

# World Journal of *Gastroenterology*

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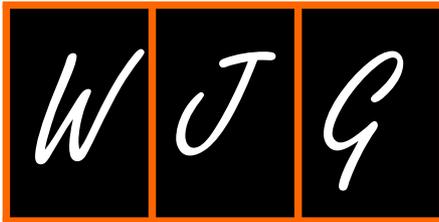
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## Autoimmune liver diseases and SARS-CoV-2

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### Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), can trigger autoimmunity in genetically predisposed individuals through hyperstimulation of immune response and molecular mimicry. Here we summarise the current knowledge about autoimmune liver diseases (AILDs) and SARS-CoV-2, focusing on: (1) The risk of SARS-CoV-2 infection and the course of COVID-19 in patients affected by AILDs; (2) the role of SARS-CoV-2 in inducing liver damage and triggering AILDs; and (3) the ability of vaccines against SARS-CoV-2 to induce autoimmune responses in the liver. Data derived from the literature suggest that patients with AILDs do not carry an increased risk of SARS-Cov-2 infection but may develop a more severe course of COVID-19 if on treatment with steroids or thiopurine. Although SARS-CoV-2 infection can lead to the development of several autoimmune diseases, few reports correlate it to the appearance of *de novo* manifestation of immune-mediated liver diseases such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) or AIH/PBC overlap syndrome. Different case series of an AIH-like syndrome with a good prognosis after SARS-CoV-2 vaccination have been described. Although the causal link between SARS-CoV-2 vaccines and AIH cannot be definitively established, these reports suggest that this association could be more than coincidental.

**Key Words:** Autoimmune liver disease; SARS-CoV-2; COVID-19; COVID-19 vaccine; Autoimmune hepatitis

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**Core Tip:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a possible trigger of autoimmunity. Patients with autoimmune liver diseases (AILDs) were considered at higher risk of SARS-CoV-2 infection and more susceptible to severe coronavirus disease 2019 (COVID-19) due to genetic background and immunosuppressive treatments. Case reports documenting autoimmune hepatitis-like syndromes after the COVID vaccine started to emerge, raising worries about a possible risk of unwanted immunological side effects, especially in individuals predisposed to autoimmune disorders. We herein discuss the consequences of SARS-CoV-2 infection in patients with AILDs and the role of the vaccines in inducing liver autoimmunity.

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## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA, enveloped, beta coronavirus causing coronavirus disease 2019 (COVID-19), which has developed into a pandemic infection in a short time since its first appearance in Wuhan, China, in December 2019[1,2]. Since then, SARS-CoV-2 has caused more than 620 million infections, with a death toll exceeding 6.5 million as of October 31, 2022, according to the World Health Organization. Although the most common presentation of COVID-19 includes respiratory symptoms such as dry cough and shortness of breath[3], gastrointestinal symptoms, including diarrhoea, anorexia, nausea and or vomiting, and abdominal pain, have been variably reported in up to half of the cases[4,5]. Furthermore, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), hallmarks of liver injury, have been widely recognised as major components of COVID-19[6]. Tissue injury is almost certainly multifactorial and related to several mechanisms, such as direct hepatocellular lesions, immune-mediated liver damage due to the severe inflammatory response, or development of endotheliopathy with hypoxic or ischaemic injury[7-9].

Furthermore, SARS-CoV-2 has also been identified as an instrumental trigger of autoimmunity. Hyper-stimulation of the immune system or molecular mimicry of the virus with human self-components may lead to the synthesis of multiple autoantibodies that could initiate autoimmune diseases in genetically predisposed individuals[10,11].

In this review, we summarised the current knowledge regarding the risk of SARS-CoV-2 infection and the course of COVID-19 in patients with autoimmune liver diseases (AILDs), as well as the role of SARS-CoV-2 in inducing *de novo* AILDs. Finally, since various case reports documenting autoimmune hepatitis (AIH)-like syndromes after receiving the COVID-19 vaccine started to emerge, we reviewed the literature to analyse the role of vaccines in inducing autoimmune responses in the liver.

## SARS-COV-2 AND PRE-EXISTING AILDs

ALDs are a heterogeneous group of inflammatory liver disorders mediated by autoimmunity, including AIH, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlapping syndromes. Patients with AILDs could theoretically present an increased risk of SARS-CoV-2 infections and poor outcomes due to lifelong immunosuppressive treatments taken to delay the progression to cirrhosis and liver failure.

