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Immune-mediated liver injury following COVID-19 vaccination: A systematic review

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Abstract

Immune-mediated liver injury (ILI) following coronavirus disease 2019 (COVID-19) vaccination is not well-characterized. Therefore, we systematically reviewed the literature on ILI after COVID-19 vaccination. We searched PubMed, Cochrane, Ovid, Embase, and gray literature to include articles describing ILI following COVID-19 vaccination. Reports without confirmatory evidence from liver biopsy were excluded. Descriptive analysis, and study quality were reported as appropriate. Of the 1,048 articles found, 13 (good/ fair quality; 23 patients) were included. Studies were primarily from Europe ($n = 8$), America ($n = 2$), Asia ($n = 2$), or Australia ($n = 1$). Patients were predominantly females (62.5%) of age 55.3 years (49.1–61.4), with an antecedent exposure to Moderna messenger RNA (mRNA)–1273 (47.8%), Pfizer-BioNTech BNT162b2 mRNA (39.2%), or ChAdOx1 nCoV-19 vaccine (13%). Pre-existing comorbidities (69.6%) were common, including liver disease in 26.1% and thyroid disorders in 13% of patients. About two-thirds of the patients were on concurrent medications (paracetamol, levothyroxine, statins, and nonsteroidal anti-inflammatory drugs). Jaundice was the most common symptom (78.3%). Peak bilirubin, alanine aminotransferase, and alkaline phosphatase levels were 10.8 (6.8–14.8) mg/dl, 1,106.5 (757.0–1,702.5) U/L, and 229 (174.6–259.6) U/L, respectively. Histological findings were intense portal lymphoplasmacytic infiltrate with interface hepatitis. Steroids were used in 86.9% of patients, and complete response, recovering course, and death were reported in 56.5%, 39.1%, and 4.3% of patients, respectively. ILI following COVID-19 vaccination is rare. The diagnosis is established on temporal correlation, biochemical findings, and histopathology. Prognosis is excellent with corticosteroids. Causality establishment remains a challenge.

INTRODUCTION

The COVID-19 pandemic has led to enormous morbidity and mortality globally. The development of vaccines at an unprecedented speed and scale has become the most decisive measure to combat this global humanitarian crisis.[1] Rare adverse events are an expected component of any vaccination strategy. Multiple rare adverse events, including hypersensitivity reactions, thrombotic thrombocytopenic purpura, and vaccine-induced immune thrombotic thrombocytopenia, have been reported with coronavirus disease 2019 (COVID-19) vaccines.[2] Vaccine-induced autoimmunity due to potential molecular mimicry and immune-mediated cross-reactions have been described with influenza (HIN1), hepatitis B, and human papilloma virus vaccines.[3] Along similar lines, possible triggering of autoimmunity due to cross-reactivity of antibodies to SARS-CoV-2 spike proteins and human tissues have been suggested.[4–6] Recently, multiple reports of immune-mediated liver injury (ILI) following COVID-19 vaccines of different technological platforms have been reported with variable characteristics. However, the incidence, patient presentation, and outcomes remain less well characterized. Therefore, we systematically reviewed the existing literature on suspected ILI following COVID-19 vaccination.

METHODS

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and guidelines for reporting synthesis without meta-analysis and submitted in PROSPERO.[7,8] PubMed, Cochrane Library, Ovid, and Embase were searched from inception until October 5, 2021, to identify literature describing ILI or autoimmune hepatitis (AIH) following COVID-19 vaccination (Table S1). The eligibility for the available literature was determined by screening the titles and the abstracts. In addition, the list of references of all original articles and systematic reviews published were hand-searched to include any study that was omitted on electronic search. Gray literature was also searched manually and through Google Scholar.

Search strategy

The criteria for study selection were decided and reviewed by three independent investigators (A.R., N.V., and S.S.). The search was performed by a librarian (P.P.) using Boolean combinations of the MeSH terms of keywords provided in Table S2. No additional filters were applied.

Eligibility criteria

All eligible original articles, case reports, case series, commentaries, and letters to the editors were included without any language restrictions. The inclusion criteria were patients with ILI or AIH following documented COVID-19 vaccination (any vaccine technology platform). Patients without corroborative evidence from liver biopsy were excluded. Review articles and systematic reviews were excluded.

