

ORIGINAL ARTICLE

Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome

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Abstract

Background and Aims: A few case reports of autoimmune hepatitis–like liver injury have been reported after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. We evaluated clinical features, treatment response and outcomes of liver injury following SARS-CoV-2 vaccination in a large case series.

Approach and Results: We collected data from cases in 18 countries. The type of liver injury was assessed with the R-value. The study population was categorized according to features of immune-mediated hepatitis (positive autoantibodies and elevated immunoglobulin G levels) and corticosteroid therapy for the liver injury. We identified 87 patients (63%, female), median age 48 (range: 18–79) years at presentation. Liver injury was diagnosed a median 15 (range: 3–65) days after vaccination. Fifty-one cases (59%) were

attributed to the Pfizer-BioNTech (BNT162b2) vaccine, 20 (23%) cases to the Oxford-AstraZeneca (ChAdOX1 nCoV-19) vaccine and 16 (18%) cases to the Moderna (mRNA-1273) vaccine. The liver injury was predominantly hepatocellular (84%) and 57% of patients showed features of immune-mediated hepatitis. Corticosteroids were given to 46 (53%) patients, more often for grade 3–4 liver injury than for grade 1–2 liver injury (88.9% vs. 43.5%, $p = 0.001$) and more often for patients with than without immune-mediated hepatitis (71.1% vs. 38.2%, $p = 0.003$). All patients showed resolution of liver injury except for one man (1.1%) who developed liver failure and underwent liver transplantation. Steroid therapy was withdrawn during the observation period in 12 (26%) patients after complete biochemical resolution. None had a relapse during follow-up.

Conclusions: SARS-CoV-2 vaccination can be associated with liver injury. Corticosteroid therapy may be beneficial in those with immune-mediated features or severe hepatitis. Outcome was generally favorable, but vaccine-associated liver injury led to fulminant liver failure in one patient.

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 has spread worldwide and caused a pandemic. Although most Covid-19 cases have mild symptoms, hospitalization and mortality rates are significant, especially in individuals with comorbid conditions.^[2,3]

Vaccination is the most effective tool against Covid-19. Due to the devastating global impact of Covid-19, several vaccines were granted a fast-track authorization. Currently, the most used vaccines are those produced by Pfizer-BioNTech, Oxford-AstraZeneca, and Moderna.^[4] These vaccines have significantly reduced major Covid-19 adverse outcomes such as hospitalization, intensive care unit admission and mortality.^[4,5] Because massive vaccination programs were started at the end of 2020, few serious adverse effects of SARS-CoV-2 vaccines have been reported.^[6] Overall, SARS-CoV-2 vaccines appear safe and well tolerated.

SARS-CoV-2 vaccines trigger the interferon pathway as part of their mechanism of action, raising some concerns regarding the possibility of vaccine-induced autoimmunity in susceptible individuals.^[5] Several organ specific or systemic immune-mediated diseases following SARS-CoV-2 vaccination have indeed been reported.^[7] To the best of our knowledge, Bril et al.^[8] reported the first case of liver injury after a first dose of Pfizer-BioNTech vaccine. Additional cases have since been reported.^[9] The clinical and histological findings of most patients resembled autoimmune hepatitis (AIH)

and all reported patients showed spontaneous resolution or responded well to corticosteroid therapy.^[9,10]

The aim of this international effort was to assemble a large case series in order to assess the clinical characteristics, efficacy of corticosteroid therapy and outcomes of patients who developed liver injury following SARS-CoV-2 vaccination.

PATIENTS AND METHODS

Patients

We retrospectively collected data from 18 countries on patients who developed liver injury after SARS-CoV-2 vaccination. All study collaborators independently identified cases and obtained predefined data from patient's medical records. Any treatment with immunosuppressive therapy was decided upon at the discretion of the local consulting physician. The Harran University Hospital at Şanlıurfa was the coordinating center (HRU/2021.17.29), and local ethical review boards of participating centers approved the study.

