Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

vaccination in triggering extremely rare autoimmune phenomena (such as AIH), coincidence should not be mistaken for causality. Therefore, patients and referring physicians should be encouraged to seek medical expert advice in rare and complex diseases such as AIH despite the pandemic restrictions.

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The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions
All authors contributed equally to the concept and writing of the manuscript. DFR and JPW analysed the data.

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Unexplained liver test elevations after SARS-CoV-2 vaccination

To the Editor:

SARS-CoV-2 vaccines were rapidly developed and authorized for use. Two of three approved vaccines in the United States – Pfizer-BioNTech and Moderna – utilize mRNA technology deployed in human vaccines for the first time. Additionally, Johnson & Johnson developed a viral vector vaccine.

No instances of liver injury were reported in phase II/III trials.[1] Cases of acute liver injury following SARS-CoV-2 vaccination have been reported[2,3] – the injury pattern is usually hepatocellular, mimicking autoimmune hepatitis. No population-based studies investigating the risk and characteristics of liver injury following SARS-CoV-2 vaccination exist. We investigated the frequency and pattern of liver injury after SARS-CoV-2 vaccination across vaccine types, injury time course, and

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recovery using the Indiana University Health Enterprise Data Warehouse. Analysis was conducted following institutional review board (IRB) approval.

Our vaccine-exposed cohort included (a) patients receiving SARS-CoV-2 vaccination between December 2020 and October 2021 (3,546,047 patients) and (b) without pre-existing liver disease, defined as alanine aminotransferase (ALT) <45 U/L, aspartate aminotransferase (AST) <45 U/L, alkaline phosphatase (ALP) <150 U/L, and total bilirubin (TB) <1.2 mg/dl on 2 consecutive occasions with no ALT/AST >45 U/L, ALP >150 U/L, and TB >1.2 mg/dl within 24 months prior to the first SARS-CoV-2 vaccine dose (470,274 patients). For comparison, we identified a control group including patients receiving the influenza vaccine in 2019 at Indiana University Health and Eskenazi Health (130,067 patients) with no pre-existing liver disease (21,784 patients). Data collection ended on 10/29/2021.

Using published criteria for investigating drug-induced liver injury (DILI) in epidemiological studies,[4–6] we defined "liver injury after vaccination" as ALT >200 U/L and/or ALP >250 U/L and/or TB >2.5 mg/dl on at least 2 consecutive occasions within 12 weeks after the first or second vaccine dose, in the absence of positive hepatitis B virus surface antigen or hepatitis C virus antibody, alcohol consumption, exposure within 3 months to common DILI drugs (amoxicillin-clavulanate, isoniazid, diclofenac, nitrofurantoin, sulfamethoxazole/trimethoprim, minocycline, infliximab, azathioprine, ibuprofen, rifampin, pyrazinamide), heart failure (ICD-10 codes I50.xx, I11.0, I13.0, I97.13, I09.8), or hospitalization within previous 3 months. Qualifying labs were collected as part of routine clinical care. R-value was calculated using initial qualifying data to identify the pattern of liver injury.[7] We compared liver injury frequencies after vaccine among SARS-CoV-2 (mRNA, viral-vector) and influenza vaccines.

Among 470,274 individuals in the vaccine-exposed cohort, 177 individuals (0.038%) met liver injury criteria after SARS-CoV-2 vaccination. Sixty percent were female, 90% White and average age at first vaccine was 70 years. The frequency of liver injury after vaccine was no different between mRNA and viral-vector vaccines (0.038% *vs.* 0.024%, $p = 0.26$). Liver injury was observed after the first dose in 14% and second dose in 86%. Average time to injury after the first dose was 29 ± 21 days and second was 45 ± 25 days. Liver injury pattern was hepatocellular in 45%, cholestatic in 35%, and mixed in 20%. Peak mean for AST, ALT, ALP and TB were 800 IU/L, 553 IU/L, 405 IU/L, and 3.1 mg/dl, respectively. 29% of patients ever had TB >2.5 mg/dl. Follow-up liver biochemistries were available in 42 patients with liver injury after vaccination and liver tests normalized in

Table 1. Demographic and clinical data of individuals with liver injury after vaccination.