Selection process

Duplicate records of the same report were removed using Endnote X9. Articles were screened by title and abstracts by two independent reviewers (A.R. and N.V.). The item was included in a full-text review by two independent reviewers (A.R. and N.V.) in case of uncertainty. In case of a lack of agreement at this stage, a third reviewer (S.S.) was consulted.

Data collection process, data items, and synthesis methods

The data were independently extracted by three reviewers (A.R., N.V., and S.S.) using a pre-piloted data extraction sheet. For each study, the author's name, country of origin, year of conduct/publication, design, number of patients, ethnicity, background comorbidities, concurrent medication use, type and dose of COVID-19 vaccine administered, the time duration between onset of liver injury and vaccination, biochemical parameters, autoimmune serologies, viral serologies, histological findings, type of treatment, and presence/absence of response was documented. Any difference between the extracted data was settled after discussion with an arbitrator (M.S.). The proportion (percentage), mean, or median (95% confidence interval [CI]) were described as appropriate. Because most of the reports were single-patient case reports, narrative synthesis was performed for most of this review.

Quality assessment

Quality appraisal for the included reports was done with a domain-based tool described by Murad et al.[9] The tool described by Murad et al. has been used frequently for quality assessment and specifically pertains to case reports and case series with focus on causality assessment. The tool gives a comprehensive assessment based on four domains of selection, ascertainment, causality and reporting, and incorporates key elements of other previously used tools.[10,11] Two authors (AR and NV) independently evaluated the

quality of included studies. We preferred reporting an overall judgment instead of aggregate scores based on the questions relevant to the case scenario under consideration.[9,12]

RESULTS

Study selection

Of the 1,048 articles searched, 320 were excluded for duplicates, and 768 were excluded after a title and abstract search. Twenty-one articles were retrieved for full-text review, of which 13 were finally included for the systematic review (Figure 1).

Study characteristics

The characteristics of the study are found in Table 1. There were 23 patients from 13 studies, of which 11 were individual case reports,[13–23] whereas two

were case series.[24,25] Most of the reports were from Europe,[15–20,22,23] whereas two reports each were from America[13,25] and Asia,[21,24] and one from Australia.[14] The largest reported series was from the United States, including 10 patients (originally had 16 cases of whom biopsy was available in 10 cases).[25] Eleven (47.8%) of the patients had prior vaccination with Moderna messenger RNA (mRNA)–1273 vaccine, whereas 9 patients (39.2%) had prior exposure to Pfizer-BioNTech BNT162b2 mRNA vaccine, and 3 patients (13%) had received ChAdOx1 nCoV-19 vaccine.

