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.

16.26% (n = 20), autoimmune hepatitis in 7.31% (n = 9), primary sclerosing cholangitis and haemochromatosis in 1.63% (n = 2) each, Wilson's disease, HCV, Budd-Chiari syndrome, and amyloidosis in 1 patient (0.81%), whereas in 8.94% (n = 11) normal liver tissue was detected. According to Metavir staging system, no fibrosis was detected in 39.84% (n = 49), while F1 stage was noted in 16.26% (n = 20), F2 in 11.38% (n = 14), F3 in 4.88% (n = 6) and F4 in 27.64% (n = 34) of patients. Procedure-related complications which included hemorrhage, pulmonary complications, peritonitis and septicemia were not recorded in our cohort. Experienced pain intensity (median 2, range 0–7) was lower compared to that anticipated (median 4, range 0.5–6), and that result was statistically significant (p <0.001). Besides possible complications, one of the main conditions associated with biopsy itself is post-procedural pain, which was experienced by 47.15% of patients (n = 58), with the median duration of pain lasting 1 hour post-intervention (range 15 minutes to 24 hours). More than one-third of patients (n = 45, 36.59%) experienced no fear prior to the intervention, while in 38.21% (n = 47) of patients fear originated from the intervention itself, in 20.33% (n = 25) from the diagnosis, while only 4.88% (n = 6) of patients feared possible biopsy-related complications.

As the most common major complication, recently published studies reported bleeding incidence ranging from 0.63% to 1.88%.[2–4] Even though studies' sample size, type of needle used, possible complication-contributing factors, as well as the definition of complication itself differ, one could come to a conclusion that severe complications, including bleeding in the first place, remain rare. That said, there are no recent studies which reflect on patient's perspective of and expectations from the procedure itself. Our results have revealed that a patient's objective prior to undergoing liver biopsy differs greatly from their experience, which highlights the importance of providing the patient with adequate information about the intervention.

To conclude, in the era when we are eagerly awaiting new developments to occur and up-to-date-practice algorithms to be established, our idea was to highlight that with every step forward, we must carefully assess what it is that we are leaving behind. In experienced hands and for the correct indications, the liver biopsy carries on being an irreplaceable diagnostic tool with a good safety profile.

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Authors' contributions
I. Ilic: Design of the letter; Analysis and interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript. T. Milovanovic: Conception and design of the letter; Interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript.

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Health status of patients with autoimmune liver disease during SARS-CoV-2 outbreak in northern Italy

To the Editor:
During the COVID-19 pandemic, questions have arisen regarding the risk to patients with autoimmune conditions receiving immunosuppressive therapies. There is mounting evidence that severe COVID-19 is characterized by an imbalanced multi-system immune-inflammatory response to the pathogen by the host, and acknowledged risk factors for poorer outcome are older age and preexisting non-respiratory chronic proinflammatory conditions such as obesity, hypertension, diabetes and cardiovascular disease.[1]

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Table 1. Demography, clinical features and COVID-19 in 148 patients with autoimmune liver disease.

Number of patients	148
Survey response rate°	100%
Female (%)	91 (61%)
Age at survey, years	47.4 (2.8-81.2)
1 to 17 years, n (%)	47 (32%)
≥18 years, n (%)	101 (68%)
Type of AILD, n (%)	
AIH	133 (90%)
ASC	11 (7%)
PSC/AIH	2 (1%)
PBC/AIH	2 (1%)
Patients on immunosuppressive treatments	148 (100%)
Prednisone monotherapy	36 (24%)
Prednisone + azathioprine	69 (47%)
Prednisone + MMF	4 (3%)
Prednisone + cyclosporine	2 (1%)
Azathioprine monotherapy	33 (23%)
Cyclosporine monotherapy	2 (1%)
MMF monotherapy	2 (1%)
Travel abroad	9 (6%)
to Europe	5
to Israel	1
to Emirates	1
to Malta	1
to Egypt	1
to China, South Korea or Iran	0
Contact with suspected case of COVID-19, n (%)	33 (22%)
Suspected cases of COVID-19, n (%)	39 (26%)
Fever	26
Cough	23
Shortness of breath	3
Confirmed cases of COVID-19*, n (%)	4 (3%)
Survived	3
Died	1
Estimated incidence	
General population	26,935 per 100,000 (n = 38 cases)
AILD patients	30,281 per 100,000 (n = 43 cases)
Discontinuation of immunosuppressive therapy, n (%)	1 (1%)
Outcome	
Survived	146 (99%)
Died§	2 (1%)

AIH, autoimmune hepatitis; ASC, autoimmune sclerosing cholangitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; MMF, mycophenolate mofetil.
°It indicates the number of patients who responded to the survey; AILD, autoimmune liver disease.
*All patients had a nasopharyngeal swab positive for SARS-CoV-2.
§1 patient died due to COVID-19 and 1 (with Down syndrome) due to septic shock.

Hypertransaminasemia, low platelet count and hypoalbuminemia have been associated with high mortality in COVID-19 pneumonia, but whether preexisting chronic liver disease is an additional risk factor for a severe course is still matter of debate.[2] Our preliminary experience suggested that patients with cirrhosis, liver transplantation, autoimmune liver disease, inflammatory bowel disease, have a benign course during the pandemic.[3,4] Nonetheless there are no granular figures on patients with autoimmune liver disease (AILD).[5]

Northern Italy has been the earliest and most extensively hit European area during COVID-19 epidemic in early 2020, and our centre is located at the epicentre of the Italian outbreak, and hosts a large hepatology and transplantation unit. Thus, our setting represents an opportunity to explore the health status and possible challenges presented by patients with AILD during this outbreak.

