Diagnostic features of autoimmune hepatitis in SARS-CoV-2-vaccinated vs. unvaccinated individuals

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Abstract. The global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of lives, leading to significant morbidity and mortality. With >772 million cases and nearly seven million deaths reported worldwide to date, the development of vaccines has been a critical step in mitigating the impact of COVID-19. However, concerns have arisen regarding the potential for SARS-CoV-2 mRNA vaccination to trigger autoimmune diseases, including autoimmune hepatitis (AIH). The present single-center, retrospective study aimed to compare the clinical and pathological features of AIH in patients with or without a history of SARS-CoV-2 mRNA vaccination. A total of 72 patients with AIH were examined. Among them, 10 had received the SARS-CoV-2 mRNA vaccination prior to AIH onset. These patients exhibited more pronounced $CD4^+$ T cell infiltration into the liver tissue compared with those who were unvaccinated. No significant differences in the levels of other liver enzymes, autoimmune antibodies, or $CD8^+$ T cell infiltration were observed between the groups. Moreover, the AIH patients with a history of SARS-CoV-2 mRNA vaccination had more extensive $CD4^+$ T cell infiltration in their liver tissues than the unvaccinated patients. These findings suggested that the immune response to SARS-CoV-2 mRNA vaccination may influence the pathogenesis of AIH, highlighting the need for further research into the relationship between SARS-CoV-2 mRNA vaccination and autoimmune liver diseases. Such studies will also help clarify the distinction between vaccine-induced liver injury and traditional AIH.

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Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; AIH, autoimmune hepatitis; IHC, immunohistochemistry; ALT, alanine aminotransferase; VILI, vaccine-induced liver injury

Key words: autoimmune hepatitis, SARS-CoV-2, vaccination, CD4, CD8

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted millions of individuals across the globe, with profound social and economic consequences. Confirmed COVID-19 cases have surpassed 772 million worldwide, with nearly seven million mortalities reported to date (1). In addition to causing COVID-19, SARS-CoV-2 may interfere with immune regulation, potentially initiating autoimmune responses. Indeed, several studies have reported the emergence of autoimmune diseases following SARS-CoV-2 infection (2-4). Vaccines against SARS-CoV-2 have been developed and widely distributed to reduce the severity of COVID-19 and the spread of SARS-CoV-2. Since December 2020, following the first approval of SARS-CoV-2 vaccine by the United States Food and Drug Administration and European Medicines Agency, 50 vaccines including Pfizer/BioNTech, Moderna, Johnson and Johnson, AstraZeneca/Oxford, Sinovac, Sinopharm, Covaxin, Covovax and Nuvaxovid have been approved worldwide and SARS-CoV-2 vaccination is recommended for everyone aged 6 months and older for the prevention of SARS-CoV-2 (5). The majority of these vaccines are delivered via intramuscular injection and have been instrumental in reducing the severity of COVID-19 and preventing fatalities. However, there is an increasing body of evidence indicating that vaccination against SARS-CoV-2 could lead to the onset of autoimmune conditions, such as autoimmune glomerulonephritis and various autoimmune rheumatic diseases (6-9).

The onset of autoimmune hepatitis (AIH) is considered to be influenced by genetics, (particularly specific human leukocyte antigens), while epigenetic, immunological and environmental factors also contribute to its development. Certain viral infections and medications have also been implicated in the onset of AIH (10-12). Recent reports have noted instances of AIH being potentially triggered by vaccines, suggesting that the SARS-CoV-2 mRNA vaccine might also be implicated in AIH development (13-19). However, no study, to the best of the authors' knowledge, has compared the clinical and pathological characteristics of AIH in patients who were or were not vaccinated against

Table I. Patient characteristics.

Characteristics	All	SARS-CoV-2 vaccinated group	SARS-CoV-2 unvaccinated group	P-value
Number	72	10	62	
Age, years	64.0 (57.3-71.0)	66.0 (47.5-71.0)	63.5 (57.8-71.0)	0.666
Sex, n male/female	13/59	2/8	11/51	0.865
AST, U/l	424.5 (222.0-767.0)	246.5 (202.5-953.0)	484.0 (226.5-741.0)	0.784
ALT, U/l	532.5 (247.5-886.0)	397.0 (264.5-772.5)	578.0 (241.8-892.5)	0.968
ALP, U/l	165.9 (128.3-217.5)	149.0 (105.8-183.3)	165.9 (134.1-231.2)	0.173
Total bilirubin, mg/dl	1.4 (1.1-7.5)	1.3 (0.8-5.3)	1.6 (1.1-7.8)	0.485
IgG, mg/dl	2,016.5 (1,656.3-2830.8)	1,711.0 (1,232.5-2,355.5)	2,087.5 (1,705.5-2,862.5)	0.5283
ANA, n				0.436
>1:80	52	6	46	
>1:40	11	3	8	
<1:40	9	1	8	
ASMA, n				0.819
>1:80	15	2	13	
>1:40	3	0	3	
<1:40	32	4	28	
NA	22	4	18	
AMA, n				0.529
>1:40	1	0	1	
<1:40	52	6	46	
NA	19	4	15	
Average alcohol intake, n				0.841
<25 g/day	66	9	57	
<60 g/day	6	1	5	
Drug history, n[a]				0.734
None	44	7	37	
Statin	15	1	14	
Chinese herbal medicine	4	1	3	
Others	9	1	8	
Other autoimmune disease(s), n	12	0	12	0.190
Diagnosis, n				0.169
Definite	56	6	50	
Probable	16	4	12	

Data are expressed as median (interquartile range) unless otherwise specified. [a]History of recent or current use of known or suspected hepatotoxic drugs. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IgG, Immunoglobulin G; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; AMA, anti-mitochondrial antibody; NA, not available.

SARS-CoV-2. The present study examined the clinical and pathological attributes of AIH patients who had or had not received the SARS-CoV-2 mRNA vaccine.

Materials and methods

Patients. The present single-center, retrospective study included 79 patients diagnosed with AIH, based on blood tests and liver biopsy findings, between July 2012 and July 2023 (20) at Aso Iizuka Hosipital. The following exclusion criteria were applied: patients with i) hepatitis B virus or hepatitis C virus, ii) those with alcohol use disorder, who had an average daily intake of more than 60 g of alcohol/day, iii) a history of SARS-CoV-2 infection and iv) those with inadequate pathology specimens. Following the exclusion of seven patients, 72 patients were included in the final analysis (Fig. 1).

The present study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Aso Iizuka Hospital (Fukuoka, Japan; approval no. 23101). The opt-out method was used to obtain consent for this study.

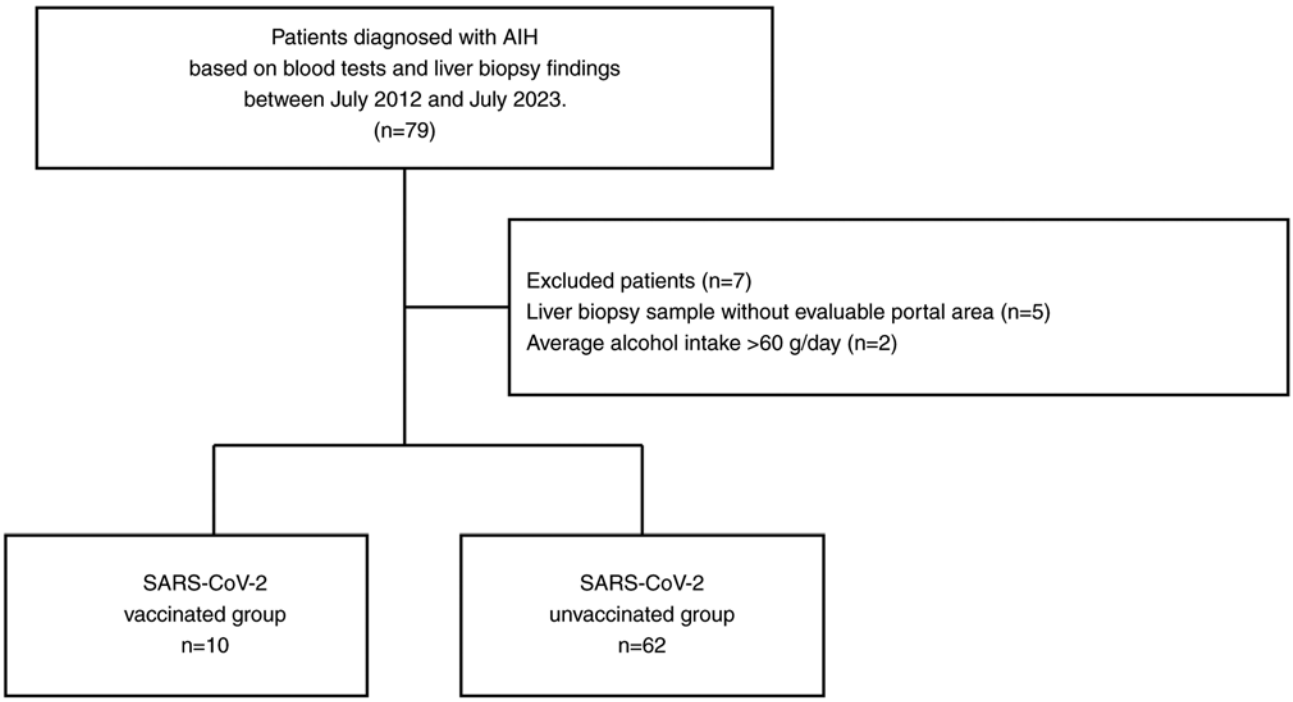

Figure 1. Patient flow chart. AIH, autoimmune hepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Immunohistochemistry (IHC). Liver biopsy specimens were fixed in 10% formalin for 10-48 h at room temperature. Subsequently, the tissue sections were dehydrated in 80, 90, 95 and 100% gradient ethanol for 2-4 h. Serial sections (5 μm) were cut from the paraffin-embedded blocks and stained with hematoxylin and eosin (hematoxylin for 3 min and eosin for 45 sec at room temperature). IHC was performed by Morphotechnology Co. Ltd. Paraffin slides were deparaffinized using two changes of xylene for 10 min each and hydrated using graded alcohol and distilled water (two changes of 100% ethanol, two changes of 95% ethanol and two changes of distilled water) for 10 min each at room temperature. Heat-induced epitope retrieval with citrate buffer was performed for 20 min at 95˚C. Slides were then cooled and rinsed with distilled water. Slides were then rinsed with 0.3% hydrogen peroxide, followed by a rinse with Tris-buffered saline. Specimens were then incubated for 60 min at room temperature with the primary antibody CD4 (clone 4B12; cat. no. NCL-L-CD4-368; 1:200, Leica Biosystems) and CD8 (clone C8/144B; cat. no. M7103; 1:150, Dako; Agilent Technologies, Inc.). Sections were incubated with peroxidase-labeled anti-goat or anti-rabbit antibodies (Histofine Simple Stain MAX PO (MULTI); cat. no. 724152; Nichirei Biosciences, Inc.) for 30 min at room temperature. Afterwards, the secondary reagent, diaminobenzidine (Histofine Simple Stain DAB solution; cat. no. 725191; Nichirei Biosciences, Inc.) was applied for 5 min and the slides were rinsed with distilled water. Counterstaining was performed with hematoxylin for 1.5 min at room temperature and slides were washed in tap water at room temperature. Slides were then blued in ammonia water, rinsed in tap water, dehydrated in graded alcohol (95 and 100% ethanol), cleared in xylene (two changes) for 10 min each at room temperature and coverslipped for light microscopic examination. The sections were visualized under a Keyence BZ-X700 microscope (Keyence Corporation). Positive cells in the selected microscopic fields (magnification, x20) of the portal region of the liver were quantified using analysis software (BZ-X analyzer, Keyence Corporation). A total of three hepatologists evaluated IHC.

Statistical analysis. JMP Pro Version 11 statistical software (SAS Institute Inc.) was used for all the statistical analyses. Data were presented as the median (interquartile range) or n (%), as appropriate. Significant differences between groups were examined using the χ^2 test. The χ^2 test or the Fisher's exact test were used for analyses involving categorical variables. The accuracy of the statistical analyses were verified by two experienced statisticians. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The characteristics of the 72 patients diagnosed with AIH are shown in Table I. Scoring parameters according to the Simplified Diagnostic Criteria or Revised Original Diagnostic Criteria for AIH were used to define the reliability of the diagnosis (i.e., 53 simplified and 19 revised diagnoses) made from the evaluation of liver injury (21). This resulted in 56 patients being diagnosed with definite AIH and 16 patients being diagnosed with probable AIH (21-23). A total of 10 patients developed AIH after receiving the SARS-CoV-2 mRNA vaccination (Pfizer/BioNTech or Moderna; the SARS-CoV-2 vaccinated group), while 62 patients were not vaccinated against SARS-CoV-2 prior to AIH onset (the SARS-CoV-2 unvaccinated group). A total of four patients received single dose of vaccine, four patients received two doses of vaccine and three patients received three doses of vaccine. AIH in SARS-CoV-2-vaccinated

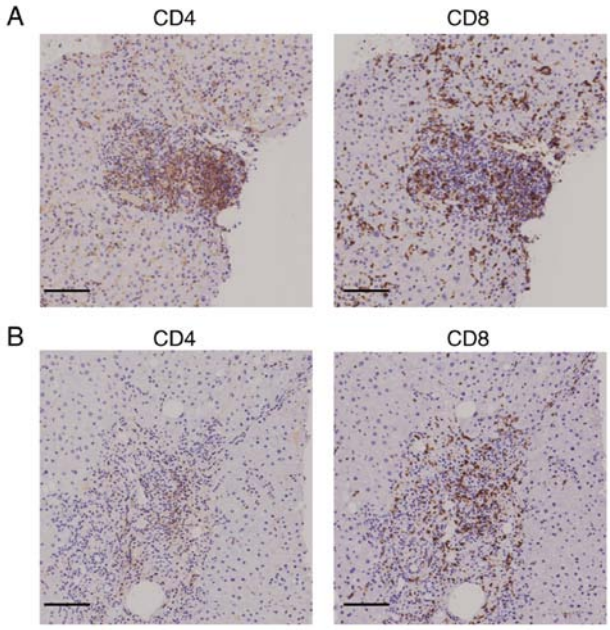

Figure 2. Immunohistochemical staining for $CD4^+$ and $CD8^+$ T cells in liver tissue of AIH patients. (A) Patients with AIH and a history of SARS-CoV-2 mRNA vaccination. (B) Patients with AIH and no history of SARS-CoV-2 mRNA vaccination. Immunohistochemical staining for $CD4^+$ and $CD8^+$ T cells was conducted in liver specimens (magnification, x100; scale bar, 100 μm). AIH, autoimmune hepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

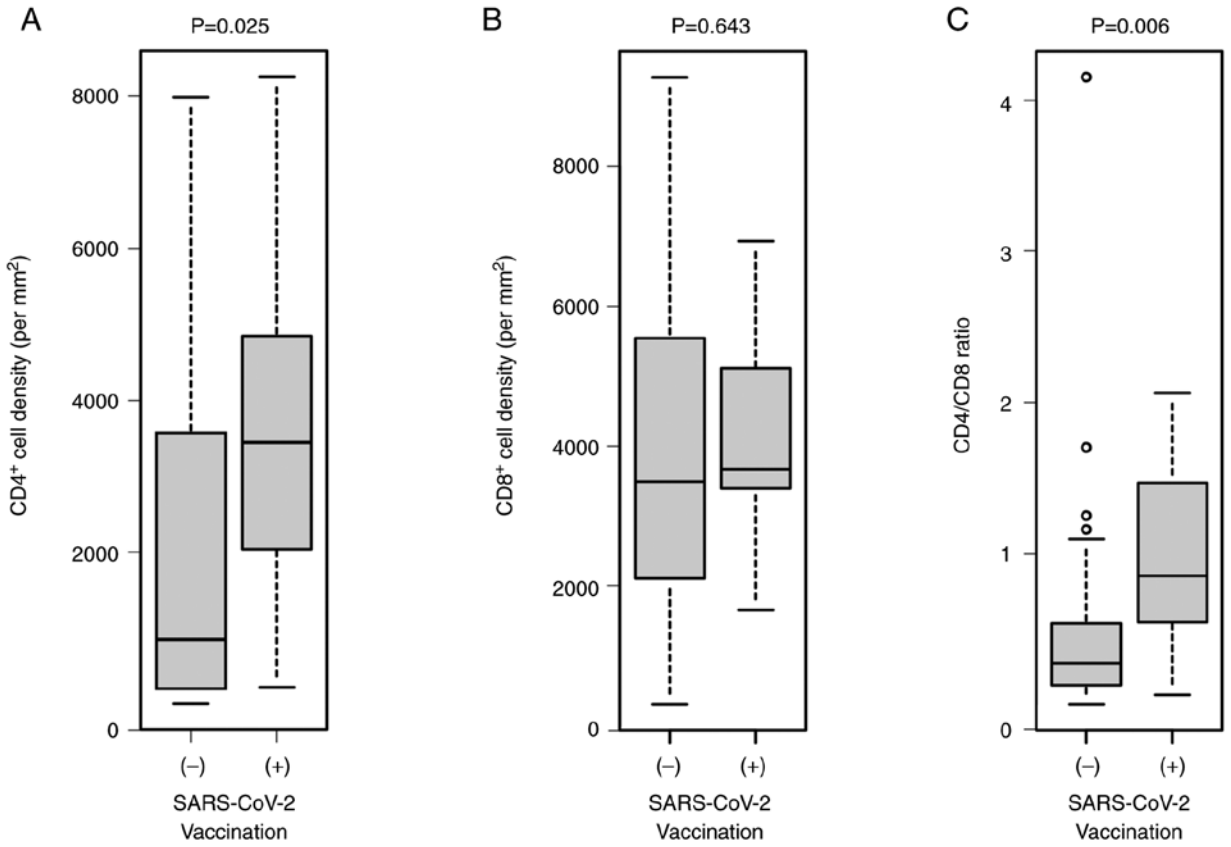

Figure 3. $CD4^+$ and $CD8^+$ T cell density in the liver portal regions of patients with autoimmune hepatitis. (A) $CD4^+$ T cells. (B) $CD8^+$ T cells. (C) $CD4^+/CD8^+$ T cell ratio. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients was diagnosed at 123.5 (44.3-165.0) days after vaccine administration. There were no significant differences in the age, sex, or the aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase level, total bilirubin, immunoglobulin G, anti-nuclear antibody, anti-smooth muscle antibody and anti-mitochondrial

antibody levels between the SARS-CoV-2 vaccinated and unvaccinated patients. History of recent or current use of known or suspected hepatotoxic drugs, average alcohol intake, or the presence of other autoimmune diseases also did not differ markedly between the two groups. All patients were treated with steroid therapy (mostly prednisone or prednisolone) without azathioprine. There were no differences in the treatment success rate between the groups.

IHC analysis of CD4⁺ and CD8⁺ T cells in liver tissue. The present study next examined the infiltration of T cells into the portal region of the liver in the two groups of patients. The IHC results showed that the extent of $CD4^+$ and $CD8^+$ T cell infiltration was comparable in the SARS-CoV-2 vaccinated group, while the extent of $CD4^+$ T cell infiltration was lower than that of $CD8^+$ T cell infiltration in the SARS-CoV-2 unvaccinated group (Fig. 2). Moreover, the density of $CD4^+$ T cells in the portal region of the liver was significantly higher in the SARS-CoV-2 vaccinated group than the unvaccinated group (P=0.025), while there was no significant difference in the abundance of $CD8^+$ T cells between the groups (P=0.643; Fig. 3). Thus, the $CD4^+/CD8^+$ T cell ratio was significantly higher in the SARS-CoV-2 vaccinated group than in the unvaccinated group (P=0.006). Moreover, serum ALT level was associated with $CD8^+$ T cell but not $CD4^+$ T cell numbers in liver tissue (P=0.0478) (data not shown).

Discussion

In the present study, the patients with AIH who had been vaccinated against SARS-CoV-2 exhibited a greater infiltration of $CD4^+$ T cells into the portal region of the liver than those who were unvaccinated. There was no difference in the extent of $CD8^+$ T cell infiltration between the two groups. Previous research indicates that both SARS-CoV-2 vaccination and infection can trigger strong $CD4^+$ and $CD8^+$ T cell responses (24-26). Notably, a previous study showed that the frequencies of both T cell subsets within the liver tissue and peripheral blood increased following SARS-CoV-2 vaccination in a patient who experienced two acute hepatitis episodes (24). SARS-CoV-2 infection typically induces stronger $CD4^+$ T cell than $CD8^+$ T cell responses (25,26).