Patient characteristics

Almost two-thirds (62.5%) of the patients were females with a mean age of 55.3 years (95% CI: 49.1–61.4) (Table 2). A substantial proportion (69.6%) of the patients had pre-existing comorbidities, with pre-existing liver disease (26.1%) and thyroid disorders (13%) being the most common. Patient ethnicity was reported for only 7 patients, of whom 4 were
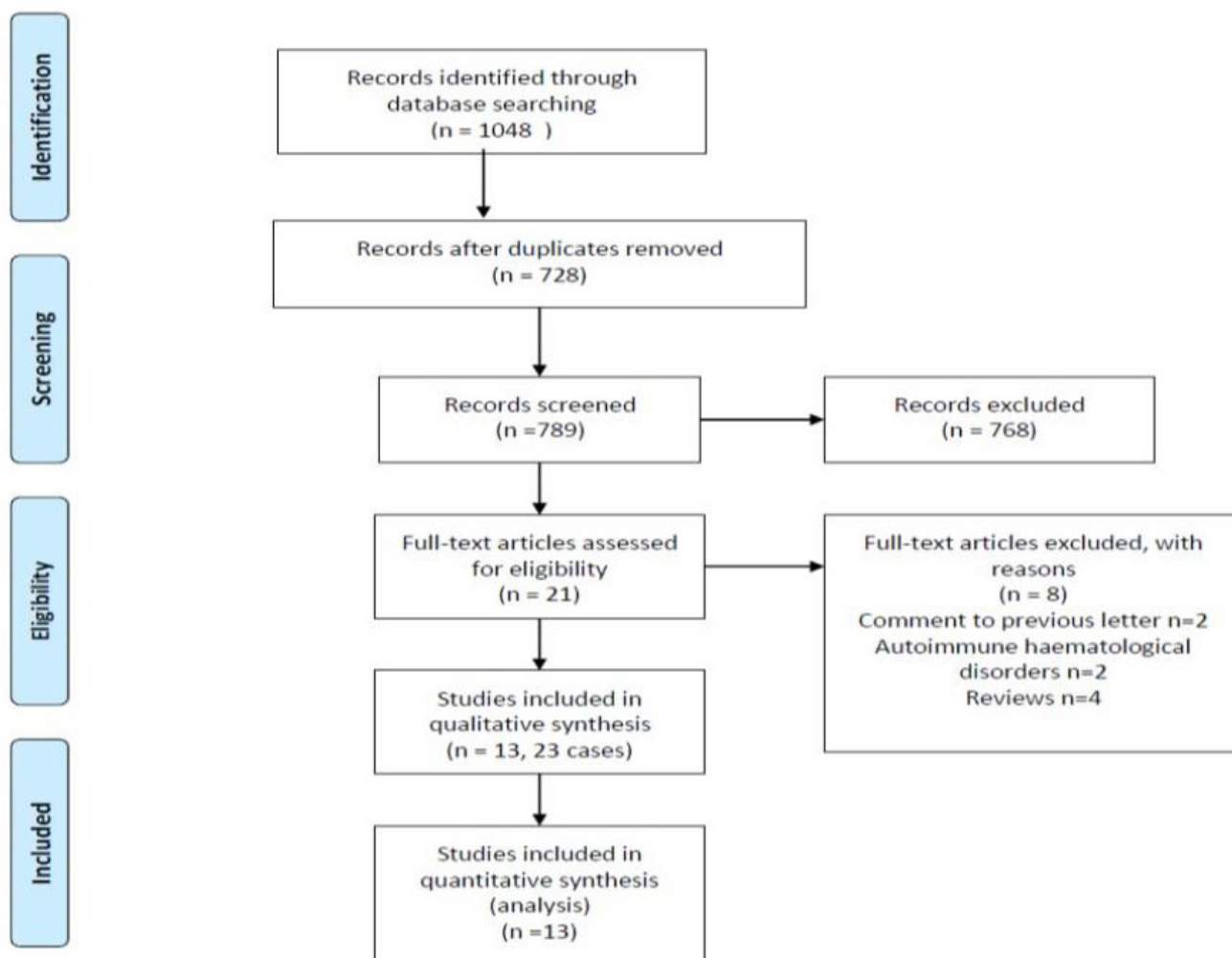

FIGURE 1 PRISMA flow diagram

TABLE 1 Characteristics of case reports/case series reporting autoimmune hepatitis after COVID-19 vaccination

Study, year	Design	Continent	Country	Number of patients	Vaccine type	Dose of vaccine preceding onset
Bril et al. 2021[13]	Case report	America	USA	1	Pfizer BionTech	1st
Clayton-Chubb 2021[14]	Case report	Australia	Australia	1	ChAdOx1 nCoV-19 vaccine (OxfordAstraZeneca)	1st
Lodato et al. 2021[15]	Case report	Europe	Italy	1	m-RNABNT162b1 Pfizer BioNTech	1st
Londono et al. 2021[16]	Case report	Europe	Spain	1	SARS-CoV-2 Moderna vaccine (mRNA-1273)	2nd
Rocco et al. 2021[17]	Case report	Europe	Italy	1	Pfizer-BioNTech BNT162b2 mRNA	2nd
Lessard et al. 2021[18]	Case report	Europe	Switzerland	1	mRNA-1273 SARS-CoV-2	1st
Rela et al. 2021[24]	Case series	Asia	India	2	Covishield (ChAdOx1)	1st
McShane 2021[19]	Case report	Europe	Ireland	1	Moderna mRNA	1st
Gheilmetti et al. 2021[20]	Case report	Europe	Switzerland	1	mRNA-1273 SARS-CoV-2	1st
Tan et al. 2021[21]	Case report	Asia	Singapore	1	Moderna-COVID-19 vaccine (mRNA-1273)	1st
Zhou et al. 2021[22]	Case report	Europe	Germany	1	Moderna mRNA-1273	1st
Shroff et al. 2021[25]	Case series	America	USA	10	6-Pfizer-BioNTech BNT162b2 mRNA 4- Moderna-COVID-19 vaccine (mRNA-1273)	1st
Tun et al. 2021[23]	Case report	Europe	United Kingdom	1	Moderna-COVID-19 vaccine (mRNA-1273)	Both 1st and 2nd

Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA.