We therefore decided to carry out a phone-based survey using a 26-query questionnaire to explore the clinical features of SARS-CoV-2 infection in patients with AILD under immunosuppression.

The infection was confirmed by a positive nasal-pharyngeal swab (NPS) for SARS-CoV-2 nucleic acid, using a real-time reverse-transcriptase PCR (RT-PCR) assay. The severity of illness was classified as mild, moderate, severe or critical according to previously reported classifications.[1,6]

At the time of the study 153 patients were followed at our centre; 148 patients (F = 91 [61%], median age 47.4 years, range 2.8–81.9) were considered eligible; 5 patients (all <18 years) were excluded: 4 because they were off-therapy, one because he moved to Canada.

Of 148 patients, 47 (32%) were children (aged from 2.8 to 17.8 years) diagnosed with autoimmune hepatitis (AIH, n = 37/47 [76%]) and autoimmune sclerosing cholangitis (ASC, n = 11/47 [23%]); 101/148 (68%) were adults (aged from 18.4 to 81.9 years) diagnosed with AIH (n = 97/101 patients, 96%), primary sclerosing cholangitis/AIH overlap syndrome (n = 2 patients, 2%), and primary biliary cholangitis/AIH (n = 2 patients, 2%).

The questionnaire was successfully filled in by all eligible patients, and the survey completeness was 100%. *Suspected COVID-19* was the presence of at least one among: 1) Acute respiratory tract infection; 2) Close contact with a confirmed or highly probable COVID-19 case. C*onfirmed COVID-19* was a patient having a positive NPS.[1] The observed incidence was weighted to expected cases using previously published models.[7]

Thirty-nine of 148 (26%) were suspected COVID-19 cases. All had symptoms: fever (26/39), cough (23/39), dyspnoea (3/39). None required admission to hospital, oxygen therapy or discontinuation of immunosuppression; 33/39 (85%, 6 children) had a close contact with a highly probable case.

Four patients were confirmed COVID-19 cases:

Patient 1: Female (47 years, AIH, on prednisone and azathioprine), close contact with the sister who had COVID-19. She developed fever and mild dyspnoea requiring hospitalisation, and oxygen therapy; immunosuppression was discontinued by the local physician in charge; she recovered completely in a few days and immunosuppression was re-started.

Patient 2: Female (78 years, AIH, on azathioprine) with hypertension, dyslipidemia, dementia. She developed fever and dyspnoea requiring hospitalisation. She developed interstitial pneumonia and died 4 days later due to COVID-19.

Patient 3: Female (73 years, AIH, on prednisone and azathioprine) developed mild fever and cough not requiring hospitalisation. Immunosuppression was not discontinued and she rapidly recovered.

Patient 4: Female (72 years, cirrhotic AIH, on prednisone with poor adherence), admitted for decompensated liver disease. She had no respiratory symptoms, despite a positive NPS. Chest X-ray was normal.

A 23-year-old female with AIH and Trisomy 21 died from septic shock unrelated to COVID-19.

The estimated incidence of SARS-CoV-2 infection in the general population was 38 cases (26,935 cases/100,000 inhabitants), *vs.* 43 observed in AILD (p = n.s.).

Overall, 146 patients survived (n = 104 asymptomatic, n = 39 suspected COVID-19; n = 3 confirmed COVID-19); 2 patients died (n = 1 due to COVID-19, n = 1 due to septic shock). Immunosuppressive therapy was only discontinued in 1 patient (3%) (Table 1).

The sudden appearance of SARS-CoV-2 has challenged healthcare systems worldwide and led to a re-think regarding the management of patients with any sort of acute or chronic illness. In this respect, hepatologists are discussing several aspects related to the care of patients with liver disease. EASL and ESCMID have recently published a joint position paper on these issues, and tried to answer important questions such as: i) Does SARS-CoV-2 cause liver injury? ii) Are patients with chronic liver disease at increased risk of developing COVID-19? iii) Are liver patients under immunosuppression at increased risk of developing COVID-19? iv) Should the management of a liver patient with COVID-19 take into account the risks related to the underlying condition and to drug interactions? Previous studies found that patients with severe pneumonia were more likely to develop abnormal transaminases compared to milder cases. Nonetheless the increase of transaminases might represent the consequence of critical illness, rather than a contributory factor.[8]

It has been suggested that COVID-19 could accelerate the onset of complications in patients with compensated cirrhosis. This remains to be determined for SARS-CoV-2. Liver cells can be infected by this virus, since its receptor, angiotensin-converting enzyme 2 (ACE2), is expressed on cholangiocytes.[2] However, indirect signs of biliary injury have not been recorded in patients with severe COVID-19.[9] Nonetheless, it is likely that cirrhotic patients in a labile compensation status are more vulnerable than the general population. For this reason, the EASL/ESCMID position paper suggests adopting several protective measures in patients with any chronic liver disease, hepatocellular carcinoma, listed for transplantation or who received a transplant recently.[8] For patients with AILD, this expert panel advises against reducing immunosuppressive treatment.

In this survey we found that a total of 25% of our patients had a close contact with a suspected or confirmed case of COVID-19. Most of our patients, though, remained asymptomatic (70%, n = 104). