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REVIEW

Autoimmune-Like Hepatitis Related to SARS-CoV-2 Vaccination: Towards a Clearer Definition

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Received: 19 July 2024 | **Revised:** 23 November 2024 | **Accepted:** 29 November 2024

Handling Editor: Luca Valenti

Funding: The authors received no specific funding for this work.

Keywords: autoimmune hepatitis | SARS-CoV-2 vaccine associated liver injury | SARS-CoV-2 vaccines | vaccine-induced liver injury

ABSTRACT

Vaccines are the most effective tool against COVID-19 and are generally safe. Very rare and heterogeneous cases of acute liver injury associated to all types of SARS-CoV-2 vaccines have been reported, mostly with autoimmune features. Epidemiological studies used heterogeneous diagnostic criteria and included different populations. Immunological studies in selected cases of acute liver injury linked to mRNA SARS-CoV-2 vaccines suggest that it has a unique pathophysiology, the vaccine-encoded spike protein playing a central role in triggering the aberrant immune response. In most series, liver injury was observed more often following the second vaccine dose. Latency from vaccination to the diagnosis of hepatitis was 1–147 days after the last vaccine dose. Raised immunoglobulin G levels and positive anti-nuclear and/or anti-smooth muscle antibodies are frequent. The vast majority of reported cases have been treated with corticosteroids, mostly associated with azathioprine. Outcome is generally favourable, but cases requiring liver transplantation or causing death have been reported. The heterogeneous clinical entity of acute liver injury linked to SARS-CoV-2 vaccines includes patients requiring long-term immunosuppression, similarly to autoimmune hepatitis, and patients with self-limiting liver damage, possibly representing a unique form of autoimmune-like hepatitis, which we suggest being referred to as SARS-CoV-2 vaccine-associated liver injury (SVALI). Further studies are needed to investigate the pathogenic mechanisms related to the immune response to the spike viral protein in the liver.

1 | Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) was first described in December 2019 in Wuhan, China [1]. SARS-CoV-2 is a highly transmissible and pathogenic virus that rapidly caused a major global health pandemic problem [1, 2]. While COVID-19 is mainly a respiratory disease, other organs, including the cardiovascular system, kidney, liver, and gastrointestinal tract, are also commonly affected [3]. Vaccines are the most effective tool against COVID-19. Several vaccine types against SARS-CoV-2 have rapidly been developed, including mRNA vaccines,

Abbreviations: AIH, autoimmune hepatitis; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibody; COVID-19, coronavirus disease 2019; DI-ALH, autoimmune-like drug-induced liver injury; DILI, drug-induced liver injury; IAIHG, international AIH group; IgG, immunoglobulin G; IRR, incidence rate ratios; LC-1, liver cytosol type 1; LKM-1, anti-liver/kidney microsome type 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLA, soluble liver antigen; SVALI, SARS-CoV-2 vaccine-associated liver injury.

Summary

What is known

- SARS-CoV-2 vaccines are the most effective tool against COVID-19 and are generally safe.
- Acute liver injury with autoimmune features after SARS-CoV-2 vaccines
  - is rare,
  - is heterogeneous and
  - has a benign course in the vast majority of cases, with or without a short immunosuppression course.
- A few cases are immunosuppression-dependent, clinically resembling AIH.
- A subgroup of patients without immunosuppression-dependence, vaccinated with mRNA vaccines, has an aberrant adaptive immune response in which the viral spike protein is involved.

What needs to be investigated

- Detailed autoimmune serological studies of clinically well-characterised cases should be carried-out, in order to identify possible autoimmune serological markers of SVALI.
- Do patients behave as AIH present more often after the second vaccine dose?
- What are the mechanisms leading to the pathophysiological role of the spike viral protein? Is it involved also in other organ-specific side effects of the SARS-CoV-2 vaccines?
- Is the adaptive immune response different in SVALI versus liver injury resembling AIH after SARS-CoV-2 vaccines?
- The adaptive immune response to SARS-CoV-2 vaccines has been studied only in recipients of mRNA-vaccines: Liver injury after non-mRNA vaccines should be investigated as well.

replication incompetent vector vaccines, inactivated vaccines, and recombinant protein vaccines [4]. Vaccination has significantly reduced COVID-19-related mortality and morbidity in healthy individuals and in high-risk populations such as those with chronic cardiovascular diseases, liver or renal failure and graft organ recipients [5, 6]. While mild to moderate injection site pain, redness and swelling, transient fever, headache and fatigue are commonly reported adverse effects of SARS-CoV-2 vaccines, severe side effects such as myocarditis and immune thrombotic thrombocytopenia have rarely been described [7].

Relapse or new onset of various organ specific or systemic immune-mediated disorders following SARS-CoV-2 vaccines have also been reported [8]. These cases suggest that vaccination may break host immunological tolerance and lead to the development of autoimmune conditions [9].

Several studies have reported cases of acute liver injury following SARS-CoV-2 vaccines [10–17]. The clinical phenotype of most cases showed features of autoimmune hepatitis (AIH), and many of these patients received immunosuppressive therapy [10].

In this review, we critically evaluated epidemiology, clinical features, pathophysiology and outcome of acute liver injury after SARS-CoV-2 vaccines. We also aim to better define and introduce a new terminology for SARS-CoV-2 vaccine-associated liver injury (SVALI).

