Affiliated Hospital of Chongqing Medical University
Dachuan Cai
The Second Affiliated Hospital of Chongqing Medical University
Dazhi Zhang
The Second Affiliated Hospital of Chongqing Medical University
Hong Ren (✉ renhong0531@cqmu.edu.cn)
The Second Affiliated Hospital of Chongqing Medical University

---

Research Article

Keywords: Severe acute respiratory syndrome coronavirus 2, Coronavirus disease 2019, Vaccine, Immunogenicity, Safety, Autoimmune liver diseases, Immunosuppressant, Neutralizing antibodies, Anti-RBD-IgG, memory B cells

Posted Date: June 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1739762/v1

Abstract

Background and aims: Little is known regarding the antibody responses of COVID-19 vaccination in patients with autoimmune liver diseases (AILD). We aim to evaluate the antibody responses and explore the impact of immunosuppressants on SARS-CoV-2 vaccines in AILD.

Methods: We conducted a prospective observational study and included participants been healthy as controls and AILD. All adverse events (AEs) were recorded. IgG antibodies against the receptor-binding domain (RBD) of spike protein (anti-RBD-IgG) and Neutralizing antibodies (NAbs) were tested after the COVID-19 vaccination. In addition, SARS-CoV-2 specific B cells were detected by flow cytometry.

Results: 76 patients and 136 healthy controls (HC) were included. All AEs were mild and self-limiting, and the incidences were similar between AILD and HC groups. The seropositivity rates of anti-RBD-IgG and NAbs in AILD were 97.4% (100% in HC, $p = 0.13$) and 63.2% (84.6% in HC, $p < 0.001$), respectively. The titers of anti-RBD-IgG and NAbs were significantly lower in AILD compared with HC. After adjusting for confounders, immunosuppressive therapy was an independent risk factor for the low-level anti-RBD-IgG (adjusted odds ratio [AOR]: 4.7; 95% confidence interval [CI], 1.5-15.2; $p = 0.01$) and reduced probability of NAbs seropositivity (AOR, 3.0; 95% CI, 1.0-8.9; $p = 0.04$) in AILD patients. However, regardless of immunosuppressants, the SARS-CoV-2 specific memory B cells responses were comparable between AILD and HC groups.

Conclusion: SARS-CoV-2 inactivated vaccine is safe, but its immunogenicity is compromised in patients with AILD. Moreover, immunosuppressants are significantly associated with poor antibody responses to the SARS-CoV-2 vaccine.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a significant global public health threat. To date, more than 528 million people have been diagnosed with COVID-19 and more than 6 million deaths were confirmed worldwide[1]. Numerous studies have shown that people with comorbidities, including chronic liver disease, are highly vulnerable and have worse outcomes from COVID-19 compared to those without liver disease [2–5]. Therefore, liver societies have recommended vaccination against SARS-CoV-2 for patients with chronic liver diseases [6, 7]. However, a series of case reports suggest that mRNA-based vaccines may induce autoimmune liver disease [8–16]. This has caused concern among hepatologists as well as patients with autoimmune liver disease (AILD) [17, 18].

AILD is a chronic immune-mediated liver disease, including a wide range of disorders such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and AIH-PBC overlap syndrome, which are frequently treated with either broad or targeted immunosuppressants. Moreover, some AILD patients are usually accompanied by other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome, which also require lifelong immunosuppressive drug therapy.

Existing data have shown that immunosuppressants can significantly reduce the antibody response to COVID-19 mRNA vaccines or Johnson & Johnson vaccine in liver transplant patients [19], and immune-mediated inflammatory disorders [20, 21].

In China, inactivated vaccines (BBIBP-CorV or CoronaVac) are widely used COVID-19 vaccines. Systematic evaluation of these vaccines' safety and immunogenicity in people with AILD has been rare. Here, we aim to evaluate the safety, antibody responses after the whole-course COVID-19 vaccination and explore the association between immunosuppressants and antibody responses to inactivated SARS-CoV-2 vaccines in patients with AILD.

Patients And Methods

Study design and participants

Between July 1, 2021, and September 30, 2021, we did a prospective observational study in the Second Affiliated Hospital of Chongqing Medical University, China. We included participants aged older than 18 years, diagnosed with any of the prespecified immune-mediated liver disorders (AIH, PBC or AIH-PBC overlap syndrome) [22-24], no SARS-CoV-2 infection before receipt of the first vaccine dose (determined based on either a negative anti-SARS-CoV-2 IgM/IgG test or the absence of a positive polymerase-chain-reaction assay result for SARS-CoV-2, with no history of suspected clinical SARS-CoV-2 infection), completed whole-course COVID-19 vaccination (2 doses of BBIBP-CorV or CoronaVac vaccine), and were able to understand and complete questionnaires. Healthy participants were included as healthy controls (HC). Participants with known pregnancy during study entry, not complete the full course of vaccination, and those who provided incomplete vaccination information (including the date of first vaccine dose and complete vaccination, and vaccine manufacturers) were excluded. Blood samples were collected for serological assays for SARS-CoV-2 at least 21 days after the whole-course vaccination from AILD patients and HC.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and accorded with the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants. This study has been registered at ClinicalTrials.gov (NCT05007665).

Variables and definitions

Clinical characteristics including age, gender, body mass index (BMI), comorbidities, history of diseases and concomitant medications of all patients were collected via a standardized questionnaire. The presence or absence of cirrhosis was confirmed using clinical or biochemical evidence, Fibroscan, liver imaging (ultrasound, CT, or MRI) and endoscopy. The concomitant medications, especially types and doses of immunosuppression, were further confirmed through the prescribing information system in the hospital.

All adverse events (AEs) within 7 days and 30 days after COVID-19 vaccination were recorded and graded according to the National Medical Products Administration of China (version 2019). AEs related to vaccination were judged by investigators. Safety was evaluated by determining the overall incidence of AEs.

SARS-CoV-2 antibody test

The SARS-CoV-2 antibody against spike protein receptor-binding domain (anti-RBD-IgG) was detected by indirect ELISA method using the SARS-CoV-2 RBD antibody detection kit (Sino Biological, Beijing, China). The lower limit of quantification is 5.0 arbitrary units per mL (AU/mL). The neutralizing antibodies (NAbs) were detected by the competitive ELISA method using the SARS-CoV-2 neutralizing antibodies detection kit (Sino Biological, Beijing, China). The details were described in our previous study [25].

SARS-CoV-2 specific B cells responses

For SARS-CoV-2 specific B cells detection, biotinylated SARS-CoV-2 spike RBD protein (Sino Biological, 40592-V08H2-B) was mixed with Streptavidin BV421 (Biolegend, 405225) at 4:1 molar ratio for one hour at 4℃ to obtain the antigen probe. According to the manufacturer's instruction, peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood by Histopaque (Sigma-Aldrich, 10771) density gradient centrifugation. After washed by FACS buffer (PBS、2% FBS), PBMCs were then stained for 30 minutes at 4℃ using antigen probe (1:33.3) and the following conjugated antibodies: anti-human CD3 (300430, Biolegend, 1:50), anti-human CD19 (302212, Biolegend, 1:50), anti-human CD21 (354918, Biolegend, 1:50), anti-human CD27 (356406, Biolegend, 1:50), anti-human IgG Fc (410722, Biolegend, 1:50), and anti-human IgM (314524, Biolegend, 1:50). After staining, cells were rewashed and resuspended in a 200ul FACS buffer. Samples were then evaluated by flow cytometry (Beckman Coulter, CytoFLEX) and analyzed using FlowJo (Treestar, 10.0.7r2).

Statistical analysis

Data are presented as median (interquartile range, IQR) for continuous variables and proportions for categorical variables. Continuous variables were compared using Student’s t-test for the variables of age and BMI. Categorical variables were compared using Fisher’s exact test or Chi-square test for gender, cirrhosis, comorbidities, immunosuppressant, and vaccine types. The one-way analysis of variance (ANOVA) was used to compare the results of multiple groups, and Tukey's correction was used to correct for comparisons between groups. The poor antibody response was defined as the anti-RBD-IgG titer being less than the median value (≤ 34.0 AU/ml) or negative for NAbs. Multiple logistic regression was used to explore the independent variables associated with poor antibody responses and presented as odds ratio (OR) (95% confidence interval, CI) with adjustment for potential confounding factors. Statistical analysis was performed using EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) and R (http://www.Rproject.org, the R Foundation). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Characteristics of participants

76 eligible AILD patients and 136 HC were included in the study. The characteristics of participants are shown in Table 1. Briefly, the median age was 54.0 years (IQR: 48.8-60.2 years) in AILD patients and 52.0 years (IQR:33.0-62.2 years) in the HC group. The majority of participants were female (85.5% [65/76] in AILD patients and 55.1% [75/136] in HC). The median BMI and proportion of vaccine types in AILD patients and HC were similar (22.5 kg/m^2 [IQR: 21.2-23.9 kg/m^2] vs. 22.9 kg/m^2 [IQR: 21.1-25.3 kg/m^2]). The median post-vaccination time was 41.5 days (IQR: 29.0-66.2 days) and 55.0 (IQR: 33.0-86.5 days) for the AILD patients and HC. Additionally, among these AILD patients, 20 (26.3%) had cirrhosis and almost half (46.1%, 35/76) received one or more immunosuppressant medications.

COVID-19 vaccination safety

The overall incidence of AEs within 7 days (25.0% [19/76] vs 17.6% [24/136]) and 30 days (25.0% [19/76] vs 17.6% [24/136]) after COVID-19 vaccination were slightly higher in AILD patients than in HC group (p = 0.20) (Table 2). All AEs were mild and none of them had any serious AEs. The common AEs in AILD patients in local AEs were pain at the injection site (4.0%, 3/76); in systemic AEs were fatigue (5.3%, 4/76) and headache (5.3%, 4/76). The most common AEs in HC was local pain at the injection site (8.1%, 11/136) (Table 2). Notably, one patient increased serum gamma-glutamyl-transpeptidase (GGT) level from 20 U/L to 90 U/L (upper limit of normal: 45 U/L) after vaccination and returned to normal after continuing the original treatment strategy during the following up. Another patient's antinuclear antibody (ANA) was positive at a titer of 1:320 before vaccination. It increased to 1:1000 after vaccination, but the liver function test, serum IgG, anti-liver-kidney microsomal, anti-smooth muscle, anti-mitochondrial antibodies, and anti-soluble liver antigen were normal, and the patient had no symptoms of discomfort.

Antibody responses after COVID-19 vaccination

The seropositivity for anti-RBD-IgG was 97.4% (74/76) in AILD patients, which was similar with HC group (100%) (p = 0.13) (Figure 1A). However, anti-RBD-IgG levels were significantly lower in AILD patients than in HC (mean: 49.1 AU/mL vs 71.9 AU/mL, p = 0.02) (Figure 1B). Regarding NAbs, seropositivity (63.2% [48/76] vs 84.6% [115/136]) and antibody titers were both significantly lower in AILD patients than in HC group (p < 0.001) (Figure 1D, 1E). Compared with controls, anti-RBD-IgG and NAbs levels seem to decrease slightly over time since the second dose vaccination in AILD patients (Figure 1C, 1F).

Effect of immunosuppressants on antibody responses

Analysis of clinical features showed no significant correlations between poor antibody responses and parameters such as age, sex, BMI, cirrhosis, and comorbidities (all p > 0.05) (Table 3). However, low-level antibodies were significantly related to the types of vaccine (p = 0.01) (Table 3, Supplementary figure 1A) and the use of immunosuppressants (p = 0.04) (Table 3, Supplementary figure 1C). Furthermore, after

adjusting for potential confounding factors (age, BMI, gender, cirrhosis, comorbidities, types of vaccine, and days between final dose and antibody test) in multiple logistic regression analysis, the use of immunosuppressants remained significantly related to low-level antibody levels (Table 4). Compared with patients with no immunosuppression medication, the crude odds ratio (OR) of low-level antibody response risk among patients who used immunosuppressants was 3.3 (95% CI, 1.3-8.5; p = 0.01), and their adjusted OR (AOR) increased to 4.9 (95% CI, 1.5-15.6; p = 0.01). Notably, the risk trend does not seem to increase with the number of immunosuppressants. The AOR of use of one and more immunosuppressive medications were 5.0 (95% CI, 1.1-23.1; p = 0.04) and 4.9 (95% CI, 1.1-19.2; p = 0.03), respectively.

Similar results were also observed for NAbs responses in the AILD patients. Negative NAbs were significantly associated with the types of vaccine (p = 0.01) (Supplementary figure 1B) and immunosuppressants (p = 0.02) (Supplementary figure 1D), except for age, gender, BMI, cirrhosis, and comorbidities (Table 3). After adjusting for confounding factors, the immunosuppressant was associated with a reduced probability of NAbs seropositivity (AOR, 3.0; 95% CI, 1.0-8.9; p = 0.04), especially when the use of ≥2 immunosuppressive medications (AOR, 4.4; 95% CI, 1.3-15.3; p = 0.02) (Table 4).

Our study suggested that immunosuppressive therapy was an independent risk factor for the poor antibody responses to COVID-19 vaccination in patients with AILD.

Specific B cells responses after COVID-19 vaccination

To furtherly investigate the humoral immune response to the SARS-CoV-2 vaccine, the frequency and phenotype of specific B cells were also detected. As expected, the percentage of specific B cells was very low in the peripheral blood of AILD patients and the HC group. No significant difference was found in the frequency of RBD-specific B cells ($CD3^-CD19^+RBD^+$) and IgG RBD-specific memory B cells (MBCs) ($IgG^+CD3^-CD19^+RBD^+CD27^+$) between AILD and HC groups, regardless of immunosuppressants (Figure 3A, 3B). However, the frequency of IgM RBD-specific MBCs ($IgM^+CD3^-CD19^+RBD^+CD27^+$) was significantly lower in AILD patients with (17.2% vs 25.3%, adjusted p < 0.01) or without immunosuppressant (19.4% vs 25.3%, adjusted p = 0.03) than HC group (Figure 3C). To better understand the functional phenotype of the RBD-specific MBCs, we further compared RBD-specific resting MBCs ($CD3^-CD19^+RBD^+CD21^+CD27^+$), RBD-specific activated MBCs ($CD3^-CD19^+RBD^+CD21^-CD27^+$), RBD-specific atypical MBCs ($CD3^-CD19^+RBD^+CD21^-CD27^-$), and RBD-specific intermediate MBCs ($CD3^-CD19^+RBD^+CD21^+CD27^-$) in between AILD patients and HC groups. Compared with HC, AILD patients without immunosuppressants had a lower frequency of RBD-specific activated MBCs (13.0% vs 16.9%, adjusted p = 0.03) and a higher frequency of RBD-specific intermediate MBCs (47.1% vs 39.9%, adjusted p = 0.02), but not in patients with immunosuppressant. Moreover, there was no significant difference in RBD-specific resting MBCs and RBD-specific atypical MBCs between AILD patients and the HC groups (Figure 3). These results indicate that patients with AILD may develop the humoral immunity as robust as in a healthy population when receiving a booster dose or against SARS-CoV-2 infection despite ongoing immunosuppression.

Discussion

AILD is a chronic disease characterized by immune-mediated disorders. Safety and immunogenicity have been of concern in patients with AILD since the vaccination against COVID-19. In this prospective observational study, we found that the inactivated SARS-CoV-2 vaccines achieve a favorable safety profile, but their immunogenicity is compromised in patients with AILD. The use of immunosuppressants has an estimated 3-5 fold increased risk of poor antibody responses to the SARS-CoV-2 vaccine. Moreover, the specific MBCs responses were comparable between patients in AILD and HC groups despite ongoing immunosuppression.

Similar to the general population and the other chronic liver diseases, such as NAFLD, liver transplantation, chronic hepatitis B, and liver cirrhosis, adverse events related to the COVID-19 vaccine in patients with AILD were mild and self-resolved within a few days after vaccination [19, 26-28]. However, post the whole-course vaccination, one patient experienced an increased serum GGT level and another experienced a sharp increased ANA titer. Because they refused liver biopsy, it is unclear whether this phenomenon reflects the fluctuation of the disease itself or vaccine induces the new-onset autoimmune diseases. Fortunately, we have not seen any clinical evidence of disease deterioration in these two patients during follow-up over 6 months. Therefore, based on these results, we believe that the COVID-19 inactivated vaccine is safe in patients with AILD.

During the AILD patients, COVID-19 inactivated vaccine showed an efficient antibody response of anti-RBD-IgG (97.4%). It was similar in a multicenter study of NAFLD patients in China (95.5%) but much higher than the reported seropositivity of SARS-CoV-2 RBD-specific antibodies in patients with chronic hepatitis B virus infection who were also vaccinated with the inactivated COVID-19 vaccines (87.25%) [27, 28]. The possible explanation for the difference is that more female patients were included in our study (85.5% vs 27.5%). Xiang *et al.* found that female patients exhibited higher seropositivity for SARS-CoV-2 RBD-specific antibodies than males with chronic hepatitis B (95.1% vs 84.3%) [28]. A similar finding that female vaccine recipients showed more robust antibody responses to COVID-19 vaccination was also reported in a clinical trial in Turkey [26]. Similar to chronic hepatitis B, the NAbs seropositivity was lower than anti-RBD-IgG in patients with AILD. We found that immunosuppressants have an estimated 3-5 fold increased risk of poor antibody responses to the SARS-CoV-2 vaccine. In a nationwide multicenter prospective cohort study of 125 patients with multiple sclerosis, Bsteh *et al*. reported that immunosuppressive therapy could significantly reduce the probability of NAbs seropositivity after symptomatic COVID-19 (OR, 0.51; 95% CI, 0.17-0.82) [29]. This finding might partly explain why the seropositivity and titer of NAbs in AILD patients are lower than those in HC.

This study found that the RBD-specific MBCs responses were comparable between patients with AILD and HC despite ongoing immunosuppression. It is consistent with Kirchner *et al*. in a small study that patients with AIH receiving immunosuppressive therapy still developed strong humoral and cellular immunity to SARS-CoV-2 [30]. Given the role of MBCs, it is speculated that patients with AILD may

develop the humoral immunity as robust as in a healthy population when receiving a booster dose or against SARS-CoV-2 infection.

There are several main limitations in this study. Firstly, a lack of longitudinal serial antibody testing limits the possibility of measuring a change in antibody levels intra-individually. Secondly, subgroup analysis was not performed due to the small sample size, such as the strength of immunosuppression and antibody responses. Thirdly, the antibody response is only part of the immunogenicity of the COVID-19 vaccine, so there is a need to explore T cell response. However, given the unprecedented nature of the COVID-19 pandemic and the low prevalence of AILD, we believe that our study offers valuable insights into the management of these patients to clinicians.

In conclusion, the COVID-19 inactivated vaccine is safe, but its immunogenicity is compromised in patients with AILD. In addition, immunosuppressive therapy is associated with poor antibody responses. For AILD patients, especially those receiving immunosuppressive therapy, it should be recommended for early determination of serum SARS-CoV-2 antibodies after the vaccination cycle, which will enable risk stratification and personalized management of patients with AILD.

Abbreviations

AEs, adverse events; AIH, autoimmune hepatitis; AILD, autoimmune liver disease; ANA, antinuclear antibody; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; GGT, gamma-glutamyl-transpeptidase; HC, healthy controls; IgG, immunoglobulin G; IQR, interquartile range; MBCs, memory B cells; NAbs, neutralizing antibodies; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Declarations

Acknowledgements

This work is supported by the National Science and Technology Major Project of China (2017ZX10202203-007, 2017ZX10202203-008, 2018ZX10302206-003) and a pilot project of clinical cooperation between traditional Chinese and western medicine for significant and complicated diseases of the National Administration of Traditional Chinese Medicine: hepatic fibrosis. We also acknowledge the support of the Kuanren Talents Program of the second affiliated hospital of Chongqing Medical University, the National Natural Science Foundation of China (81772198,81902068), Natural Science Foundation of Chongqing, China (cstc2020jcyj-msxmX0389).

Authors contributions

The authors Dachuan Cai, Dazhi Zhang and Hong Ren contributed to the conception and design, and critical revision of important intellectual content. Data collection was performed by Yuting Wang, Ling Ao,

Mingxia Ke, Zhiwei Chen, Min Chen, Mingli Peng, Ning Ling and Peng Hu. Statistical analysis was performed by Hu Li and Yuting Wang. The first draft of the manuscript was written by Hu Li. All authors approved the final version and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors have declared no conflict of interest related to the study.

References

1. Dong, E., H. Du, and L. Gardner, An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis, 2020. 20(5): p. 533-534.
2. Marjot, T., A.M. Moon, J.A. Cook, et al., Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol, 2021. 74(3): p. 567-577.
3. Sarin, S.K., A. Choudhury, G.K. Lau, et al., Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int, 2020. 14(5): p. 690-700.
4. Kovalic, A.J., S.K. Satapathy, and P.J. Thuluvath, Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis. Hepatol Int, 2020. 14(5): p. 612-620.
5. Marjot, T., G.J. Webb, A.S.t. Barritt, et al., COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol, 2021. 18(5): p. 348-364.
6. Cornberg, M., M. Buti, C.S. Eberhardt, et al., EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. J Hepatol, 2021. 74(4): p. 944-951.
7. Fix, O.K., E.A. Blumberg, K.M. Chang, et al., American Association for the Study of Liver Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease. Hepatology, 2021. 74(2): p. 1049-1064.
8. Clayton-Chubb, D., D. Schneider, E. Freeman, et al., Autoimmune hepatitis developing after the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine. J Hepatol, 2021. 75(5): p. 1249-1250.
9. Londono, M.C., J. Gratacos-Gines, and J. Saez-Penataro, Another case of autoimmune hepatitis after SARS-CoV-2 vaccination - still casualty? J Hepatol, 2021. 75(5): p. 1248-1249.
10. Garrido, I., S. Lopes, M.S. Simoes, et al., Autoimmune hepatitis after COVID-19 vaccine - more than a coincidence. J Autoimmun, 2021. 125: p. 102741.
11. Bril, F., S. Al Diffalha, M. Dean, et al., Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? J Hepatol, 2021. 75(1): p. 222-224.
12. Bril, F., Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: One or even several swallows do not make a summer. J Hepatol, 2021. 75(5): p. 1256-1257.

13. Lodato, F., A. Larocca, A. D'Errico, et al., An unusual case of acute cholestatic hepatitis after m-RNABNT162b2 (Comirnaty) SARS-CoV-2 vaccine: Coincidence, autoimmunity or drug-related liver injury. J Hepatol, 2021. 75(5): p. 1254-1256.
14. McShane, C., C. Kiat, J. Rigby, et al., The mRNA COVID-19 vaccine - A rare trigger of autoimmune hepatitis? J Hepatol, 2021. 75(5): p. 1252-1254.
15. Watad, A., G. De Marco, H. Mahajna, et al., Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. Vaccines (Basel), 2021. 9(5).
16. Vera-Lastra, O., A. Ordinola Navarro, M.P. Cruz Domiguez, et al., Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. Thyroid, 2021. 31(9): p. 1436-1439.
17. Ferri, C., F. Ursini, L. Gragnani, et al., Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. J Autoimmun, 2021. 125: p. 102744.
18. Tzioufas, A.G., A.D. Bakasis, A.V. Goules, et al., A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with systemic autoimmune and autoinflammatory rheumatic diseases. J Autoimmun, 2021. 125: p. 102743.
19. Thuluvath, P.J., P. Robarts, and M. Chauhan, Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. J Hepatol, 2021. 75(6): p. 1434-1439.
20. Sieiro Santos, C., S. Calleja Antolin, C. Moriano Morales, et al., Immune responses to mRNA vaccines against SARS-CoV-2 in patients with immune-mediated inflammatory rheumatic diseases. RMD Open, 2022. 8(1).
21. Wieske, L., K.P.J. van Dam, M. Steenhuis, et al., Humoral responses after second and third SARS-CoV-2 vaccination in patients with immune-mediated inflammatory disorders on immunosuppressants: a cohort study. Lancet Rheumatol, 2022. 4(5): p. e338-e350.
22. Liver, E.A.f.t.S.o.t., EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol, 2015. 63(4): p. 971-1004.
23. Mack, C.L., D. Adams, D.N. Assis, et al., Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. Hepatology, 2020. 72(2): p. 671-722.
24. Liver, E.A.f.t.S.o.t., EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol, 2017. 67(1): p. 145-172.
25. He, T., Y. Zhou, P. Xu, et al., Safety and antibody response to inactivated COVID-19 vaccine in patients with chronic hepatitis B virus infection. Liver Int, 2022.
26. Tanriover, M.D., H.L. Doğanay, M. Akova, et al., Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet, 2021. 398(10296): p. 213-222.

27. Wang, J., Z. Hou, J. Liu, et al., Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): A multicenter study. J Hepatol, 2021. 75(2): p. 439-441.
28. Xiang, T., B. Liang, H. Wang, et al., Safety and immunogenicity of a SARS-CoV-2 inactivated vaccine in patients with chronic hepatitis B virus infection. Cell Mol Immunol, 2021. 18(12): p. 2679-2681.
29. Bsteh, G., S. Durauer, H. Assar, et al., Humoral immune response after COVID-19 in multiple sclerosis: A nation-wide Austrian study. Mult Scler, 2021. 27(14): p. 2209-2218.
30. Kirchner, T., E. Jaeckel, C.S. Falk, et al., SARS-CoV-2-specific immunity in immunosuppressed COVID-19 convalescents with autoimmune hepatitis. J Hepatol, 2021. 75(6): p. 1506-1509.

Tables

Table 1

Characteristics of the Participants.

