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.

multicenter setting, in order to demonstrate that such an algorithm would be more useful than a "back to basics" approach using the Child-Pugh score.

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Authors' contributions
All authors contributed to the study and the final manuscript. JP collected the data, carried out the formal analyses and wrote the original draft.

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SARS-CoV-2-specific immunity in immunosuppressed COVID-19 convalescents with autoimmune hepatitis

To the Editor:

We read with interest the article "SARS-CoV-2 infection in patients with autoimmune hepatitis" by Marjot, Buescher and Sebode *et al.*[1] recently published in the *Journal of hepatology*. While immunosuppressive therapy for autoimmune hepatitis (AIH) had no negative impact on the immediate outcome of COVID-19,[1–3] the question remained, whether COVID-19 convalescents immunosuppressed for AIH (AIH-Con) have the same level of protection against SARS-CoV-2 reinfection as non-immunosuppressed convalescents (non-IS-Con).

To address this question, we prospectively quantified anti-SARS-CoV-2 antibodies against various SARS-CoV-2 antigens (Antigen Panel 1 IgG, IgM, IgA assays Millipore HC19SERM1-85K-04, HC19SERA1-85K-04, HC19SERG1-85K-04) and IFN-γ responses to anti-SARS-CoV-2 antigen pools, as previously described,[4] in patients with AIH at their first appointment at our center following SARS-CoV-2 infection. We recruited 6 AIH-Con receiving ongoing immunosuppression (prednisolone 5-80 mg/day in 4/6 patients; mycophenolate 1,000 mg/day in 2/6 patients; azathioprine 50 and 75 mg in 2/6 patients). AIH-Con were compared to a matched cohort of 24 non-IS-Con (AIH-Con *vs.* non-IS-Con (Table S1): female sex: 50% *vs.* 46% (Fisher exact test: $p = 1.0$); age (median): 47 *vs.* 51 years (Mann-Whitney *U* test $p = 0.705$); time after COVID-19 (median): 48 *vs.* 52 days ($p = 0.631$); WHO COVID-19 severity: 100% mild-moderate *vs.* 91% mild-moderate; 9% severe-critical ($p = 1.0$). Two of the AIH-Con had concomitant primary sclerosing cholangitis, 3/6 had cirrhosis, 1/6 AIH-Con acquired COVID-19 during the diagnostic work-up of AIH and COVID-19 was diagnosed in 1 patient with AIH 4 days after the first mRNA vaccination.

Quantification of anti-SARS-CoV-2 antibodies was available in 4/6 AIH-Con and for 2 of these patients we had cryo-conserved pre-pandemic samples from our biorepository. Quantification of cellular immune response was available in 5/6 AIH-Con.

Apart from lower frequencies of IgA against spike S1 peptides and IgG against the nucleocapsid, the presence of all other anti-SARS-CoV-2 IgA, IgG and IgM specificities was comparable

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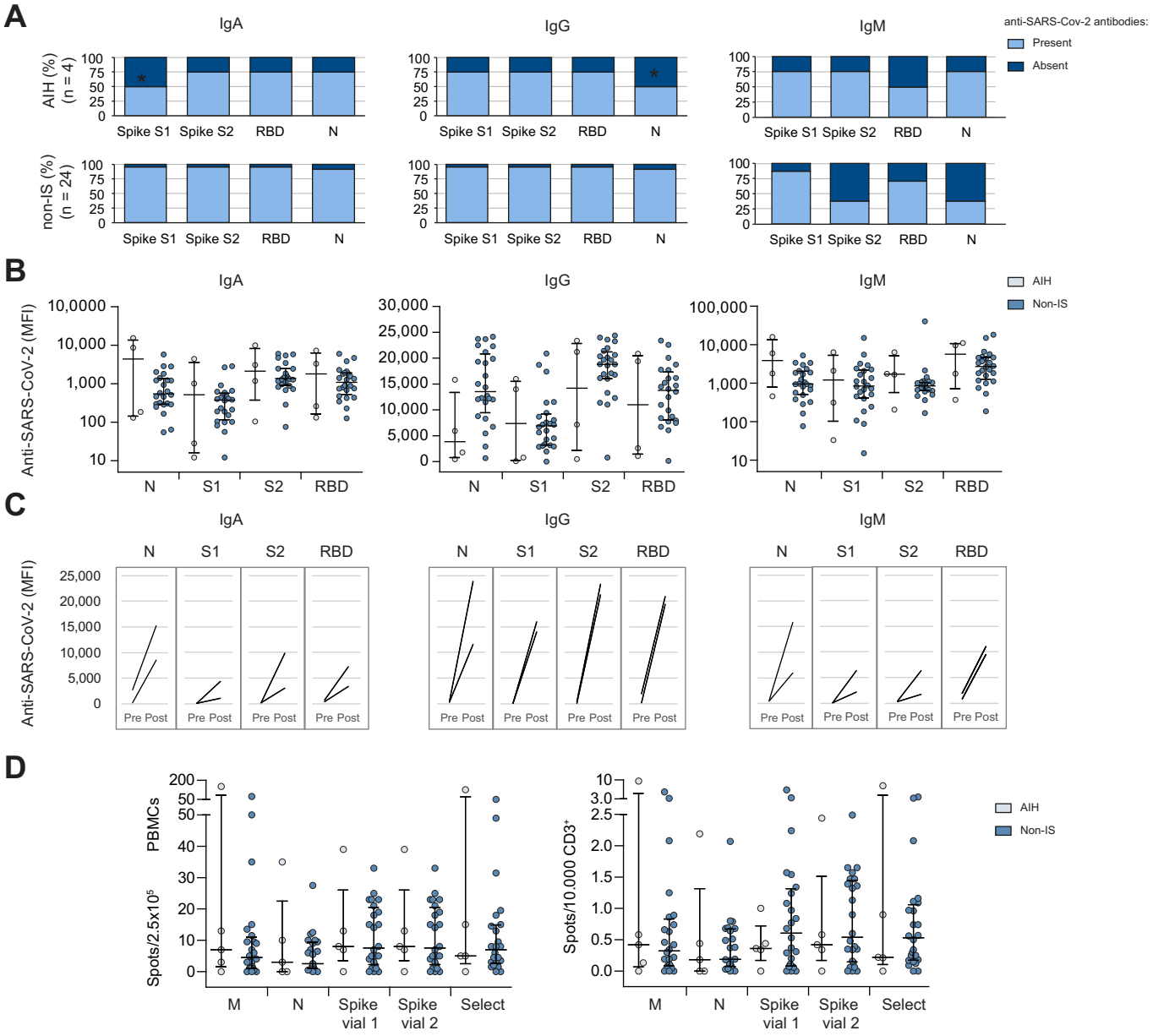