TABLE 2 Demographic, clinical, and biochemical parameters of patients with suspected autoimmune hepatitis after COVID-19 vaccination

Parameters	Values
Demography	
Age	55.3 (49.1–61.4)
Females	15 (62.5%)
Ethnicity (7 of 23)	Caucasians 4 (57.1%)
	Asians 3 (42.9%)
Continent (number of reports)	
Asia (2)	3 patients (13.0%)
Europe (8)	8 patients (34.8%)
America (2)	11 patients (47.8%)
Australia (1)	1 patient (4.3%)
Pre-existing comorbidities	
Liver disease	6 (26.1)
AIH	3[a]
Hepatitis C	1
NAFLD	1
PSC	1
Thyroid disorders	3 (13.0)
Hypertension	2 (8.7)
Diabetes mellitus	2 (8.7)
Coronary artery disease	1 (4.3)
Dyslipidemia	2 (8.7)
Recent COVID-19	1 (4.3)
Miscellaneous	3 (13.0)
None	7 (30.4)
Concurrent medications	
Thyroxine	3 (13.0)
Acetaminophen	4 (17.4)
Anti-hypertensives	2 (8.7)
NSAIDs	3 (13.0)
Statins	3 (13.0)
Antibiotics	1 (4.3)
Oral antidiabetics	2 (8.7)
Alternative medicine	1 (4.3)
None	8 (34.7)
Type of vaccine	
Moderna mRNA-1273	11 (47.8%)
ChAdOx1 nCoV-19 vaccine	3 (13.0%)
Pfizer-BioNTech BNT162b2 mRNA	9 (39.2%)
Time of onset from vaccination (days)	17.3 (11.2–23.4)
Symptoms	
Jaundice	18 of 23 (78.3%)
Pruritis	2 of 13 with reported other symptoms

(Continues)

TABLE 2 (Continued)

Parameters	Values
Fever	4 of 13 with reported other symptoms
Malaise and fatigue	7 of 13 with reported other symptoms
Choluria	4 of 13 with reported other symptoms
Anorexia, nausea, and vomiting	3 of 13 with reported other symptoms
Biochemical parameters	
Bilirubin, mg/dl (index) (13 of 23)	7.9 (4.1–11.6)
Bilirubin, mg/dl (maximum) (22 of 23)	10.8 (6.8–14.8)
AST U/L (index) (11 of 23)	868.5 (614.1–1,122.9)
AST U/L (maximum) (11 of 23)	956.4 (686.0–1,226.8)
ALT U/L (index) (13 of 23)	1,094 (820.2–1361.1)[b]
ALT U/L (maximum) (23 of 23)	1,106.5 (757.0–1,702.5)[b]
ALP U/L (19 of 23)	229 (174.6–259.6)[b]
INR (17 of 23)	1.2 (1.1–1.29)[b]
Albumin g/dL (4 of 23)	3.6 (2.0–5.2)
IgG (mg/dl)	2,308.2 (1,748.6–2,867.8)
Autoimmune markers	
Antinuclear antibody (19 of 23)	13 (56.5)
Anti-smooth muscle antibody (20 of 23)	7 (35)
Raised IgG (>1.1 times ULN) (16 of 23)	8 (50)
Treatment modality	
Steroid	20 (86.9)
Azathioprine	2 (8.7)
Plasmapheresis	1 (4.3)
Supportive only	1 (4.3)
Response	
Complete resolution	13 (56.5)
Recovering	9 (39.1)
Time to recovery (10 of 23) (days)	41.3 (23.5–59.0)

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, Immunoglobulin G; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug; PSC, primary sclerosing cholangitis; ULN, Upper limit of normal.