Variables	AILD (n=76)	Healthy controls (n=136)
Age, years	54.0 (48.8-60.2)	52.0 (33.0-62.2)
<55	39 (51.3)	78 (57.4)
≥55	37 (48.7)	58 (42.6)
Sex		
Female	65 (85.5)	75 (55.1)
Male	11 (14.5)	61 (44.9)
BMI, kg/m^2	22.5 (21.2-23.9)	22.9 (21.1-25.3)
<24	57 (75.0)	83 (61.0)
≥24	19 (25.0)	53 (39.0)
Cirrhosis		
Yes	20 (26.3)	0 (0)
No	56 (73.7)	0 (0)
Comorbidities		
NAFLD	9 (11.8)	0 (0)
Alcoholic liver disease	2 (2.6)	0 (0)
Chronic hepatitis B	2 (2.6)	0 (0)
Diabetes	10 (13.2)	0 (0)
Hypertension	12 (15.8)	0 (0)
Tumor*	9 (11.8)	0 (0)
Other autoimmune diseases**	15 (19.7)	0 (0)
Vaccine		
BBIBP-CorV	21 (27.6)	56 (41.2)
CoronaVac	49 (64.5)	72 (52.9)
BBIBP-CorV & CoronaVac	6 (7.9)	8 (5.9)
Immunosuppressant medication		
Prednisone	27 (35.5)	0 (0)
Azathioprine	17 (22.4)	0 (0)

Mycophenolate mofetil	3 (3.9)	0 (0)
Other medications***	10 (13.2)	0 (0)
Days between final dose and antibody test	41.5 (29.0-66.2)	55.0 (33.0-86.5)

Data are presented as n (%) or median (IQR). * These include liver cancer, rectal cancer, thyroid cancer, myoma of the uterus, and esophageal leiomyoma. ** These include Hashimoto's thyroiditis, Sjogren's syndrome, and polymyositis. *** These include methotrexate, tacrolimus, hydroxychloroquine and total glycoside of paeony. AILD, autoimmune liver disease; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease.

Table 2

Adverse events of COVID-19 vaccination in participants.

Variables	**AILD (n=76)**	**Healthy controls (n=136)**	***p*-value**
Overall adverse events within 7 days	19 (25.0)	24 (17.6)	0.20
Overall adverse events within 30 days	19 (25.0)	24 (17.6)	0.20
Local adverse events			
Pain	3 (4.0)	11 (8.1)	0.38
Itch	0 (0)	1 (0.7)	1.00
Redness	0 (0)	2 (1.5)	0.54
Swelling	2 (2.6)	4 (2.9)	1.00
Systemic adverse events			
Drowsiness	0 (0)	3 (2.2)	0.55
Shoulder pain	0 (0)	1 (0.7)	1.00
Fatigue	4 (5.3)	1 (0.7)	0.11
Numbness of limb	1 (1.3)	1 (0.7)	1.00
Nausea	1 (1.3)	0 (0)	0.36
Lower extremity edema	1 (1.3)	0 (0)	0.36
Headache	4 (5.3)	0 (0)	0.02
Myalgia	2 (2.6)	0 (0)	0.13
Elevated liver enzymes	1 (1.3)	0 (0)	0.36

Data are presented as n (%).

Table 3

Distribution of clinical characteristics by serum antibody titers to SARS-CoV-2 vaccine in patients with AILD.

Variables	Anti-RBD-IgG			NAbs		
	Low-level group* (n=38)	High-level group* (n=38)	*p*-value	Negative (n=28)	Positive (n=48)	*p*-value
Age, years	55.0 (52.0-58.8)	54.5 (47.5-62.2)	0.72	55.0 (48.8-60.2)	54.5 (49.8-60.5)	0.99
<55	18 (47.4)	19 (50.0)	0.82	13 (46.4)	24 (50.0)	0.76
≥55	20 (52.6)	19 (50.0)		15 (53.6)	24 (50.0)	
Sex						
Female	34 (89.5)	31 (81.6)	0.33	24 (85.7)	41 (85.4)	0.97
Male	4 (10.5)	7 (18.4)		4 (14.3)	7 (14.6)	
BMI, kg/m^2	22.5 (21.2-24.1)	22.5 (21.0-23.8)	1.00	22.9 (21.2-24.1)	22.4 (21.2-23.8)	0.71
<24	27 (71.1)	30 (78.9)	0.43	20 (71.4)	37 (77.1)	0.58
≥24	11 (28.9)	8 (21.1)		8 (28.6)	11 (22.9)	
Cirrhosis	9 (23.7)	11 (28.9)	0.60	7 (25.0)	13 (27.1)	0.84
Comorbidities						
0	16 (42.1)	16 (42.1)	1.00	10 (35.7)	22 (45.8)	0.39
≥1	22 (57.9)	22 (57.9)		18 (64.3)	26 (54.2)	
Vaccine						
BBIBP-CorV	16 (42.1)	5 (13.2)	0.01	13 (46.4)	8 (16.7)	0.01
CoronaVac	21 (55.3)	28 (73.7)		15 (53.6)	34 (70.8)	
BBIBP-CorV & CoronaVac	1 (2.6)	5 (13.2)		0 (0)	6 (12.5)	
Immunosuppressant						
0	15 (39.5)	26 (68.4)	0.04	11 (39.3)	30 (62.5)	0.02
1	9 (23.7)	5 (13.2)		4 (14.3)	10 (20.8)	
≥2	14 (36.8)	7 (18.4)		13 (46.4)	8 (16.7)	

Data are presented as n (%) or median (IQR). * Stratified by the median level of anti-RBD-IgG to SARS-CoV-2 vaccine. AILD, autoimmune liver disease; BMI, body mass index; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4

Association analysis between immunosuppressant and poor antibody responses to SARS-CoV-2 vaccine in patients with AILD using multiple logistic regression.

Variables	Anti-RBD-IgG		NAbs	
	Crude OR (95% CI), *p*-value	Adjusted OR* (95% CI), *p*-value	Crude OR (95% CI), *p*-value	Adjusted OR* (95% CI), *p*-alue
Immunosuppressant				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	3.3 (1.3-8.5), 0.01	4.9 (1.5- 15.6), 0.01	2.6 (0.9-6.7), 0.05	3.0 (1.0-8.9),0.04
Number of immunosuppressants				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1	3.1 (0.9-11.1),0.08	5.0 (1.1- 23.1), 0.04	1.1 (0.3-4.2), 0.90	1.5 (0.3-6.9), 0.60
≥2	3.5 (1.2- 10.5), 0.03	4.9 (1.1- 19.2), 0.02	4.4 (1.5-13.6), 0.01	4.4 (1.3-15.3), 0.02

Data are presented as OR (95% CI), and p-values. *Adjustment for age, BMI, sex, cirrhosis, comorbidities, types of vaccine, and days between final dose and antibody test. AILD, autoimmune liver disease; BMI, body mass index; CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figures

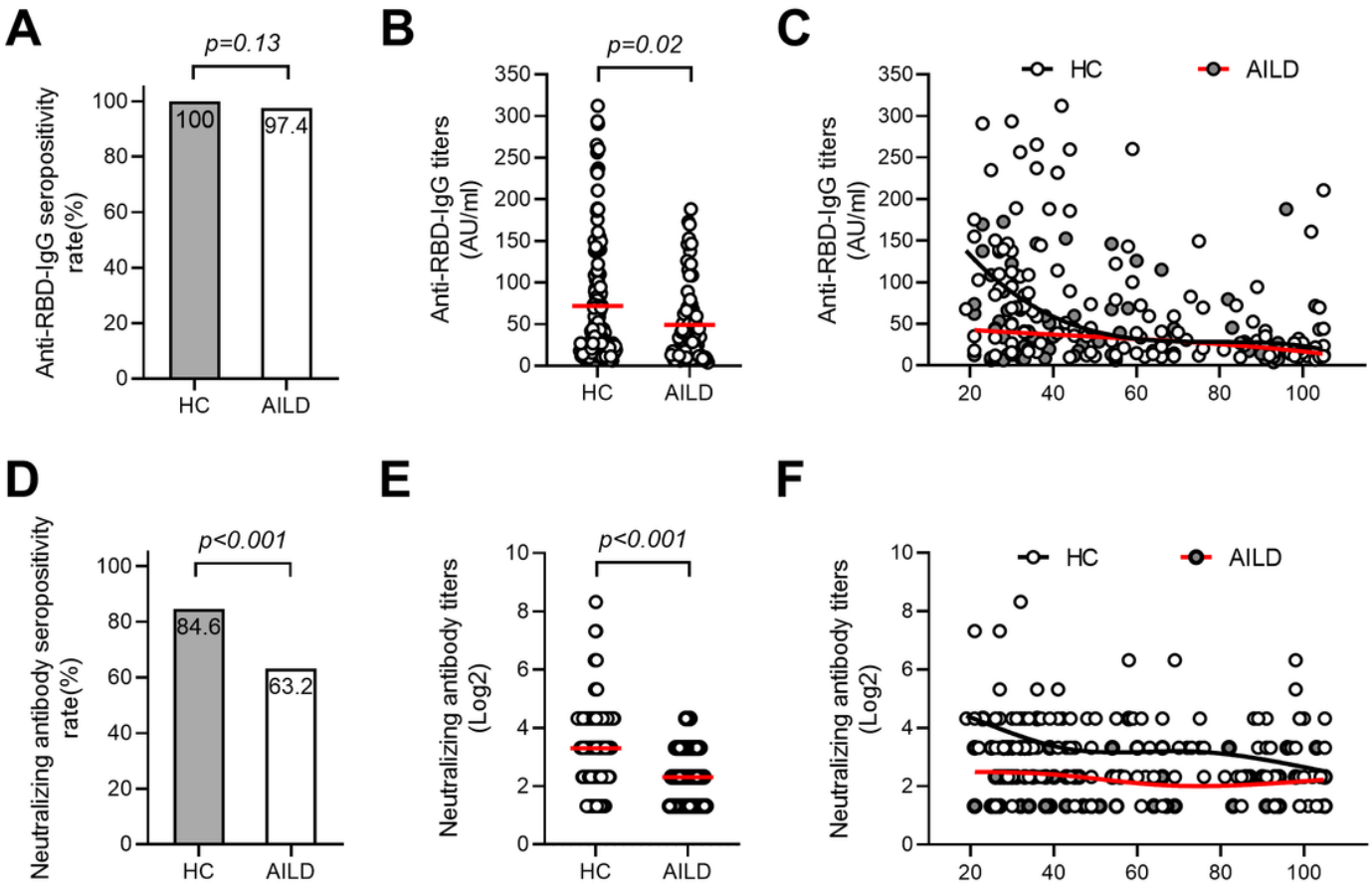

Figure 1

Antibody responses after the COVID-19 vaccination in patients with AILD and healthy controls. The seropositivity rates and titers of anti-RBD-IgG (A-B) and NAbs (D-E) in patients with AILD and healthy controls. The distribution of anti-RBD-IgG (C) and NAbs (F) antibody titers over time in patients with AILD and healthy controls. AILD, autoimmune liver disease; anti-RBD-IgG, spike receptor-binding domain IgG antibody; NAbs, neutralizing antibodies.