1.1 | Available SARS-CoV-2 Vaccines

Four types of vaccines against SARS-CoV-2 have been approved: mRNA, replication incompetent vector vaccines, recombinant protein-based and inactivated vaccines. The first three vaccine types have been developed based on the publication by the Chinese Center for Disease Control on January 10th, 2020 of the genomic sequence of the SARS-CoV-2 virus, allowing the generation of the synthetic gene of the viral spike protein [18]. Despite knowledge on mRNA vaccines dating back to the '80s', SARS-CoV-2 mRNA vaccines were the first licensed mRNA vaccines in 2020: they are based on modified mRNA encoding the SARS-CoV-2 spike protein delivered in lipid nanoparticles [19, 20]. The expression of the spike protein occurs via the host cell translational machinery; it is important to note that mRNA has intrinsic adjuvant properties, resulting in production of chemokines and cytokines [21]. Replication incompetent vector vaccines are based on the insertion into the DNA of a virus, typically an adenovirus, of genomic sequences of the SARS-CoV-2 spike protein, leading to its expression by host cells [4]. They contain adjuvants. This technology, originally used for gene therapy, has successfully been used also in influenza and Ebola vaccines [22]. Protein-based vaccines contain a recombinant viral protein, that is, either the spike protein or its receptor binding domain, and adjuvants to increase immunogenicity.

Inactivated vaccines contain intact viruses, isolated form COVID-19 patients, which have been chemically or physically inactivated, coupled to adjuvants. In contrast to the other vaccine types, they include the whole virus [4].

2 | Acute Liver Injury After SARS-CoV-2 Vaccines

Acute liver injury is a very rare side effect of SARS-CoV-2 vaccines and therefore has not been reported in clinical trials (phase II/III), which included a limited number of subjects [19, 20]. After several months of massive global vaccination programmes, Bril et al. [23] reported the first case of acute liver injury with features of AIH, that is, positive autoantibodies and compatible liver histology (serum immunoglobulin G (IgG) levels were normal in this case) in a previously healthy young woman 1 week after her first dose of the BNT162b2 mRNA vaccine. Following this first case, clinicians have started reporting similar cases observed with all types of SARS-CoV-2 vaccines (Table 1). A systematic review of acute liver injury related to SARS-CoV-2 vaccines during the period from December, 2019 to November, 2021 revealed only 32 suspected cases [24], suggesting that it is a very rare clinical

entity, needing population-based studies to evaluate its true incidence. Of importance, heterogeneous criteria have been used to define acute liver injury, ranging from any increase of liver enzymes after vaccination irrespective of pre-existing liver diseases to their elevation of ≥five times the upper limit of normal (ULN) in the absence of pre-existing liver diseases [11, 25, 26].

2.1 | Incidence

Epidemiological studies used heterogeneous diagnostic criteria and included different populations.

A large study investigated the incidence of acute liver injury related to SARS-CoV-2 vaccination using electronic medical records of the Hong Kong public healthcare authority [25]. Among 1 348 288 individuals who received at least one dose of the mRNA BNT162b2 vaccine, acute liver injury occurred in 307 individuals within 56 days after the first dose, and it occurred in 521 individuals after the second dose (335 and 334 per 100 000 person-years, respectively); among 994 877 individuals who received the CoronaVac inactivated vaccine, acute liver injury occurred in 304 individuals within 56 days after the first dose, and it occurred in 474 individuals after the second dose (358 and 403 per 100 000 person-years, respectively). Overall, the incidence of liver injury within 56 days of SARS-CoV-2 infection was 32 997 cases per 100 000 person-years, showing that the incidence of acute liver injury following SARS-CoV-2 infection is much higher than that after SARS-CoV-2 vaccination. This study also evaluated the overall frequency of acute liver injury after vaccine exposure (within 56 days of a vaccine dose) and during non-exposure periods: no increased risk of acute liver injury was observed in the 56-day risk period following the first (IRR: 0.800; 95% CI: 0.680–0.942) and second (IRR: 0.944; 95% CI: 0.816–1.091) BNT162b2 doses and the first (IRR: 0.689; 95% CI: 0.588–0.807) and second (IRR: 0.905, 95%CI: 0.781–1.048) CoronaVac doses.

A retrospective study from Argentina investigated the cumulative incidence of new onset liver biochemistry alterations after SARS-CoV-2 vaccination in patients seen in a large university hospital [26]. The study included 29 798 subjects in the SARS-CoV-2 vaccine group (viral-vector-based vaccines: Sputnik andChAdOx1nCoV-19; inactivated vaccine: Sinopharm) and compared them to 24 605 individuals who received the influenza vaccine. Liver biochemistry was studied in 7833 (26.9%) subjects in the SARS-CoV-2 vaccine group and in 8459 (34.37%) subjects in the influenza vaccine group. The cumulative incidence at 90 days of new-onset liver test alterations was similar in the SARS-CoV-2 and the influenza vaccine groups, 4.7 per 1000 (95% 4.0–5.5) vs. 5.1 per 1000 (95% 4.3–6.1) ($p = 0.489$). In this study, two cases in the SARS-CoV-2 vaccine group developed liver injury with features of AIH, both vaccinated with Sputnik: one of them had a history of AIH, having discontinued corticosteroids and azathioprine before vaccination; the second case had advanced liver fibrosis at histology, also suggesting that this patient had pre-existing, undiagnosed hepatopathy, possibly AIH that flared after vaccination. Both cases showed good response to immunosuppressive therapy.