However, the clinical impact of SARS-CoV-2 infection on the population with AILDs remains unclear. Preliminary data derived from regional observational studies driven by referral centres suggested that patients with AILDs did not carry a specific risk of becoming infected by SARS-CoV-2. In the earliest reports from Northern Italy, an area particularly affected by the virus's spread, the observed incidence of the infection in a cohort of 148 AILDs patients (133 AIH, 11 autoimmune sclerosing cholangitis, 2 PSC/AIH and 2 PBC/AIH) did not significantly differ from that estimated in the general population (43 vs 38 cases, respectively)[12]. Similarly, Verhelst *et al*[13] found a very limited SARS-CoV-2 infection ratio (1.2%) in a Belgian cohort of 110 patients with AIH[13]. More recently, a survey involving 1779 AILDs patients from 20 European countries detected a rate of COVID-19 (2.2%) equivalent to the period prevalence of the general population, thus indicating that patients with AILDs are not at elevated risk of developing COVID disease[14]. Interestingly, people suffering from autoimmune diseases do not have a higher risk of being positive for COVID-19, as indicated by a study performed in Milan that applied both a test-negative [odds ratio (OR): 0.86, 95% confidence interval (CI): 0.76–0.96] and population (OR: 0.98, 95%CI: 0.90–1.08) case-control design[15].

Regarding the impact of AILDs on the COVID-19 course, early phone-based surveys including patients with AIH ( $n = 73$ ) and PBC ( $n = 68$ ) found a rate of infection of 3.6% with a favourable outcome of COVID-19 in most cases[16]. Likewise, patients under immunosuppressive treatment for AIH show a disease course probably comparable to that reported in the non-immunosuppressed population[17]. Data combined from 3 large-scale international reporting registries, namely the European Association for the Study of the Liver supported COVID-Hep registry, the European Reference Network on Hepatological Diseases (ERN RARE-LIVER) and the American Association for the Study of Liver Diseases supported SECURE-cirrhosis registry, showed that patients with AIH, despite immunosuppressive treatment, did not present an increased risk of adverse outcomes including hospitalisation (76% vs 85%;  $P = 0.06$ ), admission in an intensive care unit (29% vs 23%;  $P = 0.240$ ), or death (23% vs 20%;  $P = 0.643$ ) when compared to other causes of chronic liver disease and matched cases without the liver disease [18]. Another retrospective study collecting data on 110 patients with AIH and COVID-19 from 34 centres in Europe and the Americas confirmed that AIH was not a risk factor for severe COVID-19 (15.5% vs 20.2%,  $P = 0.231$ ) and all-cause mortality (10% vs 11.5%,  $P = 0.852$ ) than other causes of chronic liver disease. Still, continued immunosuppression during COVID-19 was associated with a lower rate of liver injury ( $P = 0.009$ ; OR: 0.26; 95%CI: 0.09-0.71)[19]. However, in another study including 254 AIH patients, the same author observed that the use of systemic glucocorticoids (adjusted OR: 4.73, 95%CI: 1.12-25.89) and thiopurine (adjusted OR: 4.78, 95%CI: 1.33-23.50) was associated with worse COVID-19 outcome compared to patients who were not on immunosuppressive therapy[20].

These results might aid medical decisions when dealing with SARS-CoV-2 infection in immunocompromised patients. Although current expert recommendations advocate against changes in immunosuppressive treatments in patients with AIH before and after SARS-CoV-2 infection[21], data derived from larger case series support the notion of maintaining remission with the lowest effective glucocorticoid dose in AIH patients during the COVID-19 pandemic.

Nonetheless, it should be considered that cirrhotic patients, irrespective of the cirrhosis aetiology, once infected with SARS-CoV-2, are more vulnerable than the general population or patients without cirrhosis. Indeed, they have a higher risk of decompensation of liver disease and developing a more severe COVID-19 with a mortality rate of up to 30%[22,23].

## SARS-COV-2 AS A TRIGGER OF AILDS

Increasing evidence indicates that SARS-CoV-2 may have a trigger effect of, possibly pre-existing, autoimmune disease, including Guillain-Barré syndrome, systemic lupus erythematosus, myasthenia gravis, large vessel vasculitis and thrombosis, Graves' disease, sarcoidosis and inflammatory arthritis [24].

It is well-known that SARS-CoV-2 infection can result in hyperstimulation of the immune system, with increased serum concentration of pro-inflammatory cytokines, particularly monocyte chemoattractant protein 1, interferon-inducible protein-10, interleukin (IL)-6, IL-1 $\beta$ , IL-8, IL-10, IL-17, tumour necrosis factor, granulocyte-macrophage colony-stimulating factor, also referred to as "cytokine storm" or "cytokine release syndrome"[25]. In addition, due to structural homology between some components of SARS-CoV-2 and human proteins[11], the immune responses raised against the virus can cross-react with self-proteins, a concept commonly termed molecular mimicry[26]. These factors may contribute to the development of multiple autoantibodies with a trigger effect on autoimmunity (Figure 1).