Liver injury

New-onset liver injury was defined as elevations of alanine or aspartate aminotransferase (ALT or AST) $\geq 5 \times$ upper limit of normal (ULN) and/or alkaline phosphatase (ALP) $\geq 2 \times$ ULN or ALT/AST $\geq 3 \times$ UNL and bilirubin $\geq 2 \times$ ULN.^[11] All patients were categorized for liver injury pattern by using the R-value, which is defined as serum alanine aminotransferase (ALT)/upper limit of normal

(ULN) divided by serum alkaline phosphatase (ALP)/ULN. Liver injury was categorized as hepatocellular if R ratio was >5 , as mixed if 2–5 and as cholestatic if <2 . The severity of the liver injury was categorized as (1) mild if serum enzyme elevations reached criteria for liver injury but bilirubin concentration was $<2\times$ ULN; (2) moderate if either bilirubin $\geq 2\times$ ULN or symptomatic hepatitis; (3) severe if bilirubin concentration $\geq 2\times$ ULN and signs of liver failure (INR ≥ 1.5 , ascites and/or encephalopathy) or other organ failure considered to be due to liver injury; and (4) fatal if death from liver disease or the need for liver transplantation due to liver injury.^[12]

Data collection

Case report forms included comprehensive laboratory and serologic data that included anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), anti-mitochondrial antibodies (AMA), anti-liver/kidney microsome type 1 (LKM-1), anti-liver cytosol type 1 (LC-1), anti-soluble liver antigen/liver pancreas antigen (anti-SLA/LP), serum immunoglobulin G (IgG) and ceruloplasmin levels, serological tests for hepatitis virus A-C, Cytomegalovirus and Epstein–Barr virus. Autoimmune liver serology was evaluated according to local laboratory standards and a titer of 1:40 or higher was considered positive for ANA, SMA, LC-1, and LKM-1. Local pathologists in the participating centers evaluated liver biopsies; data from their reports were used in the study. Fibrosis was classified according to the METAVIR scoring system.^[13] The simplified criteria were applied for the diagnosis of AIH.^[14]

Statistical Analysis

Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL) version 26. The variables were investigated by using (Kolmogorov-Smirnov/Shapiro-Wilk's test) analytical methods and visual methods (histograms, probability plots) to determine whether or not they were normally distributed. Descriptive analyses were presented (by using tables of frequencies for the ordinal variables) median (min-max) for the non-normally distributed and ordinal variables and means and standard deviations for normally distributed variables. The Chi-square test or Fisher's exact test where appropriate was performed to compare the proportions in different groups. The Kruskal-Wallis tests were performed to compare the non-normally distributed variables and ordinal variables among the groups and Mann–Whitney *U* test was performed to calculate the significance of pairwise differences by using Bonferroni correction to adjust for the

multiple comparisons. A *p* value <0.05 was considered to represent statistical significance.

RESULTS

Characteristics of the study population

The general characteristics, clinical features, and outcomes are presented in [Table 1](#). The preliminary data of eight cases were reported previously.^[9,15–21] The median age at the time of diagnosis was 48 (range 18–79) years and 55 (63%) were female. The median body mass index (kg/m^2) was 25 (range 17–33). Twenty-four (28%) patients had been diagnosed with other autoimmune disorders before liver injury onset. Autoimmune thyroid diseases were present in 12 (14%) patients, inflammatory bowel diseases in three (3%), sarcoidosis in three (3%), systemic lupus erythematosus in two (2%), celiac disease in two (2%), rheumatoid arthritis, pemphigus vulgaris, lichen planus, and multiple sclerosis in each one patient.

Liver injury was identified after vaccination with the Pfizer-BioNTech (BNT162b2) vaccine in 51 (59%) of the cases, the Oxford-AstraZeneca (ChAdOX1 nCoV-19) vaccine in 20 (23%) and the Moderna (mRNA-1273) vaccine in 16 (18%). Forty (46%) developed liver injury after the first vaccine dose and 47 (54%) were diagnosed after the second dose. The median time from vaccination to the onset of liver injury was 15 (range: 3–65) days. Three patients had mild hepatitis after the first dose of vaccine but a more severe liver injury after a second dose of the same vaccine.

Most patients (92%) were symptomatic at presentation; fatigue 65 (75%), nausea 55 (63%) and jaundice 34 (39%) were the most reported symptoms. The pattern of liver injury was hepatocellular in 73 (84%), mixed in 9 (10%) and cholestatic in 5 (6%).

Autoantibodies were studied in 83 (95%) patients. Among these, ANA was positive in 56 (67%), SMA was positive in 15 (18%) and five (6%) cases showed seropositivity for AMA. Both anti-SLA and LC-1 were detected in one patient. The IgG level was measured in 79 (91%) patients and was high in 53 (67%) of these.