Another study from the USA compared the incidence of liver injury in 470 274 individuals who received an mRNA or viral-vector-based SARS-CoV-2 vaccine to 21 784 individuals who received an influenza vaccine [27]: the incidence of acute liver injury was 0.038% in the SARS-CoV-2 vaccine cohort (0.038% in mRNA and 0.024% in viral-vector) and 0.069% in the influenza vaccine cohort. Of note, 86% of liver injury cases occurred after the second vaccine dose.

A single-centre and non-population-based analysis from a referral autoimmune liver disease centre in Hamburg, Germany, reported no increased incidence of AIH during the SARS-CoV-2 vaccination period [28].

There are no reports on acute liver injury potentially associated to SARS-CoV-2 vaccines in children.

In conclusion, available data suggest that acute liver injury temporally associated with SARS-CoV-2 vaccines occurs after all vaccine types. It is extremely rare and is not more frequent than after exposure to the influenza vaccine or non-exposure to SARS-CoV-2 vaccines.

2.2 | Pathophysiology

Reported cases of acute liver injury after SARS-CoV-2 vaccines are heterogeneous, including flares of pre-existing AIH, self-remitting cases, cases requiring long-term immunosuppression, severe cases requiring liver transplantation or having fatal outcome and seronegative cases [10, 11, 29]. All SARS-CoV-2 vaccine types have been implicated in acute liver injury. Moreover, patients often use paracetamol, non-steroidal anti-inflammatory drugs or other compounds to treat mild vaccine side effects, such as local pain or low-grade fever, further complicating the investigation of the pathophysiology [10, 11]. However, there is a subgroup of patients with acute liver injury after SARS-CoV-2 vaccines, which probably represent genuine vaccine-associated liver injury, as suggested by two studies investigating the aberrant adaptive immune response, leading to liver damage in selected cases [30, 31]. Boettler et al. [31] reported a 52-year-old male patient presenting with jaundice and acute mixed hepatocellular/cholestatic hepatitis after the first dose of the BNT162b2 mRNA vaccine, with spontaneous resolution, followed by severe recurrence after the second vaccine dose. Serum IgG levels were marginally elevated, anti-nuclear antibody (ANA) was positive at a titre of 1:200 (substrate not reported) and anti-smooth muscle antibody (SMA) and anti-mitochondrial antibody (AMA) M2 were reported as borderline positive. Liver histology showed interface hepatitis and foci of lobular necrosis and apoptosis in the absence of fibrosis or eosinophilic granulocytes. He was initially treated with budesonide and subsequently switched to prednisolone due to persistently elevated serum transaminase levels. Deep spatial immune analysis of the liver showed that cytotoxic CD8 T cells were the most abundant immune cell subset in the inflammatory infiltrate, with a pan-lobular distribution, in contrast to B cells and plasma cells being present mostly in periportal areas. The authors identified abundant spike-specific, activated CD8 T cells in the peripheral blood and the liver, expression of activation markers on these cells correlating with disease activity. Interestingly, the intrahepatic CD8 T cell pool

TABLE 1 | General characteristics of studies that investigated liver injury after SARS-CoV-2 vaccination.

Reference	Case numbers/ geographic location	General characteristics	Biochemical and histological features	Therapy and outcome
Efe et al. [10]	*n* = 87 USA, Austria, India, Italy, Dominican Republic, Argentina, Paraguay, Australia, Mexico, Spain, Chile, Peru, Turkey, Sweden, Canada, Singapore, Switzerland, Greece and Portugal	*Median age/sex*: 48 (range:18–79) years; Female, 63% *Vaccine type*: mRNA (*n* = 67), viral vector (*n* = 20), *Causative dose*: 54% after the 2nd dose *Baseline AILD*: AIH (*n* = 2), PBC (*n* = 1), PSC (*n* = 1) *Median time to onset (days)*: 15 (range: 3–65)	*Type of liver injury*: HC: 84%, Mixed: 10%, Cholestatic: 6% *Features of AIH*: ANA+: 68%, ASMA+: 18%, Anti-SLA+: 1%, Anti-LC-1+: 1%. IgG>ULN: 67% *Histology of AIH*: Typical (*n* = 21), probable (*n* = 20), atypical (*n* = 3)	*IS*: (*n* = 46) Steroids: 53%, AZA: 10%, MMF: 2%. *Other managements*: Intravenous immunoglobulin (*n* = 1), plasma exchange (*n* = 9) *Liver transplantation*: (*n* = 1) *Successful IS withdrawal*: (*n* = 12)
Codoni et al. [11]	*n* = 59 Switzerland, Italy, Germany, Argentina, Japan, UK, Netherlands, Spain, Turkey, Austria, Lithuania, France, Denmark and Australia	*Median age/sex*: 54 (range: 19–92) years; female, 59% *Vaccine type*: mRNA (*n* = 42), viral vector (*n* = 16) inactivated (*n* = 1) *Causative dose*: 63% after the 2nd dose *Baseline AILD*: not reported *Median time to onset (days)*: 24	*Type of liver injury*: HC: 95%, Mixed: 5% *Features of AIH*: ANA+: 74%, ASMA+: 37%, LKM-1+: 8%. IgG>ULN: 68% *Histology of AIH*: Typical (*n* = 14), probable (*n* = 34), atypical (*n* = 11)	*IS*: (*n* = 52) Steroids: 88%, AZA: 12%. *Liver transplantation*: (n = 1) *Successful IS withdrawal*: (*n* = 10)
Kulkarni et al. [12]	*n* = 13 Argentina, Chile, India, Turkey	*Median age/sex*: 42 (range:22–67) years; Female, 54% *Vaccine type*: inactivated (*n* = 13) *Causative dose*: 70% after the first dose *Baseline AILD*: PBC (*n* = 1) *Median time to onset (days)*: 18 (range: 2–39)	*Type of liver injury*: HC:92%, Cholestatic:8% *Features of AIH*: ANA+: 68%, ASMA+: 18%. IgG>ULN: 50% *Histology of AIH*: Typical (*n* = 1), probable (*n* = 2)	*IS*: (n = 5) Steroids: 38%, Liver transplantation: (*n* = 1) Successful IS withdrawal: (*n* = 4)
Rigamonti et al. [13]	*n* = 12 Italy	Median age/sex: 62 (range: 32–80) years; female, 50% Vaccine type: mRNA (*n* = 9), viral vector (*n* = 3) Causative dose: not reported Baseline AILD: not reported Median time to onset (days): 48 after the first dose and 10 after the second dose	Type of liver injury: not reported Features of AIH: ANA+: 50%, ASMA+: 8%, LKM-1+: 8%. Median IgG 1.2 xULN Histology of AIH: typical (*n* = 8), probable (*n* = 3)	IS: (*n* = 12) Details not reported

(Continues)

TABLE 1 | (Continued)

Reference	Case numbers/ geographic location	General characteristics	Biochemical and histological features	Therapy and outcome
Shroff et al. [14]	$n=16$ USA	Median age/sex: 63 (range: 25–74) years; female, 63% Vaccine type: mRNA ($n=16$) Causative dose: 75% after the 2nd dose Baseline AILD: AIH ($n=4$) Median time to onset (days): 28 (range: 5–46)	Type of liver injury: HC: 81%, mixed: 13%, cholestatic: 6% Features of AIH: ANA+: 31%, ASMA+: 19% IgG>ULN ($n=1$), <ULN ($n=1$) Histology of AIH: not reported	IS: ($n=8$) Steroids: 50%, Other managements: N-acetylcysteine ($n=2$) No death/liver transplantation
Fontana et al. [15]	$n=23$ USA	Median age/sex: 58 (range: 21–83) years; female, 74% Vaccine type: mRNA ($n=23$) Causative dose: 56% after the 2nd dose Baseline AILD: AIH ($n=5$) Median time to onset (days): 51 (range: 9–430) from the first and 20 (range: 1–147) from the second dose	Type of liver injury: HC: 70%, mixed: 17%, cholestatic:13% Features of AIH: ANA+: 27%, ASMA+: 36%. IgG>ULN: 9% Histology of AIH: AIH-like hepatitis ($n=5$)	IS: ($n=6$) Steroids: 26%, *Successful IS withdrawal*: ($n=4$) *No death/liver transplantation*
Barreira-Díaz et al. [17]	$n=47$ Spain	*Median age/sex*: 57 (range:19–86) years; female, 64% *Vaccine type*: mRNA ($n=36$), viral vector ($n=11$) *Causative dose*: 56% after the 2nd dose *Baseline AILD*: AIH ($n=7$) *Median time to onset (days)*: 22 (range: 11–41)	*Type of liver injury*: HC: 81%, mixed: 13%, cholestatic: 6% *Features of AIH*: ANA+: 64%, ASMA+: 21%. IgG>ULN: 64% *Histology of AIH*: typical or probable ($n=29$)	*IS*: ($n=41$) Steroids: 75%, AZA: 66%, MMF: 4% *Liver transplantation* ($n=1$) *Liver related-death* ($n=1$) *Successful IS withdrawal*: 15%
Wong et al. [4]	$n=1606$ Hong Kong, China	*Median age/sex*: not reported *Vaccine type*: mRNA ($n=828$), inactivated ($n=778$) *Causative dose*: 62% after the second dose *Baseline AILD*: not reported *Time to onset*: within 56 days after the first and second doses	Details not reported	*No death/liver transplantation*

(Continues)

TABLE 1 | (Continued)

Reference	Case numbers/ geographic location	General characteristics	Biochemical and histological features	Therapy and outcome
Guardiola et al. [23]	$n = 177$ USA	*Median age/sex*: 70 ± 14 years; female, 60% *Vaccine type*: mRNA ($n = 171$), viral vector ($n = 6$) *Causative dose*: 86% after the 2nd dose *Baseline AILD*: not reported *Time to onset*: 29 ± 21 days after the first and 45 ± 25 days after the second dose	*Type of liver injury*: HC: 45%, mixed: 35%, cholestatic: 20% *Features of AIH*: not reported *Histology of AIH*: not reported	Details not reported

Abbreviations: AIH, autoimmune hepatitis; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibody; HC, hepatocellular; IgG, immunoglobulin G; IS, immunosuppression; LC-1, liver cytosol type 1; LKM-1, anti-liver/kidney microsome type 1; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; ULN, upper limit of normal.