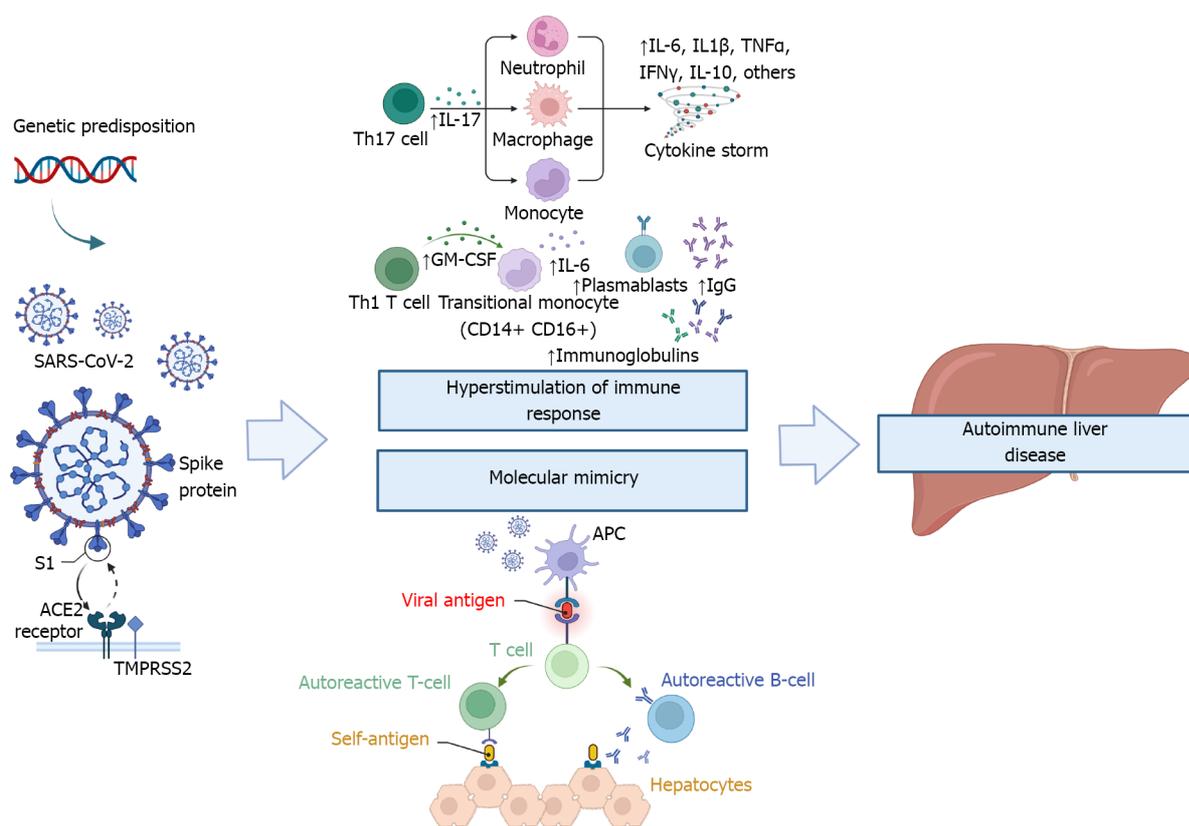
In patients with SARS-CoV-2 infection and especially severely ill patients compared with those with mild or moderate disease, numerous autoantibodies, including antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, have been detected[27,28]. Since systemic autoimmunity is known to initiate from generalised polyclonal B cell activation, the presence of autoantibodies in such kinds of patients may indicate a pre-AID[29].

However, interestingly, there have been very few reports suggesting that SARS-CoV-2 infection might reflect 'a final hit' leading to de novo manifestation of immune-mediated liver diseases such as PBC[30] or AIH/PBC overlap syndrome[31].

PBC developed concomitantly with Guillain-Barré syndrome following SARS-CoV-2 infection in a 44-year-old obese and hypertensive woman already suffering from Hashimoto's thyroiditis. During her hospitalisation for severe bilateral interstitial pneumonia, she developed an important rise in serum gamma-glutamyl-transferase (GGT) with initially normal alkaline phosphatase (ALP) levels that progressively increased later.

