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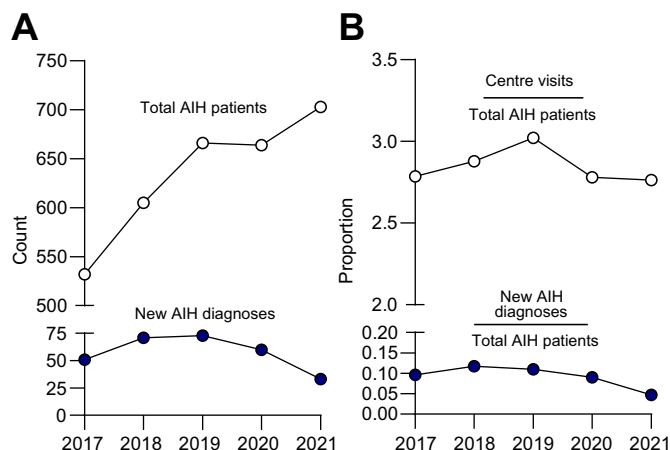
## Autoimmune hepatitis and COVID-19: No increased risk for AIH after vaccination but reduced care

To the Editor:

Several recent reports have described a temporal association between COVID-19 vaccination and the first manifestation of autoimmune hepatitis (AIH), and a possible causal role has been postulated.<sup>1–8</sup> If indeed AIH could be induced by COVID-19 vaccination, an increased incidence of AIH should be expected after widespread implementation.

In order to test this important hypothesis, we performed a systematic retrospective analysis. At our centre, one of the largest reference centres for autoimmune liver diseases in Europe, all diagnoses of AIH are coded according to the Orphanet nomenclature of rare diseases.<sup>9</sup> From 2017 to 2019, we observed an increase of new AIH diagnoses and an increase in the total number of patients with AIH at our centre. In 2020, when nationwide restrictions were enacted due to the COVID-19 pandemic, we observed a decline in new AIH diagnoses (from 73 cases in 2019 to 60 cases in 2020) and a minimal decline in the total number of patients with AIH treated at our centre (from 666 patients in 2019 to 664 patients in 2020) (Fig. 1A), resulting in a small decrease in the ratio of new AIH diagnoses to the total number of patients with AIH (Fig. 1B). COVID-19 vaccination became widely available in Germany in December 2020. Therefore, observation of an effect of vaccination would have been expected in 2021. Less strict pandemic restrictions to public life and medical care meant the absolute number of patients resumed its increase in 2021 (703 patients), yet the number of new diagnoses declined considerably (33 cases, Fig. 1A). Accordingly, the proportion of new AIH diagnoses per total AIH cases falls even more substantially in 2021 (Fig. 1B). These results do not support the assumption that COVID-19 vaccination induces AIH. We also observed a second, more worrying aspect at our centre during the pandemic: the number of visits per patient also dropped considerably (an average of 3.02 patient visits per year in 2019 vs. 2.78 in 2020 and 2.76 in 2021, Fig. 1B).

In 25 of the 33 patients who were newly diagnosed after the first approval of a COVID-19 vaccine, we obtained informed consent for a more detailed analysis. From the total of 25 patients, 5 were diagnosed 2–18 weeks after the first ( $n = 2$ ) or second vaccination ( $n = 3$ ), showing a temporal association suited for analysis of possible causal association. However, 4 of these 5 patients displayed features of definite pre-existing chronic liver disease (previous elevation of transaminases prior to vaccination and/or advanced fibrosis on histology) that were also described in some of the previously reported cases.<sup>4,5</sup> In only 1 patient (male, 70 years-old) there were no indications of pre-existing liver disease prior to vaccination. He presented to our centre 39 days after his second dose of tozinameran



**Fig. 1. Temporal development of AIH patient care at our centre before and during the COVID-19 pandemic.** (A) Absolute counts of total AIH cases and new AIH diagnoses from 2017–2021. (B) Ratios of individual patient visits per total annual AIH cases as well as new AIH diagnoses per total annual AIH cases from 2017–2021. AIH, autoimmune hepatitis.

(Comirnaty<sup>®</sup>) with jaundice and acute hepatitis (total bilirubin 16.0 mg/dl, aspartate aminotransferase 555 U/L, alanine aminotransferase 838 U/L, gamma glutamyltransferase 838 U/L, alkaline phosphatase 390 U/L). However, considering that 90% of the over 70-year-old German population were vaccinated in 2021, this one case is clearly below the rate expected by chance.

This analysis is partly limited by the fact that in the context of the pandemic, there may have been a decreased referral of patients with unknown or acute liver diseases and that, in a multi-stage healthcare system, patients can get lost between primary care and expert centres, leading to underreporting of AIH. However, the increasing referral of patients with known AIH and the clear drop in the proportion of new cases are a strong indication that COVID-19 vaccination does not induce AIH. On the contrary, there is ample reason to worry that new cases are being overlooked due to the pandemic. In addition, the decreasing number of centre visits per patient may indicate that expert care of patients with AIH may be suffering, as has been reported for other chronic inflammatory diseases.<sup>10</sup>

In summary, with all of the obvious limitations of this single-centre and non-population-based analysis, the reported data do not support the idea that COVID-19 vaccination induces AIH. Instead, decreasing numbers of new AIH diagnoses and a decline of patient visits indicate delayed and likely missed diagnoses in addition to lower levels of expert care, probably due to both hesitancy of patients to comply with the recommended follow-up and organisational problems due to the pandemic and its effect on rules, regulations and medical care provision. Even though it is not possible to rule out a role of the COVID-19

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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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### Conflict of interest

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

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

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

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2022.02.013>.

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Darius Ferenc R  ther<sup>1,2,\*</sup>,#

Jan Philipp Weltzsch<sup>1,2,#</sup>

Christoph Schramm<sup>1,2,3,4</sup>

Marcial Sebode<sup>1,2</sup>

Ansgar Wilhelm Lohse<sup>1,2,4,5</sup>

<sup>1</sup>I. Department of Internal Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

<sup>2</sup>European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany

<sup>3</sup>Martin-Zeit Centre for Rare Diseases, University Medical Centre Hamburg-Eppendorf, Germany

<sup>4</sup>Hamburg Centre for Translational Immunology (HCTI), Germany

<sup>5</sup>German Centre for Infection Research (DZIF), Partner Site Hamburg-L  beck-Borstel-Riems, Germany

\*Corresponding author. Address: I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Martinistra  e 52, 20249 Hamburg, Germany. Tel.: +4940741053910, fax: +4940741058531.

E-mail address: [d.ruether@uke.de](mailto:d.ruether@uke.de) (D.F. R  ther)

# Co-first authorship



## 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.<sup>1</sup> Cases of acute liver injury following SARS-CoV-2 vaccination have been reported<sup>2,3</sup> – 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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