was enriched for spike-specific CD8 T cells in comparison to the blood and displayed tissue-resident characteristics with expression of CXCR6, CD103 and CD69. Of note, only healthy controls and not classical AIH were included as controls. This report suggests that the liver injury may be related to the spike protein rather than to a specific vaccine type. The second paper [30] published 1 year later reported a morphologic and molecular analysis of liver injury after mRNA SARS-CoV-2 vaccines in six cases, comparing them with nine AIH cases. Importantly, all cases of vaccine-associated liver injury were carefully selected: none had a pre-existing liver disease, alternative causes of acute hepatitis were excluded, and none had fibrosis at liver histology; while five received a short course of prednisone, one improved spontaneously; all went into remission (median follow-up 18 months). AIH cases were studied at presentation before the treatment was started. While whole transcriptome profiling with bulk liver RNA showed differences between vaccine-associated liver injury and AIH patients, they were close to each other and significantly different from controls with chronic hepatitis C virus infection or alcoholic liver disease. In the AIH group, pathways associated to the immune response were overrepresented, especially genes linked to interferon response. Conversely, in the vaccine-associated liver injury cohort, pathways related to mitochondrial metabolism and oxidative stress were overrepresented. The characterisation of the liver immune infiltrate showed that it was dominated by CD8 T cells in the vaccine-associated liver injury cohort [30], similarly to the findings by Boettler et al. [31], and in the AIH cohort, $CD79a^+$ B cells and plasma cells were more abundant in the portal infiltrate. Furthermore, the clonal distribution of the adaptive immune response of the liver infiltrate showed that vaccine-associated liver injury patients had few expanded B and T cell clones, suggesting a response towards specific antigens. Many of the expanded liver-infiltrating T cell clones were also found in the peripheral blood. Lastly, there were differences in the usage of the variable and joining region of the T and B cell receptor between vaccine-associated liver injury and AIH patients [30].

Importantly, the spike mRNA was found in the cytoplasm of hepatocytes of a patient with acute liver injury after the BNT162b2 vaccine, indicating that mRNA delivered by lipid nanoparticles may be utilised by the host translational machinery to generate the spike antigen, which is subsequently presented on the surface of hepatocytes via MHC-I molecules [32].

These observations suggest that liver injury linked to mRNA SARS-CoV-2 vaccines has a distinct pathophysiology, the vaccine-encoded spike protein playing a central role in triggering the aberrant immune response (Figure 1).

2.3 | Genetic Predisposition

A recent US study evaluated genetic factors potentially contributing to the development of liver injury in 23 adults with acute hepatitis after SARS-CoV-2 mRNA vaccination included in the Drug-Induced Liver Injury Network (DILIN) [15]. Sixteen of them were high causality cases, according to the DILIN expert opinion score. HLA status was exanimated in 20 cases, and data of 14 high causality cases were used for further analysis. While AIH-predisposing HLA alleles (HLA-DRB1*03:01