Results, mean ± SD	All SARS-CoV-2 vaccines	Pfizer	Moderna	J&J	Influenza vaccine
Total vaccinated individuals, n	3,546,047	2,062,837	1,230,887	252,323	130,067
Vaccine-exposed cohort, n	470,274	257,254	188,097	24,923	21,784
Total individuals with liver injury, n	177	87	84	6	15
Individuals with liver injury, %	0.038%	0.034%	0.045%	0.024%	0.069%
Age, years, mean ± SD	70 ± 14	71 ± 14	70 ± 14	52 ± 16	56 ± 19
Females (%)	60	60	59.5	n/a	60
Whites (%)	90	88.5	92	n/a	80
Liver injury after 1st dose, %	14	9	12	100	100
Time from 1st vaccine dose to 1st abnormal liver test	29 ± 21	26 ± 24	24 ± 16	43 ± 19	12 ± 24
Liver injury after 2nd dose, %	86	91	88	n.a.	n.a.
Time from 2nd vaccine dose to 1st abnormal liver test	45 ± 25	46 ± 26	45 ± 24	n.a.	n.a.
Baseline labs					
AST (U/L), mean ± SD	20 ± 7	20 ± 6	21 ± 8	19 ± 6	21 ± 8
ALT (U/L), mean ± SD	18 ± 9	17 ± 8	18 ± 9	19 ± 7	23 ± 10
ALP (U/L), mean ± SD	83 ± 25	85 ± 25	81 ± 25	77 ± 21	78 ± 26
TB (mg/dl), mean ± SD	.5 ± .22	.51 ± .22	.49 ± .23	.45 ± .14	.52 ± .23
Pattern of liver injury					
R ≥5 (hepatocellular), %	45	39	54	0	n.a.
R <2 (cholestatic), %	35	38	31	50	n.a.
2 ≤R < 5 (mixed), %	20	23	15	50	n.a.
Peak liver tests after vaccination					
AST (U/L), mean ± SD	800 ± 1757	657 ± 1454	983 ± 2058	313 ±147	443 ± 731
ALT (U/L), mean ± SD	553 ± 721	477 ± 578	650 ± 855	313 ± 176	494 ± 626
Alkaline phosphatase (U/L), mean ± SD	405 ± 429	345 ± 266	465±1015	443 ± 477	251 ± 199
Total bilirubin at peak (mg/dl), mean ± SD	3.1 ± 4.2	3.3 ± 4.4	3 ± 4	2.8 ± 4	2.9 ± 2.2
Cases ever with TB >2.5 mg/dl, %	29	34	23	33	47
Follow-up					
Cases with follow-up labs, n	42	21	20	1	n.a.
Cases with normalization, n	20	10	10	0	n.a.
Time to normalization from first abnormal to first normal lab value (days)					
AST	43 ± 39	36 ± 30	49 ± 46	n.a.	n.a.
ALT	50 ± 35	42 ± 30	56 ± 40	n.a.	n.a.
ALP	30 ± 40	15±11	44 ± 47	n.a.	n.a.
TB	8 ± 14	7 ± 11	8 ± 16	n.a.	n.a.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin. Frequencies of liver injury after vaccination compared using the Chi-Square test.

48% of them (defined as serum ALT <45 U/L, ALP <250 U/L and TB <2.5 mg/dl). Mean duration between first abnormal to first normal TB was 8 ± 14 days. Compared to influenza control, SARS-CoV-2 vaccination was associated with a lower frequency of liver injury after vaccination (0.038% *vs*. 0.069%, p = 0.04) (Table 1).

Liver injury after vaccination is a rare adverse effect that has been associated with other vaccines.[8,9] A latency of injury of between 6 and 46 days after the first SARS-CoV-2 vaccine dose was reported in a case series which included individuals with baseline liver disease.[3] We observed longer latency and most injury occurred after the second dose. This difference may be related to our exclusion of those with a history of liver disease or our cohort may be a more comprehensive sample. Underlying mechanisms remain unclear, but toll-like receptors 3, 7, and 8 have been hypothesized to contribute as they recognize RNA and have the potential to induce inflammatory responses. Modification of mRNA to limit innate and adaptive immune responses was key for vaccine development.[10]

Limitations include a retrospective approach, application of inclusion and exclusion criteria using electronic health record data, identification of liver injury after vaccine using surrogate biochemical criteria, and extrapolation to individuals with previously elevated liver biochemistries. We were unable to conduct manual chart review to adjudicate the liver injuries to determine the causal relationship between vaccine and liver injury.

Unexplained liver test abnormalities are seen in 0.038% individuals following SARS-CoV-19 vaccination – a lower frequency than following influenza vaccination. This study adds to the growing body of evidence demonstrating the safety of SARS-CoV-19 vaccines relative to other vaccines that are standard of care.

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Authors' contributions
JG: design, data interpretation, manuscript drafting. CL: design, data interpretation, and manuscript editing and preparation. ET: data collection NC: Study concept, design, data interpretation, and manuscript editing.

Data availability statement
Analytical methods and study material are described in the manuscript. Additional details can be obtained by contacting the corresponding author.

Supplementary data
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