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.

The underlying mechanism is unknown but might be related to impaired innate immunity to the virus. In particular, there are abundant ACE2 receptors in the small intestine and clinically, patients complain of abdominal pain and diarrhea. Circulation of the virus via the hepatic reticular system is expected, given the rich supply of blood to the liver from the small bowel. The liver contains the largest number of macrophages (Kupffer cells) in the body and is a potent cytokine producer. Impaired hepatic innate immune status might play a critical role in COVID-19 outcome. We postulate that in patients with NAFLD, the polarization status of hepatic macrophages might be skewed from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, leading to progression of COVID-19.[10] However, a better understanding of the role of NAFLD in COVID-19 may have therapeutic implications.

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Conflicts 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
DJ, DZ, JX, and EQ treated the patients.DJ, GC, YW and GL processed statistical data and drafted the manuscript. DJ and GL had the idea for and designed the study.

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

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Management of patients with autoimmune liver disease during COVID-19 pandemic

To the Editor:

Although coronavirus disease 2019 (COVID-19) is mainly characterised by respiratory symptoms that can progress to acute respiratory distress syndrome (ARDS),[1,2] abnormalities in liver enzymes have been reported during severe infections.[3] Many liver centres worldwide have faced the challenge of managing patients with liver diseases during this pandemic[3] and particular concerns have been raised about immunocompromised patients. This is mainly based on previous data on the higher risk of severe respiratory viral infections in patients treated with immunosuppressive medications.[4,5] However, preliminary experience from Bergamo, Lombardy, suggests that immunosuppressed patients are not at

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increased risk during COVID-19;[6] while Chinese data from the epicentre of the infection show that patients with chronic liver disease were only a minority among those infected with COVID-19.[2]

One area of major concern are patients with autoimmune liver diseases (AILDs), particularly those with autoimmune hepatitis (AIH) or cirrhosis receiving immunosuppressive therapy, due to the lack of evidence-based treatment recommendations. This may lead to an empirical reduction of immunosuppressive agents, particularly antimetabolites, which is probably not justified. Herein, we present a brief description of the management protocol developed and implemented for patients with AILD in 3 referral centres in Europe during the present pandemic (Fig. 1).

Patients should be stratified based on risk of complications to avoid unnecessary visits to the hospital. Indeed, patients with stable chronic AILD on long-term therapy are at low risk of complications and/or progression. While available data may suggest that immunosuppressed patients are not at increased risk of ARDS,[6] a flare of AIH secondary to unnecessary drug reduction/withdrawal, would require a higher dose of steroids and thus potentially increased risk of infection. In this low-risk scenario, we suggest to: (i) postpone follow-up visits until the emergency is over; (ii) be proactive in sending general information and recommendations to your patients (*i.e.* mailing list) ahead of time; (iii) use web-based consultation upon request in addition to telephone-based consultations; and, (iv) organise drug dispensation with the local pharmacy for therapy maintenance.

Patients with cirrhosis, of any cause, that present with an acute complication are at high risk of morbidity and mortality independent of the viral epidemic. Indeed, severe flares of AIH, obstructive jaundice in primary sclerosing cholangitis, severe cholangitis, and/or gastrointestinal bleeding are associated with high short-term mortality and thus require urgent care and treatment. Even though the risk of COVID-19 in fragile patients seems to be relatively high, the underlying liver disease in these patients presents such a high-risk condition that hospital care is mandatory. We therefore suggest to: (i) organise an independent flow for urgent access to the hospital in order to avoid any contact with COVID-19 positive patients (*e.g.* avoid access through the general emergency department); (ii) limit invasive procedures such as endoscopy to emergency interventions avoiding screening, and follow local protocols in case of emergencies (*i.e.* obstructive jaundice, bleeding);[7] (iii) start standard therapy at the usual dose for treatment of acute flare of AIH; (iv) coordinate care in case of hepatic failure with the regional transplant centre; finally, (v) in case of infection reduce immunosuppression – particularly antimetabolites in those with lymphopenia – and be timely in tapering steroids. Careful hospital hygiene procedures should be followed, and outpatient follow-up care organised in order to keep hospitalization as short as possible.

Finally, conditions conferring medium risk, including acute onset of symptoms in non-cirrhotic patients and chronic management of decompensated cirrhotic patients, should be consciously evaluated and managed to avoid unnecessary visits to the hospital.[8] Although there is no available data, we indeed work under the assumption that pulmonary infection due to COVID-19 might lead to a worse outcome in these fragile populations. Non-cirrhotic clinically stable patients that present with abnormal liver tests should: (i) defer invasive diagnostic procedures that require hospital visits (*i.e.* liver biopsy); (ii) start empiric (*i.e.* steroids in AIH) therapy using web-based