As a result of the ALP increase combined with high-titre anti-mitochondrial (AMA) positivity (1:640), the patient underwent a liver biopsy showing histological findings consistent with an initial phase (stage I in Scheuer and Ludwig classifications) of PBC.

A case of AIH/PBC overlap syndrome has been described in a 57-year-old man suffering from hypertension, beta-thalassemia minor, and diabetes. He developed arthralgias, elevated liver enzymes and hyper hyperferritinemia one month after recovering from moderate COVID-19 disease. Although a liver biopsy was not performed, the patient presented a concomitant seropositivity for AMA and anti-double-stranded DNA antibodies (anti-ds DNA) that can be considered the serological profile of AIH/



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**Figure 1** The severe acute respiratory syndrome coronavirus 2 infection may lead to autoimmune liver disease through hyperstimulation of the immune system and molecular mimicry with human self-components. S1: Spike protein subunit 1; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane Serine Protease 2; TH: T helper cells; IL: Interleukin; TNF- $\alpha$ : Tumour necrosis factor alpha; IFN $\gamma$ : Interferon-gamma; APC: Antigen-presenting cell; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IgG: Immunoglobulin G; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

PBC[32].

On the other hand, liver involvement has been frequently reported in COVID-19. Abnormal liver function test, mainly elevated ALT, hypoalbuminemia, and elevated GGT, has been described in 14.8-53% of SARS-CoV-2 infected patients and up to 78% of those with severe manifestations of COVID-19 disease[8] being independent risk factors for adverse clinical outcomes such as intensive care unit admission, use of invasive mechanical ventilation or longer hospital stay[33].

The pathogenic mechanisms of liver injury during COVID-19 are not fully understood. SARS-CoV-2 cell entry is mediated by the interaction of the virus's spike (S) protein with the host angiotensin-converting enzyme 2 receptor (ACE2). S protein is then cleaved by the transmembrane serine protease 2, allowing the internalisation by endocytosis and the release of the viral genome from the endosome[10]. The liver is a possible target for SARS-CoV-2 due to a high expression, almost in the same percentage of type 2 pneumocytes, of ACE2 receptors in cholangiocytes and, to a lesser extent, hepatocytes[34].

However, rather than direct cytotoxicity derived from active viral replication of SARS-CoV-2 in the liver, current data suggest that tissue injury is likely due to immune dysregulation or cytokine storm and development of endotheliopathy and microthromboses with hypoxic or ischaemic injury[35,36]. Exacerbation of underlying liver disease or drug-induced liver injury can also contribute[37,38].

## AILDS FOLLOWING SARS-COV-2 VACCINES

Given the dramatic socio-economical effect of the pandemic, vaccines against SARS-CoV-2 have been rapidly developed. In December 2020, two mRNA vaccines (BNT 162b2 Pfizer-BioNTech[39] and mRNA-1273 Moderna[40]) and one adenovirus (ADV) vector-based vaccine (ChAdOx1 nCoV-19 Oxford University/Astra Zeneca)[41] obtained approval under Emergency Use Listing from the most important drug regulatory agencies. As of October 31, 2022, approximately 68% of the global population has received at least one dose of the anti-SARS-CoV-2 vaccine, with 12.9 billion doses being administered worldwide[42].

Both the mRNA and ADV vaccines encode the intracellular production of the SARS-CoV-2 spike protein, the primary target for neutralising antibodies generated from natural infection and triggering both innate and adaptive responses. *Via* their recognition by innate intracellular sensors, including toll-like receptors 3, 7, 9 and inflammasome components, vaccines stimulate innate immunity through cellular activation and consequent release of interferon I or other pro-inflammatory cytokines, thus promoting differentiation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells into effector and memory subsets[43].

Although the safety profiles of all vaccines have been extensively studied in large placebo-controlled trials, after their widespread diffusion, case reports and case series describing a range of liver diseases following COVID-19 vaccination started to emerge[44].

In the summer of 2021, Bril *et al*[45] first described an AIH-like syndrome developed after vaccination against SARS-CoV-2[45]. AIH is an inflammatory disease of the liver characterised by circulating autoantibodies, mainly ANA, elevated serum globulin levels, specific histological alterations and response to immunosuppressive therapy. The clinical picture is non-specific and varies among patients, ranging from asymptomatic liver enzyme elevation to acute liver failure[46]. SARS-CoV-2 vaccination has also been linked to other forms of immune-mediated liver injury, such as AIH-PBC overlap syndrome[47] or a specific CD8<sup>+</sup> T-cell-dominant hepatitis[48].

Cases of *de novo* AIH or vaccine-induced AIH relapse after vaccination against SARS-CoV-2 are reported in Table 1[45,49-78]. A summary of patient information and disease presentation is shown in Table 2. Laboratory data, treatment, and outcome are reported in Table 3.

Most patients (83%) were female, with a mean age of 58.7 years (range 27-82). In 25 patients, race and ethnicity were not specified, whereas, among the remaining cases, 11 patients were Caucasian, three were Asian, and 1 was Arabic. Seventeen patients (42.5%) had a history of either liver (6) or autoimmune disease (11). One patient was three months postpartum[45].

Although five patients were taking potentially hepatotoxic medication, including substitutive hormonal therapy[62], statin[49,58,76,77], azathioprine[51,76], pegylated interferon for polycythaemia vera[53] and nitrofurantoin[73], each patient had been taking their medications for a long time without recent regimens changes. The patient who reported nitrofurantoin completed a three-day course nearly 90 d before the vaccine, and thus nitrofurantoin-induced liver injury was considered highly improbable. Two patients[63,73] took acetaminophen soon after receiving the first dose, whereas one patient[78] was on chronic treatment. The trigger vaccine was Pfizer-BioNTech in 17 cases (43%), Moderna in 11 (28%), Oxford AstraZeneca in 10 (20%), while CoronaVac, an inactivated whole-virion vaccine, was the trigger of AIH in two cases (5%).

Symptomatic AIH was observed in most cases (78%), with a latency time after receiving the COVID-19 vaccine of about two weeks ( $16.6 \pm 12.8$  d, range 2-60). The most common symptoms were jaundice (60%), asthenia/fatigue (33%), choloria (25%) and pruritus (20%), whereas other symptoms such as fever, abdominal pain, nausea, and vomiting were variably reported. Interestingly, two patients presented worsening symptoms after receiving the second dose[62,68]. At the laboratory, most cases showed a hepatocellular pattern of liver injury, with markedly elevated transaminases (mean values of AST and ALT of  $936 \pm 521$  U/L and  $1060 \pm 567$  U/L, respectively). Mean GGT, ALP, and bilirubin were  $312 \pm 220$  U/L,  $209 \pm 95$  U/L, and  $9.8 \pm 8.5$  mg/dL, respectively. Immunoglobulin G was  $> 20$  g/L in 13 patients (46.5%) with a mean value of 21.7 g/L. Thirty-seven patients (93%) had at least one positive autoantibody, and ANA was positive in 33 (83%). The scoring systems, such as the Simplified AIH score [79] and the Revised Original Score[80], guided the diagnosis of AIH in 18 cases. A liver biopsy was performed in almost all cases (98%). Findings were typical with AIH in 3 patients and compatible with AIH in 31 cases.

Steroids were used as a first-line treatment in 38 patients (95%), and azathioprine was used as a second agent in 8 patients. The mean time to the first improvement and disease resolution were 4.6 and 45.9 d, respectively. Improvement in laboratory data or complete resolution was seen in 37 out of 40 patients (93%). Three patients died of AIH triggered by viral vector vaccine (AstraZeneca), one after refusing liver transplantation[66], while the other two died of liver failure and sepsis[52,76].

Notably, vaccine-induced AIH has been previously described following other vaccinations than that against SARS-CoV-2, such as hepatitis A[81,82] or influenza virus[83,84].

Although the precise mechanisms have not been elucidated, molecular mimicry is one of the major explanations of autoimmunity after vaccination. Significant homology of amino acid sequences between determinants of vaccines and self-antigen may result in the synthesis of anti-spike antibodies that cross-react with structurally similar host peptide proteins[85]. Other proposed mechanisms include bystander activation (defined as an intense stimulation of innate immunity after administration of adjuvants) and epitope spreading (immune responses to endogenous epitopes resulting from the release of self-antigens during chronic autoimmune/inflammatory processes)[86].

Cases of AIH reactivation after vaccines underline the necessity for close follow-up in individuals with a pre-existing diagnosis of AILDs.

Current knowledge does not allow us to clearly define whether these cases represent a true AIH triggered by vaccine or transient vaccine-induced liver injury, which could have similar clinical, laboratory and histological characteristics.