Fig. 1. SARS-CoV-2-specific immunity in immunosuppressed COVID-19 convalescence with autoimmune hepatitis. (A) IgM, IgA and IgG with reactivity against various SARS-CoV-2 antigens (spike protein, RBD, N) were measured in COVID-19 convalescents with AIH and in a local cohort of non-immunosuppressed convalescents (non-IS) (*p <0.05 in Fisher's exact test compared to IS-Con). (B) Concentration of anti-SARS-CoV-2 antibodies (measured as MFI) in AIH and non-IS convalescents. Non-significant differences in Mann-Whitney U tests were not outlined. (C) Anti-SARS-CoV-2 antibody concentrations measured longitudinally before and after COVID-19 in 2 patients with AIH with available pre-pandemic blood samples. (D) IFN-γ production upon stimulation with various SARS-CoV-2 antigen sets in ELISPOT assays normalized to numbers of circulating PBMCs as well as $CD3^+$ T cells in immunosuppressed COVID-19 convalescents with AIH and non-IS. Non-significant differences in Mann-Whitney U tests were not outlined. AIH, autoimmune hepatitis; non-IS, non-immunosuppressed convalescents; MFI median fluorescence intensity; N, nucleocapsid; PBMCs, peripheral blood mononuclear cell; RBD, receptor binding domain.

in AIH-Con and non-IS-Con (Fig. 1A). The actual antibody concentrations, quantified by the mean fluorescence intensity (MFI) in the assays, were not significantly different between AIH-Con and non-IS-Con (Fig. 1B). IgA cross-reacting with nucleocapsid peptides (1/2 patients), IgA and IgM cross-reacting with the receptor binding domain (RBD) of the spike protein (2/2 and 1/2 patients) and IgA cross-reacting with the spike S1 peptides (1/2 patients) were found in 2 AIH-Con in pre-pandemic samples. However, the concentration of anti-SARS-CoV-2 antibodies relevantly increased during COVID-19 in AIH-Con irrespective of whether preformed cross-reactive antibodies were present or not (Fig. 1C). AIH-Con produced similar amounts of IFN-γ normalized to numbers of peripheral blood mononuclear cells (PBMCs) and T cells like non-IS-Con (Fig. 1D). Similarly, the interferon-γ response against other respiratory viruses (endemic corona viruses (HCoV-OC43; HCoV-229E), RSV, influenza) were not different between AIH-Con and non-IS-Con (Fig. S1).

With all the limitations inherent to a statistical analysis of such a small study we found no evidence for a relevant reduction in humoral or cellular immunity against SARS-CoV-2 in AIH-Con compared to matched non-IS-Con. Although the frequency of some antibody specificities (anti-spike S1 IgA; anti-nucleocapsid IgG) was significantly lower in AIH-Con, the actual antibody concentrations were not different between AIH-Con and non-IS-Con. Similar findings of slightly reduced humoral but otherwise robust cellular immunity against SARS-CoV-2 have been reported for liver transplant recipients (LTRs), who usually receive much stronger immunosuppression.[5–7] As for patients with AIH, COVID-19 mortality did not seem to be higher in LTRs,[1–3,8,9] while the association of COVID-19 with the intake of mycophenolate and tacrolimus was ambiguous in 2 LTR studies.[8,9] In light of these recent studies from more immunosuppressed LTRs, a comparable immunity against SARS-CoV-2 in AIH-Con is not surprising but is reassuring. However, the development of an immunity against SARS-CoV-2 as strong as in non-IS-Con is remarkable especially with respect to the high cirrhosis rate of 50% in AIH-Con. Similar to LTRs, AIH-Con developed robust immunity even after mild COVID-19.[6,7] Unfortunately, the AIH-Con cohort is too small to allow for subgroup analyses, *e.g.* strength of immunosuppression or COVID-19 severity.