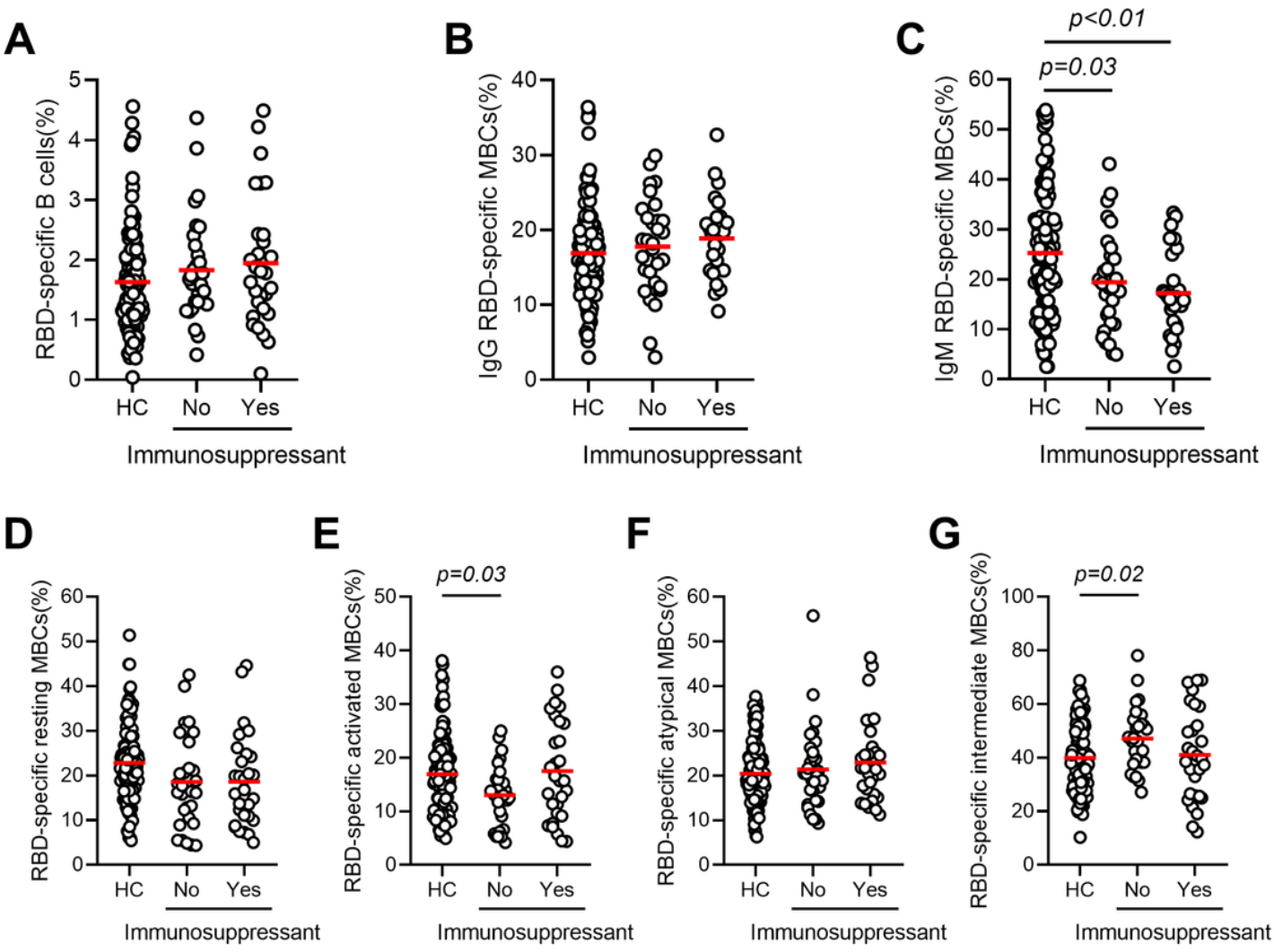

Figure 2

RBD-specific B cell responses after the COVID-19 vaccination in patients with AILD and healthy controls. Frequency of RBD-specific B cell (A), IgG RBD-specific MBCs (B), IgM RBD-specific MBCs (C), RBD-specific resting MBCs (D), RBD-specific activated MBCs (E), RBD-specific atypical MBCs (F) and RBD-specific intermediate MBCs (G) in patients with AILD and healthy controls. AILD, autoimmune liver disease; MBCs, memory B cells; RBD, receptor-binding domain.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif
- SupplementaryMaterial.docx