AIH development is thought to result from a combination of genetic susceptibility and environmental triggers (27). Molecular mimicry between viral- and self-antigens may cause immune dysregulation and involve a complex network of cells such as $CD4^+$ T cells, regulatory T cells, $CD8^+$ T cells and B-cell-derived autoantibodies (28,29). However, the precise process leading to increased $CD4^+$ T cell infiltration in the liver following SARS-CoV-2 vaccination remains to be elucidated.

In Japan, the Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) mRNA vaccines are most commonly administered. These vaccines work by delivering the mRNA which encodes the SARS-CoV-2 spike protein into host cells, where it is translated into the spike protein. The SARS-CoV-2 spike protein is then identified by the immune system, initiating strong $CD8^+$ and $CD4^+$ T cell responses (30). Bystander activation, which refers to the antigen-independent activation of T or B cells, aids in pathogen elimination; however, it can also contribute to AIH development (31,32). Serum ALT level was associated with $CD8^+$ T cell but not $CD4^+$ T cell numbers in liver tissue in this study. Until recently $CD4^+$ T cells were considered to be critical for development of AIH; previous studies reported identical $CD8^+$ T cells were universally present throughout the liver of AIH and $CD8^+$ T cells played a significant role in the immune pathogenesis of AIH (33,34).

Vojdani and Kharrazian (35) demonstrated cross-reactivity between SARS-CoV-2 antibodies and human tissue antigens in the 21 out of 50 patients with autoimmune disease examined, suggesting that molecular mimicry could potentially lead to autoimmune damage and AIH in predisposed individuals. The development of AIH following vaccination for influenza, hepatitis A, measles-mumps-rubella, typhoid, polio and diphtheria/tetanus, has been documented, indicating that vaccine-induced AIH is not exclusive to SARS-CoV-2 vaccines (14-18).

Uzun *et al* (36) explored the morphologic and molecular features of SARS-CoV-2 vaccine-induced liver injury (VILI), highlighting the challenges in distinguishing VILI from AIH, as these conditions share clinical, biochemical, morphological and serological characteristics. However, not all VILI cases meet the AIH diagnostic criteria (23,36-39). While VILI is typically marked by $CD8^+$ T cell dominance, AIH features a stronger presence of $CD4^+$ T cells and B/plasma cells (36). Moreover, VILI can be identified in patients as early as at 2-28 days post-vaccination, whereas AIH is typically diagnosed at a later stage. In the present study, AIH in SARS-CoV-2-vaccinated patients was dominated by $CD4^+$ T cells and was diagnosed at 30-532 days after vaccine administration. These findings confirmed that our SARS-CoV-2-vaccinated patients had AIH rather than VILI.

The present study had several limitations, including the small sample size, single-center scope and the absence of the type of vaccine and gene expression analysis of liver tissues. However, it showed that SARS-CoV-2-vaccinated patients with AIH had more extensive $CD4^+$ T cell liver infiltration compared with those who were not vaccinated. In addition, no significant difference was observed in the amount of $CD8^+$ T cell infiltration between the two groups. Our understanding of AIH pathology has been altered by the COVID-19 pandemic. Further studies are needed to differentiate between AIH and VILI.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AK, SN, MY and KT designed the study. AK, SN, YK, KT and MY assisted with data analysis. AK wrote the initial draft of the manuscript. AK and SN performed and analyzed pathological examinations, including immunostaining. AK and KT contributed to the analysis and interpretation of the data. MY, AM and KM assisted with the preparation and critical review of the manuscript. All authors agreed to be accountable for all aspects of the work presented within. AK and KT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study protocols were performed in accordance with the principles and ethical guidelines of the 1975 Declaration of Helsinki. The present study received approval from the Aso Iizuka Hospital Ethics Committee (Fukuoka, Japan; approval no. 23101). An opt-out method was used to obtain consent for this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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