This study has many limitations beyond the small sample number. The cross-sectional approach at a single time point cannot describe longitudinal changes over time, like declining anti-SARS-CoV-2 antibody in LTRs within 3-6 months after COVID-19.[10] Furthermore, we cannot exclude a bias towards false high IgG antibody concentrations in AIH-Con with persistent hypergammaglobulinemia (Table S1). However, the parallel quantification of IgA antibodies, that are usually not elevated in AIH and which confer mucosal immunity, did not suggest a relevant bias by a hypergammaglobulinemia in AIH-Con. Fortunately, the success of the vaccination programs prevented a further recruitment of non-immunized patients with AIH, because nearly all patients with ongoing immunosuppression and/or advanced liver disease are already vaccinated at our center.

In summary, patients with AIH develop immunity against SARS-CoV-2 as robust as in matched non-IS-Con despite ongoing immunosuppression. This finding might explain in part the missing negative impact of immunosuppression on COVID-19 outcomes in patients with AIH.

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Conflict of interest

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Authors' contributions

TK acquired, handled and evaluated the patient data. CSF and BEV performed measurements of humoral and cellular immunity. EJ, CSF, BEV, RT acquired funding. All authors evaluated the data and drafted the manuscript. RT designed and supervised the study.

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Supplementary data

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Prognostic value of histologic parameters in alcoholic hepatitis: A word of caution

To the Editor:

We read with great interest the article by Lackner *et al.* on the development of the SALVE grading and staging system, a histologic prognostic score for alcohol-related liver disease (ALD).[1] The authors suggested using this score to assess patient prognosis across the whole clinical spectrum of ALD. While we acknowledge that histologic features may have some prognostic value in ALD, we have some concerns about their robustness in alcoholic hepatitis (AH).

More than 40% of the study population in the Lackner study had histological AH. While the landmark study from Altamirano *et al.*[2] already identified several histologic prognostic factors in AH, we failed to confirm their results in 2 independent cohorts of patients.[3] Interestingly, several histologic features of the SALVE scoring system developed by Lackner *et al.* were also assessed in our study. We agree that fibrosis is the most robust histologic prognostic factor in AH. When patients without cirrhosis and those with Laennec stage 4A cirrhosis were considered together and compared to patients with Laennec stages 4B and 4C, there was a trend toward better survival in the former group (91% *vs.* 68% at 3 months, $p = 0.13$; and 82% *vs.* 64% at 6 months, $p = 0.2$, respectively). This observation was expected as the extent of liver fibrosis is correlated to the degree of portal hypertension and related complications.[4] However, we failed to identify any prognostic value of bilirubinostasis. This finding could be due to several confounders that may explain the association observed between the risk of death and the presence of cholestasis in patients with AH. Of note, infection is a common feature that occurs in up to 50% of patients in this context, either at admission or during hospitalization.[5] Interestingly, the presence of bilirubinostasis was associated with the development of infection in the Altamirano study,[2] a finding that suggests that cholestasis may be an indirect marker of sepsis in AH. Indeed, bacterial products such as lipopolysaccharide downregulate some bile transporters, a factor which may explain cholestasis, as correctly pointed out by Lackner *et al.*

Another point of concern is related to the treatment that patients with AH received. While the authors stated that patients received "standard of care", no data were provided concerning the use of corticosteroids. Similarly, the Lille score was not included in the multivariate analysis, despite its well demonstrated prognostic value in this setting.[6] In the end, as non-response to steroids may explain the development of infection and, as there is no doubt that these factors drive prognosis in patients with AH, cholestasis may be an indirect marker of non-response to steroids and/or to sepsis rather than a factor that itself impacts the prognosis of patients with AH. Another point of interest would be to assess if histologic parameters can predict response to steroids.

Lastly, the study by Lackner *et al.* assessed the impact of abstinence, a factor which is recognized to have the greatest impact on long-term prognosis both in patients with compensated and decompensated ALD[7] and in patients with AIH, regardless of whether the Maddrey discriminant function is <32[8] or >32.[9,10] If alcohol use was associated with the prognosis of patients with compensated ALD, it is surprising that abstinence was not associated with the risk of death in the subgroup analysis performed in decompensated patients with or without AH.

Thus, we believe that the Lackner study represents a valuable effort to improve the assessment of prognosis of patients with ALD. However, their results should be validated in other independent prospective cohorts of patients with AH that should take into account all prognostic factors including sepsis and response to corticosteroids.

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Authors' contributions

Pierre Deltenre: study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision.

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