[a]Two cases had pre-existing cirrhosis.
[b]Median (95% confidence interval).

Caucasians and 3 were Asians. A temporal course between vaccination and the onset of liver dysfunction was shown in all of the reports. Most cases were reported after the first dose of vaccination, and two[16,17] developed ILI after the second dose of vaccine. In contrast, in one case, there was an injury

after both doses of vaccine.[23] The mean duration between receiving the vaccine dose (either first or second) and subsequent onset of liver injury was 17.3 (11.2–23.4) days. Jaundice was the most typical presenting symptom (78.3%). A total of 65.3% were on concurrent medications (single or multiple), with the most common medications being paracetamol, levothyroxine, statins, and nonsteroidal anti-inflammatory drugs. Except for one report[15] in which *Gingko biloba* was consumed 100 days before the onset of the event, no other use of complementary or alternative medicine was reported.

Biochemical tests

Most of the studies reported liver function tests and coagulogram. Liver function tests primarily reflected a hepatic pattern of liver injury with peak values of bilirubin, alanine transaminase, aspartate transaminase, and alkaline phosphatase being 10.8 (6.8–14.8) mg/dl, 1106.5 (757.0–1702.5) U/L, 956.4(686.0–1226.8) U/L, and 229 (174.6–259.6) U/L, respectively. Except for two cases from the largest case series (21), all of the studies excluded typical viruses (hepatitis A, E, B, and C). One study did not report the exclusion of hepatitis E.[13] Atypical viruses were also excluded in most of the studies. One case had positive immunoglobulin G (IgG) for hepatitis A.[19] Antinuclear antibody (ANA) test was reported in 19 of the 23 cases, while anti-smooth muscle antibody (ASMA) was reported in 20 of the 23 cases. ANA was positive in 56.5% and anti-smooth muscle antibody (ASMA) in 35.5% of cases. IgG levels were reported in 16 of the 23 patients and were raised in 50%. Four (17.3%) issues were seronegative for standard autoimmune markers.

Histopathological findings

Liver biopsy was available for all patients. The histological patterns and findings are found in Table 3. Steroids, commonly oral prednisolone, was used with variable dosage regimens (1 mg/kg or 20–60 mg). Of the 23 patients, complete response was achieved in 13 (56.5%) patients, while 1 patient (4.3%) died (at 3 weeks), and 9 (39.1%) were recovering at the time of respective publication. Scoring parameters (simplified diagnostic criteria for AIH or revised original score for AIH) were reported in only 7 of 23 (30.4%) of the cases reported. We recalculated the simplified AIH score from available data and in a total of 11 cases. Of them, 4 had probable AIH, and 7 had a diagnosis of definite AIH as per the simplified scoring system. Only 1 patient satisfied the criteria of challenge-rechallenge, implying the causality.[23]

TABLE 3 Histological parameters on liver biopsy in patients with suspected AIH after COVID-19 vaccination

Parameter	Number (%)
Type of inflammation (22 of 23)	
Portal	13 (59.1)
Portal and lobular	7 (31.8)
Pan lobular	2 (9.1)
Severity of inflammation (21 of 23)	
Mild	4 (19.0)
Moderate	6 (28.6)
Intense	11 (52.4)
Type of infiltrate (22 of 23)	
Lymphocytic/lymphoplasmacytic	19 (86.4)
Mixed	3 (13.6)
Interface hepatitis	16 (69.6)
Central perivenultis	3 (13.0)
Cholestasis	6 (26.1)
Bile ductular changes	9 (39.1)
Any fibrosis (metavir F1 or above)	5 (21.7)
Cirrhosis	2 (8.7)
Eosinophilic infiltrate	8 (34.7)

DISCUSSION

This systematic review collated the available literature on potential ILI following COVID-19 vaccination, conclusively backed by histopathological evidence. The demographic characteristics of the reported population constituted mostly elderly females, with most of the reports originating from European countries. Biochemically and histologically, most of these cases with ILI resembled AIH, and most had an exquisite response to steroids. However, because the diagnosis and use of the term AIH is specifically attributed to patients with characteristic clinical findings, autoantibodies, histology, and exclusion of other potential etiologies like drug-induced liver injury we preferred using the term ILI in description of these reports.[26] An interesting finding however, was the presence of background autoimmune diseases (pre-existing AIH, Hashimoto thyroiditis, primary sclerosing cholangitis) in one-fourth of the patients, which suggests vaccine as a possible trigger for an ILI in a predisposed individual (Table 4).