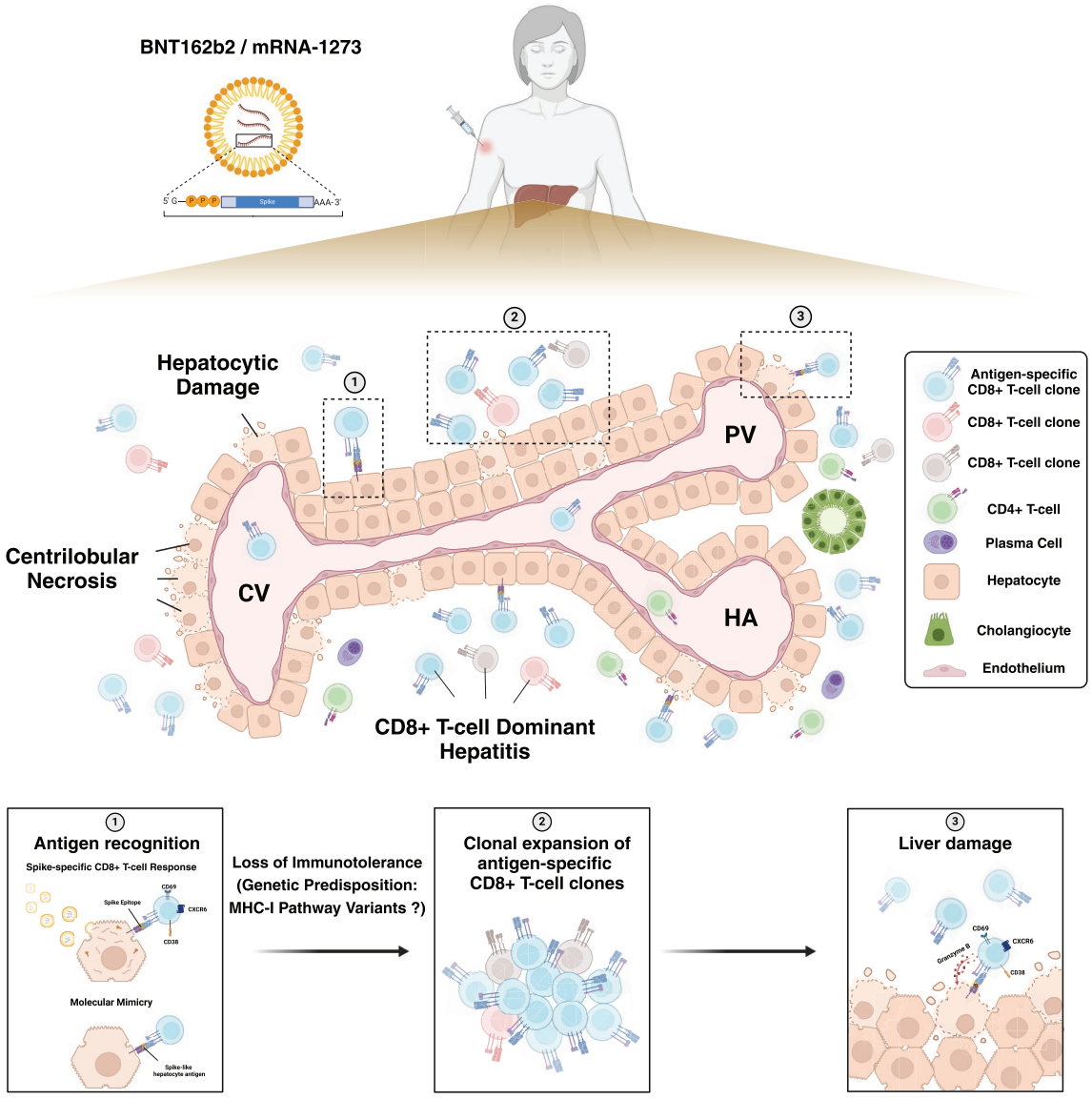

FIGURE 1 | Following the administration of the mRNA vaccines BNT162b2 and mRNA-1273 into the deltoid muscle, lipid nanoparticles were demonstrated to be distributed throughout the body, with the liver identified as one of the major organs where they localised following plasma clearance. The presence of spike mRNA in the cytoplasm of hepatocytes was confirmed in the liver of a SVALI patient, indicating that mRNA delivered by lipid naoparticles may be utilised by the translational machinery to generate the spike antigen, which is subsequently presented on the surface of hepatocytes via MHC-I molecules. Another proposed mechanism involves molecular mimicry between the spike antigen and human peptides. Previous studies have demonstrated a high degree of peptide homology between the SARS-CoV-2 spike glycoprotein and human proteins (see Box 1). In patients with SVALI, the sustained expression of spike protein or antigenic mimicry, coupled with potential intrinsic susceptibility factors—such as genetic variants in MHC-I pathway proteins—may contribute to the disruption of immune tolerance. Upon antigen recognition, antigen-specific $CD8^+$ T cells can undergo clonal expansion, which leads to an oligoclonal T-cell immune repertoire, predominantly characterised by $CD8^+$ T cell-driven hepatitis. Consistent with this, spike antigen-specific $CD8^+$ T cells have been identified in the liver biopsy of a SVALI patient, where they were characterised as tissue-resident memory T cells with an activation phenotype (see Box 2). The dysregulated activity of these effector T cells can result in significant hepatocyte damage and necrosis, ultimately manifesting as elevated liver enzyme levels (see Box 3).

and HLA-DRB1*04:01) were not overrepresented in the 16 vaccine-associated liver injury cases compared to the control population, the Hap6 haplotype of the endoplasmic reticulum aminopeptidase 1 (ERAP-1) and a variant (rs1263907) of the ERAP-2 gene were significantly overrepresented in the patients with vaccine-associated liver injury. ERAP-1 and ERAP-2 are involved in antigen processing in the liver. Despite the low number of genetically characterised cases, these results suggest that acute hepatitis associated with COVID-19 vaccines is a rare but unique DILI form, in which the SARS-CoV-2 spike glycoprotein triggers an inappropriate immune response in predisposed individuals. Of note, one third of the high causality cases had pre-existing AIH, suggesting a shared predisposition between autoimmunity and vaccine-associated liver injury. Finally, it is important to note that only a minority of the patients required corticosteroid treatment.

2.4 | Clinical Features

A recent study reviewed the clinical characteristics of liver injury following SARS-CoV-2 vaccine cases included in the four largest published case series [33]. This study identified a total of 175 (61% female) patients with age ranging from 42 to 63 years at the time of diagnosis, the majority (71%) having received mRNA vaccines, 21% viral vector vaccines (ChAdOx1 nCoV-19 or GAMCOVID-Vac) and 7% inactivated vaccines. Acute liver injury was diagnosed following the second vaccine dose in 58% of the reported cases [33]. Latency from vaccination to the diagnosis of hepatitis was 1 to 147 days after the last vaccine dose. In a large international cohort including 87 cases, 24 (28%) had pre-existing extra-hepatic autoimmune disorders, autoimmune thyroiditis being the most common (12 cases, 14%) [10]. In two studies [10, 14], 14% and 50% of cases had pre-existing various liver disorders. Twelve patients had a diagnosis of AIH and were on immunosuppressive therapy when liver injury developed (most received m-RNA-based vaccine) [10, 14, 15, 17]. The majority of these AIH patients had stable serum transaminase levels before vaccination with good adherence to immunosuppressive therapy. In these patients, symptoms developed within a few days after vaccination, suggesting causality rather than a spontaneous flare of AIH.

