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.

These findings raise the question as to whether COVID-19 mRNA vaccination can, through activation of the innate immune system and subsequent non-specific activation of autoreactive lymphocytes, lead to the development of autoimmune diseases including AIH or trigger a drug-induced liver injury with features of AIH. The trigger, if any, may become more apparent over time, especially following withdrawal of immunosuppression. As with other autoimmune diseases associated with vaccines the causality or casualty factor will prove difficult to tease apart and should not distract from the overwhelming benefits of mass COVID-19 vaccination. But it does beg the question of whether or not these individuals should receive the second dose of an mRNA COVID-19 vaccine.

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Authors' contributions
Dr Cathy McShane, Dr Clifford Kiat & Dr Órla Crosbie - involved in clinical care of patient and writing of manuscript. Dr Jonathan Rigby – interpreted histology and involved with writing of manuscript.

Supplementary data
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An unusual case of acute cholestatic hepatitis after m-RNABNT162b2 (Comirnaty) SARS-CoV-2 vaccine: Coincidence, autoimmunity or drug-related liver injury

To the Editor:
We read with interest the article "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty?" by Bril *et al.* recently published in *Journal of Hepatology*.[1] In this case, autoimmune hepatitis had some atypical features such as the absence of immunoglobulin G elevation and the presence of eosinophils on liver histology.

We recently observed a case of severe cholestatic hepatitis occurring after the administration of m-RNA-BNT162b1 (Comirnaty©, Pfeizer Biontech), with no development of autoantibodies and with the presence of eosinophil infiltrate at liver histology. The patient responded well to steroid treatment, similarly to autoimmune hepatitis.

The patient, a 43-year-old woman, presented to the hospital on February the 4th with jaundice and itching. At admission, total bilirubin was 17.54 mg/dl (direct bilirubin 12.94), alanine aminotransferase (ALT) 52 U/L, aspartate aminotransferase (AST) 51 U/L. Personal history was negative, except a mild dyslipidaemia with intermittent ALT increase, treated with diet (ALT and cholesterol maximum level 50 U/L and 285 mg/dl, respectively). Because of venous insufficiency, she took ginkgo-biloba in August 2020, withdrawn next October, more than 100 days before admission. She was a sanitary assistant so she received the Comirnaty vaccine (first dose January the 12th, second February the 2nd). Itching started on January 27th and by

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February the 4th, she noticed jaundice. No other adverse events related to the vaccine were reported.

Abdominal examination was negative; she had mild abdominal pain in right hypochondrium. Ultrasonography, CT scan and cholangioMRI showed normal liver and biliary system. Sero-markers ruled out hepatitis A, B, C, and E; CMV, EBV and HIV. HCV-RNA and HBV-DNA tested also negative. Autoimmune study was negative (anti-nuclear antibodies, anti-smooth muscle, anti-liver/kidney microsomal type-1, antimitochondrial, anti-extractable nuclear antigens). Finally, gamma-globulins (including sub-classes), coagulation, ceruloplasmin, blood count, platelets, iron status, IL-6 and thyroid function were normal. Serum albumin was slightly low (2.8 g/dl) and molecular tests for SARS-CoV-2 on rhino-pharyngeal swabs were repeatedly negative, while antibodies for SARS-CoV-2 showed effective immunological response to vaccination (SARS-CoV-2 S1-S2 IgG 179 UA/ml).

Liver biopsy showed moderate portal inflammatory infiltrate and interface hepatitis in the portal tract with biliary injury and mild ductular proliferation; in the lobule, we observed spotty necrosis, lymphocytes along the sinusoid, focal moderate steatosis and intranuclear glycogen inclusions. No sinusoidal dilatation or fibrosis. Immunostaining with cH7-Ab, showed mild ductular proliferation and diffuse immunoreactivity in hepatocytes zone 1-2 (Fig.1).

N-acetyl-cysteine (9 g i.v. for 3 days) was administered at day 3 from admission. Nevertheless, bilirubin increased to 29.15 mg/dl (direct bilirubin of 19.9 mg/dl) with ALT 171 U/L and AST 132 U/L on day 10. Therefore, steroids were started (methyl-prednisolone 1 mg/kg/day) observing a slow decrease of liver function tests until complete normalization in 8 weeks' time.

The case was reported to Italian sanitary authority (AIFA, Agenzia Italiana del Farmaco) and the patient was warned about re-exposure to the vaccine.

The new mRNA vaccines protect against infectious diseases by triggering an immune response. In registration trials, no cases of hepatitis were recorded.[2] The association between vaccine and autoimmune manifestations has been reported in different settings.[3–6] Our patient did not develop autoantibodies, nor liver histology showing typical signs of autoimmune damage. Nevertheless, 2 factors suggest immune-mediated hepatitis: the first is the timeline from vaccine to liver alteration which may correspond with the development of the immune response. The second, is the excellent response to steroids. Besides these hypotheses, the pathogenetic mechanism of this possible form of hepatitis obviously remains to be clarified. Drugs can induce toxic hepatitis,[7] SARS-CoV-2 infection has been associated with the development of autoimmunity[3] and there are also cases of drug-induced hepatitis with features of autoimmunity.[8] Like the case reported by Bril *et al.*,[1] eosinophil infiltrate was present at histology; this feature is more often observed in toxic or drug-related liver injury but also in autoimmune hepatitis.[7] Our patient had non underlying chronic liver disease but only an intermittent observation of mild hypertransaminasemia related to hyperlipidaemia. With regard to the previous use of ginkgo-biloba, it seems unlikely related to hepatitis as it was discontinued about 100 days before the onset of jaundice. Moreover, the antioxidant properties of ginkgo-biloba have been described to prevent liver fibrosis in patients with chronic viral hepatitis[9] and, although potential hepatic toxicity has been proposed,[10] it has never been reported to cause severe liver damage before.