Immune-mediated features

Serum autoantibody profile and IgG level were assessed in 79 cases, of whom 45 (57%) showed an immune-mediated phenotype (positive autoantibodies and elevated IgG levels). Forty-four patients also underwent a liver biopsy. General characteristics, biochemical findings, patterns of liver injury, frequency of severe liver injury were similar in patients with and without features of immune-mediated hepatitis ([Table 2](#)). Among the 44 with liver histology, 34 (77%)

TABLE 1 General characteristics of the study population

	Overall (n = 87)	Corticosteroid therapy (n = 46)	No corticosteroids (n = 41)	p value
Age (years), median (min, max)	48 (18–79)	47 (20–69)	49 (18–79)	0.529
Sex, female, n (%)	55 (63.2)	29 (63)	26 (63.4)	0.971
Pre-existing liver disease, n (%)	12 (13.8)	3 (6.5)	9 (22)	0.037
Symptoms at liver injury onset, n (%)				
Jaundice	34 (39.1)	22 (47.8)	12 (29.3)	0.077
Nausea	55 (63.2)	30 (65.2)	25 (61)	0.682
Fatigue	65 (74.7)	36 (78.3)	29 (70.7)	0.420
Fever	10 (11.5)	4 (8.7)	6 (14.6)	0.386
Abdominal pain	21 (24.1)	9 (19.6)	12 (29.3)	0.291
Rash	7 (8)	3 (6.5)	4 (9.8)	0.580
Itching	10 (11.5)	4 (8.7)	6 (14.6)	0.386
Peak ALT × ULN	16.7 (3.1–203.7)	21.9 (5–203.7)	9.2 (3.1–81.8)	<0.001
Peak AST × ULN	15.4 (1.8–250)	23.4 (2.7–250)	9.2 (1.8–70.1)	<0.001
Peak ALP × ULN	1.3 (0.4–7.1)	1.3 (0.4–7.1)	1.4 (0.4–6.5)	0.595
Peak total bilirubin × ULN	2.6 (0.3–23.2)	5.3 (0.6–23.2)	1.1 (0.3–19.5)	0.003
INR	1.1 (0.6–3.8)	1.3 (0.7–3.8)	1 (0.6–2.4)	<0.001
Pattern of injury, n (%)				
Hepatocellular	73 (83.9)	44 (95.7)	29 (70.7)	0.020
Mixed	9 (10.3)	2 (4.3)	7 (17.1)	0.052
Cholestatic	5 (5.7)	-	5 (12.2)	0.015
ANA positivity, n (%)	56 (67.5)	33 (73.3)	23 (60.5)	0.215
SMA positivity, n (%)	15 (18.1)	11(24.4)	4 (10.5)	0.101
AMA positivity, n (%)	5 (6)	4 (8.9)	1 (2.6)	0.233
IgG × UNL	1.09 (0.41–2.71)	1.19 (0.71–2.71)	1.02 (0.41–1.97)	0.001
IgG > UNL, n (%)	53 (67.1)	35 (77.8)	18 (52.9)	0.020
Fibrosis stage 0-2, n (%)	41 (93.2%)	34 (91.9)	7 (100)	0.435
Severity score, n (%)				
Grade 1	38 (43.7)	14 (30.4)	24 (58.5)	0.008
Grade 2	31 (35.6)	16 (34.8)	15 (36.6)	0.861
Grade 3	17 (19.5)	15 (32.6)	2 (4.9)	0.001
Grade 4	1 (1.1)	1 (2.2)	-	0.342
Liver transplant, n (%)	1 (1.1)	1 (2.2)	-	0.342
Days from peak ALT to normalization	46 (15–185)	60 (15–185)	39 (18–114)	0.085

Note: Values reported as median (min-max) range.

Abbreviations: AMA, anti-mitochondrial antibody, ANA, anti-nuclear antibody and SMA, smooth muscle antibody were studied in 83 patients; IgG, immunoglobulin G, was measured in 79 patients; ULN, upper limit of normal; liver histology was performed in 44 patients.

were ascribed as probable/definite AIH according to the simplified criteria. Among 35 cases who did not have a liver biopsy, 12 (34%) still reached a score of probable AIH. Corticosteroid therapy was more often given to patients who had immune-mediated hepatitis than to those without (71.1% vs. 38.2%, $p = 0.003$), but median time from liver injury to biochemical resolution was similar. Follow-up duration after resolution of liver injury was longer in patients with immune-mediated hepatitis than in those without (120 vs. 80 days, $p = 0.036$).