In the analysis of 87 cases [10], 92% were symptomatic: fatigue (75%), nausea (63%), jaundice (39%), abdominal pain (24%), fever (12%), itching (11%) and rash (8%) were reported symptoms at presentation. In other studies [15, 17], most of reported cases had at least one of the above-mentioned symptoms.

2.5 | Laboratory Findings

Approximately 80%–90% of acute liver injury cases following SARS-CoV-2 vaccines showed a hepatocellular or mixed pattern of liver injury according to the R value [33, 34]. In two studies [10, 12], 20% and 15% of cases had laboratory features of severe-fatal liver injury. Severe liver injury was noted in 9% (2/23) of cases in another study [15]. A recent retrospective series from Spain reported that 19% (9/47) had severe liver injury, including a fatal case and a patient requiring liver transplantation [17].

Overall serum IgG levels were elevated in 65% (99/152) and 76% (19/25) of cases [17, 33], while a recent study [15] reported elevated IgG levels in only 9% (2/23) of the cases.

Autoantibodies are a key diagnostic marker of AIH; however, laboratory testing lack standardisation, and autoimmune serology results from different laboratories cannot be directly compared [35–37]. An in vitro study showed that the anti-SARS-CoV-2 spike protein antibody and anti-nucleoprotein antibody cross-react with a variety of human tissue antigens, suggesting that antibodies targeting viral proteins may lead to a loss of tolerance towards autoantigens [38]. Autoantibodies were tested centrally in 31 patients included in the paper by Codoni et al. [11], and at least one autoantibody was positive in 29 (94%) of patients. According to the review by Shroff [33], among 167 cases, ANA was positive in 67% and SMA in 24%. Anti-liver cytosol type 1 (anti-LC-1) and anti-soluble liver antigen/liver pancreas antigen (anti-SLA/LP), which are highly specific markers of AIH, were also detected in a few cases [10, 11]. A more recent study of 47 cases reported 64% and 21% seropositivity rates for ANA (titre $\geq$ 1/80, unreported substrate) and SMA (titre $\geq$ 1/40) [17]. AMA is the serological hallmark of primary biliary cholangitis but it may also be detected in some patients with pure AIH or with acute liver failure [35, 36]. Among 87 cases of acute liver injury following SARS-CoV-2 vaccines [10], five (6%) were AMA-positive, this proportion being 10.6% in another study of 47 cases [17]. Ghielmetti et al. [39]. reported an interesting case of AIH-like hepatitis following mRNA-1273 SARS-CoV-2 vaccine. This case was seropositive for AMA at indirect immunofluorescence, which was not mirrored by positivity in molecular-based assays, the authors naming this autoantibody "atypical AMA". The same patient was ANA-positive on a rodent liver substrate and on HEp2 cells with a rim-like anti pattern but was negative for anti-gp210 at molecular testing, suggesting a unique ANA. Such a detailed autoimmune serological analysis has not been reported in other cases.

2.6 | Liver Histology

Liver histology of acute liver injury associated with SARS-CoV-2 vaccines has been best investigated in the study by Codoni et al. [11], in which all 59 patients had their liver biopsy centrally reviewed by an expert liver pathologist. Three quarters ($n = 45$) of the patients had a predominatly lobular injury, mainly ($n = 33$) with confluent necrosis; a minority ($n = 5$) had a cholestatic hepatitis. A predominatly portal injury was observed in 10 (17%) cases. Advanced fibrosis was more frequent among patients with a predominatly portal injury ($p = 0.006$) and in patients requiring long-term immunosuppression [40]. According to the simplified International AIH Group (IAIHG) scoring system [41], 82% of the patients were classified as typical or probable AIH, and according to the new European rare disease network histological criteria [42, 43], 92% were classified as likely or possible AIH.

2.7 | International AIH Group Simplified Scoring System

The IAIHG simplified scoring system was applied to the 44 cases with available liver histology data included in the large series published by Efe et al. [10], 77% (34/44) scoring as probable or definite AIH. Similarly, a recent study reported that 70% (23/33) of cases reached a probable or definite AIH diagnosis using the same score [17].

2.8 | Treatment and Outcome

The vast majority of published cases were treated with steroids, with or without azathioprine or mycophenolate mofetil [10–15]. In a few cases, other immunosuppressive drugs, including cyclosporine and tacrolimus, or intravenous immunoglobulins or plasma exchange were used in addition to steroids [10, 11]. Since all published cases are retrospective, the decision to start immunosuppression was made according to the judgement of the treating physicians, resulting in heterogeneous criteria for

treatment initiation and diverse schedules. However, severe cases are more often treated [10]. The reported initial steroid dose is highly variable, ranging from 20 mg to more than 100 mg predniso(lo)ne equivalent dose, with higher doses used in more severe cases, at times given intravenously [10, 11]. SARS-CoV-2 vaccine-associated hepatitis is reportedly often treated similarly to AIH, with rapid taper of the predniso(lo)ne dose under close monitoring of the laboratory liver values; azathioprine, or, more rarely, mycophenolate mofetil, is added if transaminase levels stop decreasing or increase during steroid dose reduction. Relapse during steroid tapering suggests AIH, and treatment should be continued long-term [44]. Of note, relapse after initial spontaneous improvement has been reported; therefore, close follow-up of untreated cases with spontaneous improvement is advisable.