We are aware that a clear causality between vaccine and hepatitis cannot be established and our aim is not to discourage clinicians from investigating other causes or questioning the importance of vaccination against COVID-19. Despite this and in the light of the previous case, we believe it is important to inform the scientific community as we could be facing a possible immune-mediated hepatitis, induced by vaccine and presenting with different features, which shows excellent response to steroid therapy.

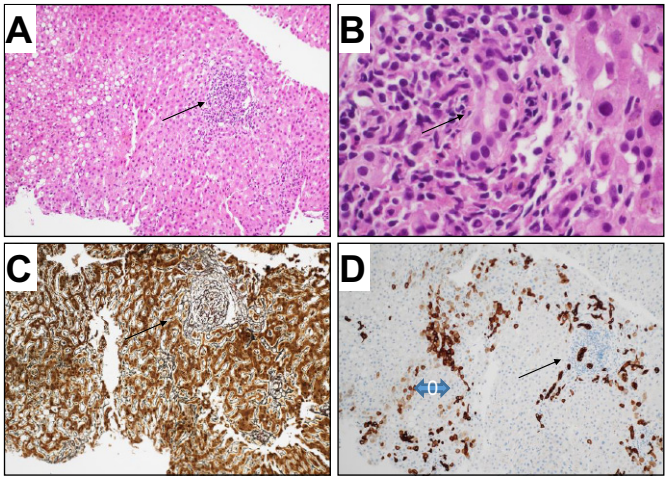

Fig. 1. Histology of liver biopsy. (A) H&E stain shows the histology of liver biopsy. The portal tract does not show fibrosis (C reticulin stain), but a moderate inflammatory infiltrate with interface hepatitis (arrow). The bile duct is surrounded by inflammatory cells and shows polymorphism of cholangiocytes (arrow). CK7 immunoreactivity is evident both in bile ducts and in hepatocytes (zone 1 and 2 blue arrow). (A,C,D 20x; B 60x).

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Authors' contributions
Francesca Lodato: patient's care, writing of the manuscript and revision of the final version of the manuscript. Anna Larocca: patient's care and revision of the final version of the manuscript. Antonietta D'Errico: pathology examination. Vincenzo Cennamo: made a critical revision of the letter to the Editor and revision of the final version of the manuscript.

Supplementary data
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Author names in bold designate shared co-first authorship

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Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: One or even several swallows do not make a summer

To the Editor:

I read with interest the comments to our letter by Londoño *et al.*,[1] Clayton-Chubb *et al.*,[2] Tan *et al.*,[3] McShane *et al.*,[4] and Lodato *et al.*,[5] and I appreciate their contribution. All these authors presented similar cases of autoimmune hepatitis (AIH) that developed after coronavirus disease 2019 (COVID-19) vaccine, with the exception of Lodato *et al.*,[5] who actually described a case of acute liver injury with some features of autoimmunity.

First of all, I was glad to see the repercussions of our manuscript, as it triggered the publication of many similar cases. Only by sharing experiences we will be able to learn more about COVID-19 infection and the effects of its vaccines. Our observation was evidently not an isolated finding, and similar presentations were observed worldwide.

Capecchi *et al.*[6] suggested that a period of time of 6 days after vaccine administration, as seen in our case,[7] seemed inconsistent with an immunopathologic reaction. However, among these 5 other cases, the latency period was similarly short and ranged from only 4 to 35 days. With some small variations, the cases also shared similar biochemical, immunological, and histological characteristics (Table 1). Indeed, a peculiarity among all these cases was a histology with characteristics of an immune process with features of drug-induced toxicity. Moreover, the rate and speed of improvement with glucocorticoids appeared to be similar in all the cases, and no relapses have been observed thus far. Only a longer follow-up will help us assess the risk of relapses in these cases. Further supporting a link between the vaccines and AIH, some of the authors even observed worsening of the symptoms after the second dose of the vaccine.[1,5]

However, while the resemblance of all these cases suggests a potential causal link between the vaccine and AIH, as the title of this article suggests, this cannot be taken as proof that this link really exists. Considering an annual incidence of 1 case per 100,000 habitants as previously reported,[8] and assuming an even distribution during the 12 months, we can estimate 1 monthly case per 1,200,000 habitants. Based on CDC data, during the first month of the US COVID-19 vaccination program, approximately 13,000,000 people received at least 1 dose of the vaccine (available at https://covid.cdc.gov/covid-data-tracker/#vaccinations). Based on AIH incidence, we can therefore roughly estimate that ~10 people from this vaccinated cohort would have developed AIH within a month of getting the vaccine. Thus, it should not be surprising that we will all continue to see these cases as we continue with our vaccination efforts. Epidemiological studies assessing changes in AIH incidence may

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