The occurrence of immune-mediated reactions after vaccination is not a novel entity. Reports of narcolepsy, Guillain-Barré syndrome, and demyelinating neuropathies have been previously reported with H1N1 and hepatitis B vaccines.[27–29] The principal mechanisms linked to such occurrences involve molecular mimicry and immune cross-reactivity in genetically predisposed individuals following exposure to vaccines.[3] Even for COVID-19 vaccines, similar pathophysiological mechanisms of molecular mimicry have been proposed with

TABLE 4 Quality assessments of case reports/case series reporting immune-mediated liver injury after COVID-19 vaccination

Domain[a]	Selection[a]	Ascertainment		Causality			Enough follow-up length	Reporting[b]	Overall judgment of quality
Study		Exposure adequately ascertained	Outcome adequately ascertained	Alternative causes ruled out	Challenge-rechallenge phenomenon	Dose–response effect			
Bril et al. 2021[13]	✓	✓	✓	x	x	na	✓	✓	Fair
Clayton-Chubb 2021[14]	✓	✓	✓	✓	x	na	✓	✓	Fair
Lodato et al. 2021[15]	✓	✓	✓	✓	x	na	✓	✓	Fair
Londono et al. 2021[16]	✓	✓	✓	✓	x	na	✓	✓	Fair
Rocco et al. 2021[17]	✓	✓	✓	✓	x	na	✓	✓	Fair
Lessard et al. 2021[18]	✓	✓	✓	✓	x	na	✓	✓	Fair
Rela et al. 2021[24]	✓	✓	✓	x	x	na	✓	✓	Fair
McShane 2021[19]	✓	✓	✓	x	x	na	✓	✓	Fair
Gheilmetti et al. 2021[20]	✓	✓	✓	x	x	na	✓	✓	Fair
Tan et al. 2021[21]	✓	✓	✓	x	x	na	✓	✓	Fair
Zhou et al. 2021[22]	✓	✓	✓	✓	x	na	✓	✓	Fair
Shroff et al. 2021[25]	✓	✓	✓	✓	x	na	✓	✓	Fair
Tun et al. 2021[23]	✓	✓	✓	x	✓	na	✓	✓	Good

Abbreviation: na, not applicable.

[a]Does the patient represent the whole experience of the investigator (center), or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?

[b]Is the case described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

the hypothesis that vaccine-induced immunologic responses like polyclonal–B cell expansion triggers underlying dysregulated pathways.[4,6] This phenomenon may be even more prominent in genetically predisposed individuals due to epitope spreading and bystander activation processes.[30] A recent meta-analysis of suspected vaccine-induced immune-mediated thrombotic thrombocytopenia ChAdOx1-S recombinant COVID-19 vaccine showed a pooled incidence of 0.73 per 100,000 persons receiving the first dose of the vaccine (95% CI: 0.43–1.23).[31] Although the literature on individual vaccine technology is not robust, it has been postulated that mRNA-based vaccine is possibly associated with an increased risk of immune-mediated disease.[5] Such an association has been linked to mRNA's intrinsic immunostimulatory properties, which is recognized by intracellular receptors including toll-like receptors 3, 7 and results in downstream activation of proinflammatory cytokines.[32] Incidentally, most of the reported cases in the current systematic review were after mRNA-based vaccines. Literature from surveillance data of 2 million persons with 11.8 million doses who received mRNA vaccines and followed up until 21 days have shown conjectural associations with myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, and thrombosis with thrombocytopenia syndrome. Notably, ILI was not reported in the analysis.[33]