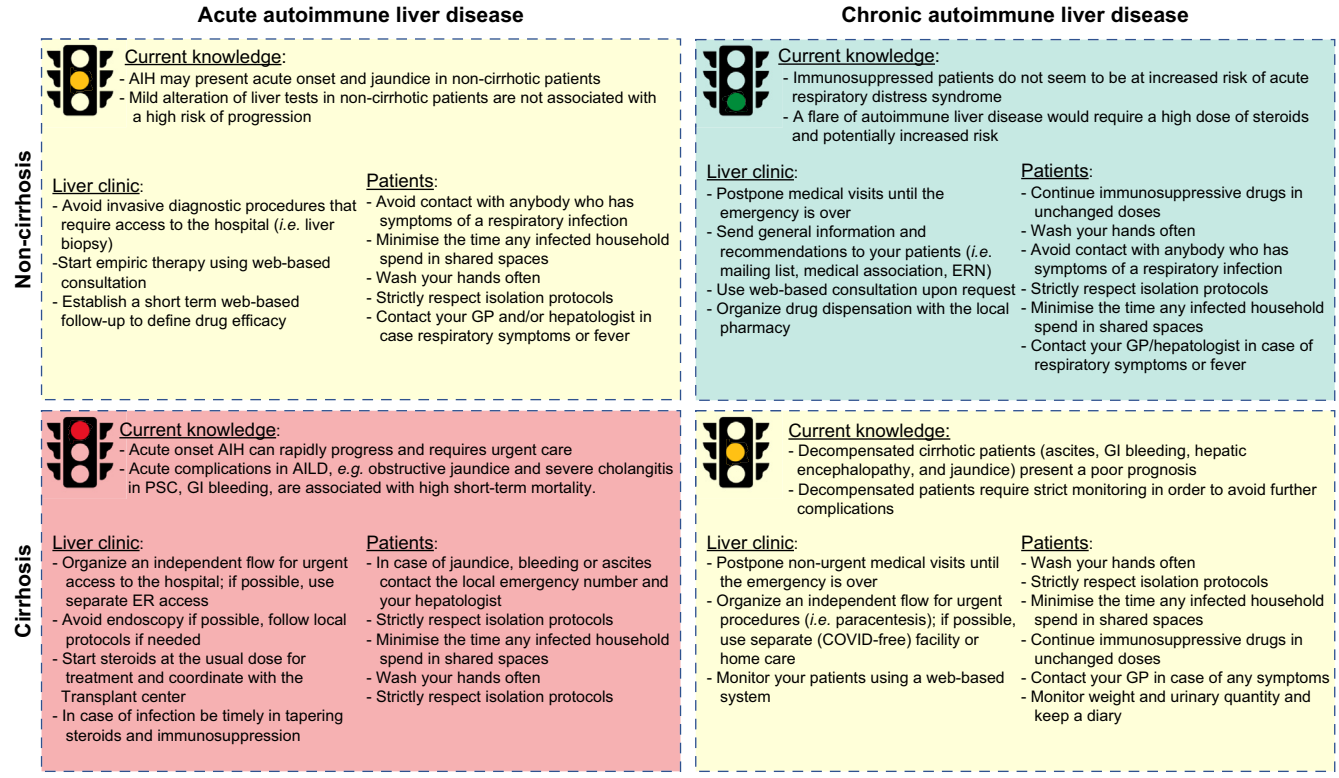

Fig. 1. Management protocol for patients with autoimmune liver diseases during the COVID-19 pandemic. AIH, autoimmune hepatitis; AILD, autoimmune liver disease; COVID-19, coronavirus disease 2019; ER, emergency room; ERN, European reference network; GI, gastrointestinal; GP, general practitioner; PSC, primary sclerosing cholangitis. (This figure appears in color on the web.)

consultation; and (iii) establish a short-term web-based follow-up to define drug efficacy and adapt treatment accordingly. Thus, in this particular situation the diagnosis of AIH may be given without histology, if typical biochemical and serological results are followed by a convincing treatment response. Prove of the diagnosis can be undertaken later, either by a relapse upon therapy reduction, or a follow-up liver biopsy when conditions are safer. As already reported in China,[8] advanced liver cirrhosis and decompensated patients can be monitored with a web-based system and all non-urgent medical visits should be postponed until the emergency is over. Urgent procedures (*i.e.* paracentesis) should be organised using a COVID-19-free path in the hospital, another COVID-19-free facility or home care. Finally, we recommend strict adherence to standard social distancing protocols and social isolation and emphasise, in cirrhotic patients, the importance of vaccination for *Streptococcus pneumoniae* and *seasonal flu* and of reinforcing social distancing measures. Further data are needed in order to demonstrate the real impact of COVID-19 infection in immunocompromised patients. Until then, and while vaccination is not available, we suggest continuing a cautious approach during low-level seasonal persistence of COVID-19 in the years to come.

Although we cannot currently evaluate the efficacy of our management protocol, we believe this framework might be a useful tool for management of AILD for the time being.

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Conflict of interest
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Authors' contributions
AL, MC, PI, AL, AG: concept design and writing; all authors revised and approved the final version.

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Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury

To the Editor:
We read with interest the paper "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study", in which 43 (43.4%) of 99 patients had differing degrees of liver function abnormality.[1] For patients with COVID-19 in intensive care, liver function was significantly worse than in those who were not in intensive care.[2] Similar features were reported in a study of 138 hospitalized patients in Wuhan, China.[3] On the basis of these clinical findings, there was widespread concern regarding liver injury in COVID-19.[4] There is currently no data focusing on clinical characteristics and outcomes in patients with COVID-19 who develop liver injury.

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