Concomitant medications

Twenty-three (26%) patients were taking medication for concomitant diseases prior to the onset of liver injury. Thirteen had hypertension and/or diabetes mellitus. Therapy was not discontinued in any of these. Six patients were on statins since more than 2 years. Therapy was discontinued in three of these. No patient had relapse of liver injury following readministration of the same drug. Mesalazine was not withdrawn in three patients with inflammatory bowel diseases.

TABLE 2 Characteristics of cases according to features of immune-mediated hepatitis

	With immune-mediated hepatitis (n = 45)	Without immune-mediated hepatitis (n = 34)	p value
Age, median years (range)	49 (30–76)	48 (18–79)	0.556
Sex (female), n (%)	29 (64.4)	19 (55.9)	0.440
Pre-existing liver disease, n (%)	4 (8.9)	4 (11.8)	0.675
Autoimmune disease, n (%)	15 (33.3)	6 (17.6)	0.118
Peak ALT × ULN	18.8 (3.1–81.8)	10.7 (3.3–203.7)	0.305
Peak AST × ULN	18.1 (2.6–250)	13.1 (1.8–174.3)	0.078
Peak ALP × ULN	1.3 (0.4–7.1)	1.4 (0.6–6.5)	0.770
Peak total bilirubin × ULN	5.8 (0.6–23.2)	2.2 (0.3–17.9)	0.079
INR	1.2 (0.6–3.8)	1.1 (0.6–3.6)	0.662
Pattern of injury, n (%)			
Hepatocellular	40 (88.9)	27 (79.4)	0.245
Mixed	3 (6.7)	4 (11.8)	0.430
Cholestatic	2 (4.4)	3 (8.8)	0.429
Fibrosis stage 0–2, n (%)	28 (90.3)	13 (100)	0.245
Grade 3–4 liver injury, n (%)	12 (26.7)	5 (14.7)	0.200
Corticosteroid therapy, n (%)	32 (71.1)	13 (38.2)	0.003
Liver transplant, n (%)	-	1 (2.9)	0.247
Time from liver injury to normalization (days)	54 (15–185)	40 (15–120)	0.137
Follow-up duration after normalization (days)	120 (35–182)	80 (45–192)	0.036

Note: Eight patients (six without complete laboratory assessment and two with known AIH diagnosis) were not included in immune-mediated phenotype analysis. Of these eight patients, one received corticosteroid therapy.

One patient had active breast cancer and was under systemic chemotherapy (carboplatin, docetaxel and trastuzumab) when liver injury was observed. The chemotherapy protocol was not suspended and liver biochemistry spontaneously improved. One patient with AIH and other patient with pemphigus vulgaris were receiving azathioprine therapy, which was maintained during and after the period of liver injury. One patient was on weekly pegylated interferon alfa-2a for polycythemia for two years. This therapy was not discontinued at the onset of liver injury. Three patients used both ibuprofen (400–1200 mg/day) and acetaminophen (1–3 g/day) for 3–4 days prior to the diagnosis of liver injury. No patient was taking an anti-TNF- α agent prior to the onset of liver injury.

Patients with pre-existing liver diseases

Twelve (14%) patients who developed liver injury attributed to SARS-CoV-2 vaccination had pre-existing liver disorders. Seven patients had NAFLD based on liver ultrasound and mildly elevated liver tests. Their ALT levels were 0.8–1.6× UNL in the last follow-up before vaccination and peak ALT reached 5.2–28.5× UNL following vaccination. Two patients with AIH were in complete biochemical remission for more than one year before

developing liver injury after vaccination (peak ALT > 10× UNL). One had spontaneous resolution and in the other biochemical response was obtained by increasing the prednisolone dose. A patient with primary biliary cholangitis (PBC) whose ALT levels were normal at last follow-up before vaccination, presented with liver injury (ALT > 5× UNL and IgG 1.41× UNL) 20 days after vaccination. Laboratory values returned to normal levels without specific therapy. One patient with cured for previous HCV and another patient who was many years earlier transplanted for primary sclerosing cholangitis developed liver injury following vaccination. Both patients had spontaneous resolution of laboratory values during follow-up.

For any reasons, 54 (62%) patients had checked aminotransferase levels on a median of 120 (20–340) days prior to the onset of liver injury. Aminotransferase levels were normal in 48 patients and were >1–3× UNL in six of whom four had pre-existing NAFLD. On the other hand, only four of patients showed clinical or histological findings of advanced fibrosis.