There are few data available on the duration of treatment, with many patients being treated long-term with low-dose immunosuppression. However, clinicians should be aware that SARS-CoV-2 vaccines-associated liver injury, similarly to autoimmune-like drug-induced liver injury (DI-ALH) [45], may not require long-term immunosuppression, and a trial of treatment discontinuation under close monitoring is often justified, particularly in patients with a swift response to steroids, reaching transaminase level normalisation within weeks of starting treatment [10, 11]. Fatal infections on immunosuppression have been reported [11]. The vast majority of published cases have a favourable outcome, with or without immunosuppression [10, 11]. However, rare severe cases have been reported, including at least three cases requiring liver transplantation: one exposed to an inactivated vaccine not treated with steroids, one re-exposed to the same mRNA vaccine after having developed a mild acute hepatitis after the first vaccine dose and one without reported information on treatment or vaccine type [10–12, 17, 29]. One fatal case has also been reported [17]. A subgroup of patients relapses during immunosuppression tapering or after withdrawal, therefore having a clinical course similar to AIH [40].

Most SARS-CoV-2 vaccines require a booster dose a few weeks after the first dose; in patients with acute hepatitis after the first dose, severe recurrence has been reported following the booster dose. In contrast, exposure to a different vaccine type after complete resolution of the liver injury, on low-dose immunosuppression, has reportedly been well tolerated [10, 11, 29, 31].

3 | Nomenclature

Based on the available literature summarised above, we conclude that acute liver injury temporally associated with SARS-CoV-2 vaccines is a very rare, heterogeneous condition, where two subgroups of patients are of special interest; the first group includes patients requiring long-term immunosuppression, that is, with relapse after treatment discontinuation or during treatment reduction, resembling AIH, and the second group includes patients with a self-limited liver damage, that is, recovering spontaneously or with a short immunosuppression course without relapse. Immunological studies and clinical observations of patients in the latter group, all having received an mRNA vaccine, suggest a pathophysiological role of the viral spike protein, which either reaches the liver via the blood stream or is synthetised in the liver after mRNA vaccination. Therefore, we suggest referring this condition as SVALI. The triggering/pathogenic role of SARS-CoV-2 vaccines in patients with a clinical course resembling AIH remains unknown.

Acute liver injury with autoimmune features is a heterogeneous condition, with several pathogenic pathways leading to the same initial clinical phenotype, including AIH, DI-ALH [45], unidentified infection and inborn errors of immunity [46–48]. SVALI may be added to the list of conditions with the AIH phenotype. Long-term immunosuppression dependence is considered the most reliable feature allowing to distinguish classical AIH from DI-ALH [45]. Vaccines against other infectious organisms, particularly against hepatitis A [49], have been reported as possible triggers of DI-ALH, as well as drugs and herbal remedies [45]. The Brighton Collaboration, an international scientific network aiming at enhancing the safety of vaccines by providing standardised methods to assess and monitor vaccines side effects, has recently issued guidelines to define AIH following SARS-CoV-2 vaccination [50]; while the experts include in their case definition liver histology, IgG levels, autoantibodies and exclusion of other causes of hepatitis, they do not include response to immunosuppression, challenging the distinction between AIH and SVALI.

4 | Expert Opinion on the Diagnosis and Management of Patients Presenting With Acute Liver Injury After SARS-CoV-2 Vaccines

Patients presenting with acute liver injury within 3 months after a SARS-CoV-2 vaccine should be thoroughly investigated for all causes of acute hepatitis, including viral hepatitis, DILI, exposure to herbal remedies and potentially hepatotoxic agents or alcohol, rare genetic diseases and AIH. The presence of liver cirrhosis signs should be carefully investigated. Severe cases, that is, patients with impaired liver function assessed with the serum bilirubin level, coagulation status and presence of hepatic encephalopathy, should be treated with corticosteroids at a starting dose of 0.5–1 mg/kg body weight of predniso(lo)ne, similarly to AIH; predniso(lo)ne should be tapered at weekly intervals to 5 mg/day under strict monitoring of serum transaminase levels and liver function tests [51]. If transaminase levels stop decreasing during steroid tapering, azathioprine (once jaundice is resolved) or mycophenolate mofetil should be added. A few months after serum transaminase level normalisation, immunosuppression should be slowly withdrawn, maintaining strict liver test monitoring, and restarted or increased in case of relapse. Relapsing patients should be treated long-term and considered to have AIH.

5 | Conclusion and Future Perspectives

Acute liver injury temporally associated to SARS-CoV-2 vaccines is an extremely rare event, mostly self-remitting; therefore, concern about possible hepatotoxicity should not restrain clinicians from using the vaccines, which remain by far the most effective and safest tool against COVID-19. It is a highly heterogeneous condition, including SVALI and AIH potentially triggered or unmasked by the vaccine.

Author Contributions

C.E., M.S.M. and B.T.B.-P. conceptualised the study. C.E., M.S.M. and B.T.B.-P. interpreted data and prepared manuscript. US made the figure and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Acknowledgements

We kindly acknowledge Giorgina Mieli-Vergani and Diego Vergani for the critical review of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Permission to Reproduce Material From Other Sources

The authors have nothing to report.

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Author names in "*" designate shared first authorship.

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