Table 1 Cases of autoimmune hepatitis-like syndromes after the coronavirus disease 2019 vaccine

Ref.	Sex, age	Comorbidity	Vaccine	Time onset after vaccination	Symptoms	Antibodies	Histology	Treatment	Outcome
Bril <i>et al</i> [45]	F, 35	None	Pfizer-BioNTech	7 d after dose I	Jaundice, pruritus, choloria	ANA, anti-Ds-DNA	Compatible with AIH	Prednisone	Remission
Ghielmetti <i>et al</i> [49]	M, 63	Type II diabetes, ischemic heart disease	Moderna	7 d after dose I	Jaundice, fatigue, anorexia	ANA	Typical for AIH	Prednisone	Remission
Avci and Abasiyanik [50]	F, 61	Hashimoto thyroiditis, hypertension	Pfizer-BioNTech	30 d after dose I	Jaundice, malaise, fatigue, anorexia	ANA, ASMA	Compatible with AIH	Prednisone + AZA	Remission
Mahalingham <i>et al</i> [51]	F, 32	OLT post-AIH, hypertension	Pfizer-BioNTech	21 d after dose III	/	SLA/LP	Compatible with AIH	Methylprednisolone	Remission
Erard <i>et al</i> [52]	F, 80		Pfizer-BioNTech	10 d after dose II	All asthenia, pruritus, jaundice	ANA	Compatible with AIH	Steroids	Remission
	F, 73		Moderna	21 d after dose I		ANA		Steroids	Remission
	F, 68		AstraZeneca	20 d after dose I		ANA, ASMA		Listing for liver transplantation	Death after 3 d
Garrido <i>et al</i> [53]	F, 65	Polycythaemia Vera	Moderna	14 d after dose I	Abdominal pain, jaundice, pruritus, acholia, choloria	ANA	Compatible with AIH	Prednisolone	Remission
Goulas <i>et al</i> [54]	F, 52	/	Moderna	14 d after dose I	Malaise, jaundice	ANA, ASMA		Prednisolone + AZA	Remission
Cao <i>et al</i> [55]	F, 57	AIH	CoronaVac	14 d after dose I	Choloria, acholia, jaundice	ANA	Compatible with AIH	Methylprednisolone + AZA + UDCA	Remission
Vuille-Lessard <i>et al</i> [56]	F, 76	Hashimoto thyroiditis, urothelial ca.	Moderna	3 d after dose I	Choloria, fatigue, jaundice	ANA, ASMA, ANCA	Typical for AIH	Prednisolone + AZA	Remission
Suzuki <i>et al</i> [57]	F, 80	GERD	Pfizer-BioNTech	10 d after dose II	Jaundice	ANA	Compatible with AIH	Prednisone	Remission
	F, 75	Dyslipidemia	Pfizer-BioNTech	4 d after dose II	Choloria	ANA, AMA		Prednisone	Remission
	F, 78	Primary biliary cholangitis	Pfizer-BioNTech	7 d after dose I	Fever, malaise	ANA, AMA		Prednisone	Remission
Tan <i>et al</i> [58]	F, 56	/	Moderna	42 d after dose I	Jaundice, malaise, anorexia	ANA, AMA	Compatible with AIH	Budenoside	Remission
Zhou <i>et al</i> [59]	F, 36	Primary sclerosing cholangitis, ulcerative colitis	Moderna	11 d after dose I	/	ANA, Ds-DNA	Compatible with AIH	Prednisone + Azathioprine	Remission
Kang <i>et al</i> [60]	F, 27	/	Pfizer-BioNTech	8 d after dose II	Nausea, vomiting, headache, fever, dark urine	ANA	Compatible with AIH	Prednisolone	Remission
Rocco <i>et al</i> [61]	F, 80	Hashimoto thyroiditis Glomerulonephritis	Pfizer-BioNTech	7 d after dose II	Jaundice	ANA	Typical for AIH	Prednisone	Remission
Londoño <i>et al</i> [62]	F, 41	Premature ovarian failure	Moderna	7 d after dose II	Choloria, jaundice, epigastric pain, nausea, and vomiting	ANA, AMA, SLA/LP	Typical for AIH	Prednisone	Remission
McShane <i>et al</i>	F, 71	/	Moderna	4 d after	Jaundice	ASMA	Compatible	Prednisolone	Remission