Case characteristics according to vaccine type

The general characteristics, laboratory values and outcomes of the patients according to SARS-CoV-2 vaccine

type are presented in the [Table 3](#). An immune-mediated phenotype was observed in similar proportions of patients who developed liver injury following vaccination with the Pfizer-BioNTech, Oxford-AstraZeneca and Moderna vaccines (59.6%, 55.6%, and 50%, $p = 0.810$). The rates of patients treated with corticosteroids were similar (47.1%, 60%, and 62.5%, $p = 0.429$). Overall, treatment response and outcomes were also similar among the three vaccine groups.

Treatment and outcome

Corticosteroids (20–100 mg/day, prednisolone equivalent dose) were given to 46 patients of whom 11 also received a second immunosuppressive drug, including azathioprine (50–100 mg/day) in nine and mycophenolate mofetil (1000 mg/day) in two. Plasma exchange (3–6 cycles) was performed in nine patients and three of these also received corticosteroid therapy. One patient received intravenous immunoglobulins in addition to corticosteroids. Corticosteroids were more often given to patients with grade 3–4 liver injury than to those with grade 1–2 liver injury (88.9% vs. 43.5%, $p = 0.001$). The median time from the onset of liver injury to normalization of aminotransferases was 46 (15–185) days, not significantly different between corticosteroid-treated and nontreated patients (60 vs. 39, $p = 0.085$).

One patient developed mild liver injury after a first dose of Pfizer-BioNTech vaccine but presented with severe liver injury following a second dose of the same vaccine. Treatment with prednisolone (40 mg/day, intravenously) and plasma exchange did not improve the liver function. The patient progressed into liver failure with hepatic encephalopathy and underwent living donor liver transplantation. Review of the liver biopsy showed features of immune-mediated liver injury ([Figure S1](#)).

Two patients who developed liver injury following Oxford-AstraZeneca vaccination were switched to Pfizer-BioNTech for the second vaccine dose. Neither of these two had a liver injury after the second vaccine dose. Immunosuppression was withdrawn in 26% (12/46) of the patients during the study period and none of these relapsed after 44–140 days of follow-up. Similarly, 41 cases who showed spontaneous resolution of liver injury did not develop relapse during a median 69 days of (35–172) follow-up.

DISCUSSION

The current study describes the clinical presentation, laboratory features and prognosis of 87 patients who developed liver injury associated with SARS-CoV-2 vaccination. Overall outcomes with or without steroid therapy were good except for one patient who

TABLE 3 General characteristics of the study population according to type of SARS-CoV-2 vaccine

	Pfizer-Biontech (n = 51)	Oxford-AstraZeneca (n = 20)	Moderna (n = 16)	p value
Age, median years (range)	46 (18–71)	47 (20–76)	57 (21–79)	0.157
Sex, female, n (%)	32 (62.7)	10 (50)	13 (81.3)	0.154
Pre-existing liver disease, n (%)	7 (13.7)	2 (10)	3 (18.8)	0.751
Peak ALT × ULN	16.7 (3.1–203)	11.7 (3.2–63.8)	21.7 (5–66.4)	0.519
Peak AST × ULN	14.9 (1.8–250)	14 (2.6–169)	21.4 (3.4–55)	0.608
Peak ALP × ULN	1.3 (0.6–6.5)	1.2 (0.7–2.2)	1.3 (0.4–5.6)	0.970
Peak total bilirubin × ULN	2.6 (0.5–19.5)	5.4 (0.5–22.1)	1.1 (0.3–23.2)	0.210
INR	1.1 (0.7–3.6)	1.3 (0.6–3.8)	1 (0.6–2.7)	0.289
Pattern of injury, n (%)				
Hepatocellular	43 (84.3)	17 (85)	13 (81.3)	0.948
Mixed	5 (9.8)	2 (10)	2 (12.5)	0.952
Cholestatic	3 (5.9)	1 (5)	1 (6.3)	0.985
ANA positivity, n (%)	31 (63.3)	15 (75)	10 (71.4)	0.603
SMA positivity, n (%)	8 (16.3)	5 (25)	2 (14.2)	0.643
IgG × UNL	1.12 (0.41–2.61)	1.05 (0.5–2.71)	1.08 (0.60–1.84)	0.833
Immune-mediated phenotype, n (%)	28 (59.6)	10 (55.6)	7 (50)	0.810
Grade 3-4 liver injury, n (%)	9 (17.6)	6 (30)	3 (18.8)	0.501
Liver transplant, n (%)	1 (2)	-	-	0.700
Corticosteroid therapy, n (%)	24 (47.1)	12 (60)	10 (62.5)	0.429

progressed into fulminant liver failure and required liver transplantation.

The liver injury was predominantly hepatocellular and showed features of immune-mediated hepatitis. Among 44 patients with complete laboratory and histological work-up, 34 (77%) had probable or definite AIH according to the simplified AIH criteria. Previously reported cases of post-SARS-CoV-2 vaccine-induced liver injury also mostly had features of AIH.^[8–10,15–21] The exact mechanism of SARS-CoV-2 vaccine-induced liver injury is not known. The two vaccine formulations (mRNA and viral vector) encode the SARS-CoV-2 spike (S) protein. The entry of S protein in the human body elicits a strong stimulus to innate immunity, which results in cellular activation leading to proinflammatory cytokine and chemokine production.^[5] Due to molecular similarity between S protein and liver specific proteins, an activated immune system may lead to destruction of liver proteins. A recent study showed that anti-SARS-CoV-2 S protein antibodies reacted to human tissue antigens, which resulted in significant elevations of immune-mediated markers, such as ANA, anti-actin and AMA.^[22]

Previous reports suggest corticosteroid treatment in patients with immune-mediated liver injury.^[23] A high proportion of individuals with immune-mediated hepatitis received corticosteroid therapy in the present study. Corticosteroids were well tolerated by 46 treated patients and no patient experienced severe side effects. Corticosteroid therapy was also more often used in patients with laboratory features of severe hepatitis. This may explain why the time from peak aminotransferase to normalization was longer in corticosteroid-treated patients.

One patient progressed into liver failure. To our knowledge, this is the first reported case to be transplanted due to liver failure attributed to SARS-CoV-2 vaccination.^[24] Another 42-year-old woman had laboratory findings of severe hepatitis and developed low grade hepatic encephalopathy. This patient was listed for liver transplantation but fortunately improved after plasma exchange and corticosteroid therapy. A few cases of SARS-CoV-2 vaccine-induced liver injury have been reported and all had good response to therapy. These reports provide limited information about severity of liver injury, but some had features of severe liver injury.^[9,10]

Distinguishing immune-mediated liver injury following vaccination from new-onset or flare of a pre-existing AIH is challenging.^[25,26] In our study population, 48 patients had normal aminotransferase levels in the year prior to vaccination. Also, 41 patients who showed spontaneous resolution of liver injury did not develop relapse during follow-up. Although immune-mediated liver injury can show histological features resembling AIH, the presence of advanced fibrosis is highly suggestive of AIH.^[27] Among the 44 biopsied patients,

liver histology showed advanced fibrosis in only three (7%), and one had laboratory, imaging, and endoscopic features of cirrhosis. Another patient was seropositive for both anti-SLA and anti-LC-1, which are both highly suggestive of AIH and rarely detected in other liver disorders.^[28] The distinction between immune-mediated liver injury and AIH is also facilitated by steroid response and outcome. In previous studies, patients with drug induced-AIH were successfully withdrawn from corticosteroid therapy, whereas relapse is common in AIH.^[26,29] Corticosteroid therapy was discontinued in 12 patients and none of these had relapse during follow-up. These results suggest that most of our patients had new-onset immune-mediated liver injury rather than flare or unmasking of an underlying classical AIH.

Determining causality can be challenging also in the context of pre-existing conditions and concomitant medication. Two AIH patients who had normal aminotransferases at last follow-up developed liver injury following vaccination. Both were strictly adherent to immunosuppressive therapy. A spontaneous flare of AIH was therefore unlikely. Baseline aminotransferases were normal also in a woman with PBC who presented with features of hepatitis after vaccination. Importantly, all three patients developed symptoms within a few days after vaccination, which also suggests causality.

Statin therapy which in rare instances can lead to liver injury,^[30] was discontinued in three of six patients. Reintroduction of the same drug did not result in relapse of liver injury. Interferon therapy is another known cause of immune-mediated liver injury.^[31] One patient was under pegylated interferon therapy which was not discontinued. Some patients used acetaminophen and/or ibuprofen for postvaccine symptoms. Acetaminophen doses were used in therapeutic doses in these patients and those who used ibuprofen also had an immune-mediated hepatitis, which is not typical in ibuprofen-associated induced liver injury.^[32] These medications were therefore very unlikely to be causative.