Biochemical findings in the reported patients were consistent with ILI resembling AIH. ANA and ASMA were positive in 56.5% and 35.5% of the cases, with seronegative status in 17%. Positivity for autoimmune markers like ANA and SMA, although commonly associated with AIH, is not pathognomonic for AIH and can be positive in a wide variety of etiologies of severe liver injury including viral hepatitis, acute liver failure, and drug-induced liver injury.[34–36] Furthermore, patients who have presentations like an acute AIH tend to be seronegative in 30% of cases.[26] Global literature shows an ANA positivity rate of 80% and SMA positivity of 63% in patients with the first presentation as AIH, with lower ANA positivity rates in those presenting as acute and severe AIH.[37,38] Interestingly, in addition to having a unique ANA pattern, one of the reports also reported an atypical anti-mitochondrial antibody positivity.[20]

One of the merits of this study was the corroborative histopathological evidence of ILI resembling AIH, with intense portal-based lymphoplasmacytic infiltrate as the most consistent finding. Intriguingly, more than a third of the patients also had an eosinophilic infiltrate, a finding often associated with drug-induced liver injury.[39,40] This brings to question whether vaccine incites a phenomenon similar to drug-induced-AIH (DI-AIH) or triggers an idiopathic AIH. Literature suggests a significant overlap between idiopathic AIH and DI-AIH cases. The presence of advanced fibrosis and relapse after withdrawing immunosuppression has been suggested to favor idiopathic ILI resembling AIH.[39] Apart from 2 cases with pre-existing cirrhosis, no patient had advanced fibrosis, suggesting vaccine-induced ILI. However, we believe the data are still limited for a clear interpretation, especially in patients with pre-existing chronic liver diseases such as autoimmune diseases.

The foremost challenge in the reports was establishing the causality, and none of the cases reported causality assessment scores. With the rampant upscaling of vaccination strategies, such reported events may be mere associations than causations. In this regard, except for 1 case,[23] none of the cases reported rechallenging with the vaccine to prove the causality. Concurrent use of drugs (statins, antibiotics) adds further confounding that may trigger autoimmunity and pose questions on the causality. However, those on statins specifically had a prolonged exposure that makes them unlikely as triggers.[20] Additionally, in patients with pre-existing autoimmune diseases, the possibility of the AIH presenting incidentally as a flare remains a glaring probability.

This systematic review aimed to aggregate the rapidly evolving evidence based on individual cases about a potential for ILI following COVID-19 vaccination. However, we reinforce that such evidence should not be used as a tool to promote vaccine hesitancy in the general population. The advantages of vaccination against COVID-19 in terms of lives saved and reduced severity of infections far outweigh the risk of AIH demonstrated in this review.

This review has several limitations. Given the rarity of events and the nature of available data, we could only perform a narrative synthesis. Although exact pooled incidences for the event could not be determined given the nature of the data, the crude incidence of post-vaccination ILI appears to be far below the reported global incidence of AIH in the general population, thus re-enforcing the rarity of the event.[41] Case reports and letters to editors lacked sufficient details and methodology. Such findings would suggest merely an association of AIH with the COVID-19 vaccination. However, on a cautionary note, there is a possibility of many unreported cases of post-vaccination I. The exact pathogenesis of ILI after COVID vaccination remains unexplored.

In conclusion, ILI following COVID-19 vaccination is a rare but important event. Temporal co-relation, biochemical findings, and histopathology are used in conjunction to establish the diagnosis. The prognosis is excellent with corticosteroids treatment. The COVID vaccine as a trigger, causation, or mere association with ILI is still unclear. This study gives no reason for promoting vaccine hesitancy in the general population. A close follow-up after COVID vaccination is recommended in individuals predisposed or affected with autoimmune diseases. Further

prospective global studies are needed to evaluate epidemiology, pathophysiology, and outcomes of ILI after COVID-19 vaccination.

CONFLICT OF INTEREST
Nothing to report.

AUTHOR CONTRIBUTIONS
Study concept and design: Akash Roy and Nipun Verma. *Manual search for data*: Akash Roy. *Data extraction*: Akash Roy, Nipun Verma, and Surender Singh. *Validation of the data, statistical analysis, manuscript draft*: Akash Roy. *Critical revisions to the manuscript*: Akash Roy, Nipun Verma, Surender Singh, Sunil Taneja, and Meenu Singh. *Final manuscript approval*: Akash Roy and Nipun Verma. *Systematic search of the literature*: Pranita Pradhan. *Arbitrator and study supervision*: Meenu Singh.

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