[63]				dose I			with AIH		
Clayton-Chubb <i>et al</i> [64]	M, 36	Hypertension	AstraZeneca	26 d after dose I	Fever	ANA	Compatible with AIH	Prednisolone	Remission
Palla <i>et al</i> [65]	F, 40	Sarcoidosis	Pfizer-BioNTech	30 d after dose II	/	ANA	Compatible with AIH	Prednisolone	Remission
Rela <i>et al</i> [66]	F, 38	Hypothyroidism	AstraZeneca	20 d after dose I	Jaundice, fever, fatigue	ANA	Compatible with AIH	Prednisolone	Remission
	M, 62	Diabetes	AstraZeneca	16 d after dose I	Anorexia, fever, jaundice	/		Prednisolone	Death after 3 wk
Camacho-Dominguez <i>et al</i> [67]	M, 79	/	AstraZeneca	15 d after dose I	Abdominal pain, pruritus, acholia, choloria	ANA, ASMA	Compatible with AIH	Hydrocortisone; Prednisone; Prednisolone	Remission
Zin Tun <i>et al</i> [68]	M, 47	/	Moderna	3 d after dose I and 3 d after dose II	Malaise, jaundice	ANA	Compatible with AIH	Prednisolone	Remission
Torrente <i>et al</i> [69]	F, 46	Hypothyroidism	AstraZeneca	21 d after dose I	/	ANA	Compatible with AIH	Prednisone + AZA	Remission
Fimiano <i>et al</i> [70]	F, 63	Hypothyroidism	Pfizer-BioNTech	54 d after dose III	Abdominal pain, nausea, jaundice, choloria	-	Compatible with AIH	Methylprednisolone + AZA	Remission
Izagirre <i>et al</i> [71]	M, 72	Ischemic heart disease, 30 gr/day alcohol consumption	Pfizer-BioNTech	46 d after dose II	/	ANA	Compatible with AIH	Prednisone+ Azathioprine	Remission
	F, 62	Celiac disease	AstraZeneca	4 d after dose II	/	ANA		Prednisone+ AZA	Remission
	F, 72	/	Pfizer-BioNTech	14 d after dose II	/	ANA		Prednisone	Remission
	F, 59	Hypothyroidism	Pfizer-BioNTech	9 d after dose I	/	ANA	Not performed	No treatment received	Spontaneous improvement
Hasegawa <i>et al</i> [72]	F, 82	Hepatitis C virus	Pfizer-BioNTech	7 d after dose I	Malaise	ANA	Compatible with AIH	Prednisone	Remission
Shroff <i>et al</i> [73]	F, 59	/	Moderna	31 d after dose I	/	ANA	Compatible with AIH	Steroids	Remission
Efe <i>et al</i> [74]	M, 53	/	Pfizer-BioNTech	30 d after dose II	Abdominal pain, pruritus, erythematous skin eruption	/	Compatible with AIH	Prednisolone	Developed HE and liver transplantation
Shahrani <i>et al</i> [75]	F, 59	Dyslipidemia	AstraZeneca	12 d after dose II	Jaundice	/	Compatible with AIH	Prednisolone	Remission
	F, 72	/	Pfizer-BioNTech	10 d after booster	Jaundice	AMA	Compatible with AIH	Prednisolone	Remission
Nik <i>et al</i> [76]	F, 63	Primary sclerosing cholangitis, ulcerative colitis	AstraZeneca	14 d after dose I	Jaundice, pruritus	ANA	Compatible with AIH	Prednisolone	Death after 2 wk for sepsis
Mekritthikrai <i>et al</i> [77]	F, 52	Dyslipidemia, hypertension	Coronavac	After dose II	Jaundice	ANA, ASMA	Compatible with AIH	Prednisolone + AZA	Remission
Mathew <i>et al</i> [78]	F, late 20s	Headache	AstraZeneca	10 d after dose I	Jaundice	ANA	Compatible with AIH	Prednisolone	Remission

ANA: Antinuclear antibody; anti-Ds-DNA: Anti-double stranded DNA; AIH: Autoimmune hepatitis; ASMA: Anti-smooth muscle antibody; AZA: Azathioprine; OLT: Orthotopic liver transplantation; SLA/LP: Anti-soluble liver antigen/liver-pancreas; UDCA: Ursodeoxycholic acid; ANCA: Anti-neutrophil cytoplasmic antibodies; GERD: Gastroesophageal reflux disease; AMA: Anti-mitochondrial antibodies; HE: Hepatic encephalopathy.