A recent report described rapid onset liver injury after a first Moderna mRNA vaccine dose in a patient who developed severe AIH after a second dose.^[33] Three of the patients in the current study experienced mild liver injury after the first vaccination but more severe liver injury following the second dose of the same vaccine (one underwent transplantation). Two cases did not experience liver injury when another vaccine type was chosen for the second dose. This data suggests that re-exposure to the same vaccine type should be avoided after SARS-CoV-2 vaccine-induced liver injury. A recent study demonstrated that heterogeneous vaccination (Oxford-AstraZeneca followed by Moderna or Pfizer-BioNTech) had significantly greater efficacy than twice homologous Oxford-AstraZeneca vaccination.^[34]

Data in the present study was derived from experienced hepatologists in 18 countries across Europe and the Americas. The strength of the study is the large

number of cases with liver injury following SARS-CoV-2 vaccination. The retrospective nature of our study is one of the limitations. Due to the design of the study, the frequency of SARS-CoV-2 vaccine-induced liver injury could not be estimated. It is also difficult to predict the long-term impact of liver injury in these patients. Thirty-four (39%) of patients were still on immunosuppression at the last follow-up, which is rather short. A more recent study showed that corticosteroid-treated patients with infliximab induced liver injury did not have a relapse after stopping immunosuppression.^[35] It thus seems prudent to try to discontinue immunosuppression in patients with vaccine-induced liver injury. If no relapse occurs, this would support that vaccination was indeed the etiology.

We do not discourage SARS-CoV-2 vaccination. The overall benefits of vaccination during the pandemic clearly outweigh the risks of liver injury and other rare side effects. The number of patients described here is minuscule compared to the population vaccinated worldwide. The current study rather aimed to increase awareness about this rare side effect, to promote early recognition and to provide guidance for adequate management. New-onset or flares of immune-mediated conditions are known phenomena after different vaccinations,^[36] such as AIH following hepatitis A vaccination.^[37] That SARS-CoV-2 vaccination can trigger immune-mediated hepatitis is therefore not unexpected. We did not compare safety profiles and our data do not suggest a difference between vaccine types. That about half of our cases with liver injury were attributed to the Pfizer-BioNTech vaccine rather reflects differences in vaccination strategies and vaccine availability between countries.

In conclusion, this large international case series provides evidence for the hepatotoxicity potential of SARS-CoV-2 vaccines (Pfizer-BioNTech, Moderna and Oxford-AstraZeneca). The clinical phenotype is mostly hepatocellular and can show features immune-mediated hepatitis. Spontaneous resolution was common, steroid response was good and prognosis favorable. One patient however progressed into liver failure and underwent liver transplantation.

AUTHOR CONTRIBUTIONS

Cumali Efe, Thomas D. Schiano, Staffan Wahlin, and Ezequiel Ridruejo conceptualized the study. Cumali Efe, Anand V. Kulkarni, Benedetta Terziroli Beretta-Piccoli, Tugrul Purnak, Bianca Magro, Mustafa Cengiz, Staffan Wahlin, and Ezequiel Ridruejo collected and analyzed data. Mustafa Cengiz performed statistical analysis. Cumali Efe, Anand V. Kulkarni, Benedetta Terziroli Beretta-Piccoli, Bianca Magro, Albert Friedrich Stättermayer, Mustafa Cengiz, Daniel Clayton-Chubb, Craig Lammert, Christine Bernsmeier, Özlem Gül, Fatima Higuera-de la Tijera, Margarita Anders, Ellina Lytvyak, Mete Akin, Rodrigo Liberal, Mirta Peralta, Berat Ebik, Serkan Duman,

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CONFLICTS OF INTEREST

Eric M. Yoshida received grants and honoraria from Intercept. He received grants from Gilead, Merck, AbbVie, Intercept, Genfit, Madrigal, Allergan, Celgene, Pfizer, Paladin Laboratories, and Novodisk. He received honoraria from Lupin. Stefano Fagioli advises and is on the speaker's bureau for AbbVie, Gilead, Novartis, and Kedrion. He is on the speakers' bureau for Intercept.

ETHICS STATEMENT

We confirm that the requirement for informed consent was waived by the institutional review committee. No donor organs were obtained from executed prisoners or other institutionalized persons.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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