**Table 2** Cases of autoimmune hepatitis-like syndromes after coronavirus disease 2019 vaccine: Demographics, patient information, and disease presentation

<b>Classification</b>	
<b>Number of patients</b>	40
<b>Females, <i>n</i> (%)</b>	32 (83)
<b>Age (years, mean <math>\pm</math> SD)</b>	58.7 $\pm$ 16
<b>Race/ethnicity, <i>n</i> (%)</b>	
Caucasian	11 (27)
Asian	3 (8)
Arabic	1 (3)
Unspecified	25 (62)
<b>Predisposing conditions, <i>n</i> (%)</b>	
History of liver disease	6 (15)
History of autoimmune disease	11 (28)
<b>Medications, <i>n</i> (%)</b>	
Acetaminophen	3 (8)
Other hepatotoxic drugs (statins, peg-IFN, AZT)	5 (13)
<b>Vaccine, <i>n</i> (%)</b>	
Pfizer-BioNTech	17 (43)
Moderna	11 (28)
AstraZeneca	10 (25)
Coronavac	2 (5)
<b>Symptom onset (days after a dose, mean <math>\pm</math> SD)</b>	16.6 $\pm$ 12.8
<b>Symptoms, <i>n</i> (%)</b>	
Jaundice	24 (60)
Asthenia/Malaise/Fatigue	13 (33)
Choluria	10 (25)
Pruritus	8 (20)
Abdominal pain	4 (10)
Fever	5 (13)
Loss of appetite	4 (10)
Nausea/vomiting	5 (13)

Peg-IFN: Pegylated interferon; AZT: Azathioprine.

A longer follow-up could be helpful to rule out vaccine-induced liver injury since biochemical and histological resolution can spontaneously occur, and immunosuppressive treatment can be withdrawn without the risk of relapse.

In summary, although a causative link between AIH and SARS-CoV-2 vaccination cannot be confirmed, emerging case reports suggest this association could be more than coincidental.

## CONCLUSION

Since the initial stage of the COVID-19 pandemic, concerns about the risk of poorer outcomes following SARS-CoV-2 infection have been raised in patients with pre-existing chronic liver disease. We found that people with AILDs are not at increased risk of being infected by SARS-CoV-2, despite immunosuppressive treatment that, however, may predispose them to develop a more severe course of the disease.

**Table 3** Cases of autoimmune hepatitis-like syndromes after coronavirus disease 2019 vaccine: Diagnostics, treatment, and clinical outcomes

<b>Diagnostics</b>	
<b>Peak laboratory values (mean ± SD)</b>	
AST (IU/l)	936 ± 523
ALT (IU/l)	1060 ± 567
GGT (IU/l)	312 ± 220
ALP (IU/l)	209 ± 95
Bilirubin (mg/dL)	9.8 ± 8.5
IgG (g/L)	21.7 ± 6.7
<b>Antibodies, n (%)</b>	
ANA	33 (83)
ASMA	7 (18)
SLA/LP	2 (5)
AMA	5 (13)
Others (ANCA, DS-DNA)	3 (8)
<b>Liver biopsy</b>	
Performed	39
Not performed	1
<b>Morphologic characteristics, n (%)</b>	
Interface hepatitis	31 (78)
Lymphoplasmacellular infiltrates	36 (90)
Rosette formation	5 (13)
<b>Treatment</b>	
<b>First agent</b>	
Budesonide	1
Prednisone	15
Prednisolone	17
Methylprednisolone	3
Hydrocortisone	1
Steroids	3
No treatment	2
<b>Second agent</b>	
Azathioprine	8
Prednisolone	2
<b>Clinical outcomes</b>	
Time to the first improvement, days (mean ± SD)	4.6 ± 2.9
Time to resolution, days (mean ± SD)	44.6 ± 37
Alive	37
Dead	3

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; IgG: Immunoglobulin G; ANA: Antinuclear antibody; ASMA: Anti-smooth muscle antibody; SLA/LP: Anti-soluble liver antigen/liver-pancreas; AMA: Anti-mitochondrial antibodies; ANCA: Anti-neutrophil cytoplasmic antibodies; Ds-DNA: Anti-double stranded DNA.

Furthermore, increasing evidence highlighted the intrinsic capability of the virus to hyper-stimulate immune response leading to the development of autoimmune disease. However, only two reports identify SARS-CoV-2 as a trigger instrument for developing AILDs, making any correlation not feasible.

Post-vaccine AIH-like syndrome raises worries about a risk of unprecedented immunological side effects, especially in individuals predisposed to autoinflammatory disorders. However, COVID-19 vaccine-induced AIH is extremely uncommon and has an exceptional prognosis. Hepatologists should consider AIH in patients with jaundice or elevated liver enzymes following COVID-19 vaccination to readily initiate further work-up and treatment with steroids.

## FOOTNOTES

**Author contributions:** Sgamato C and Rocco A drafted the manuscript; Compare D, Minieri S, and Marchitto SA participated in the acquisition, analysis, and interpretation of the literature; Maurea S and Nardone G revised the manuscript for important intellectual content; All authors have read and approved the final manuscript.

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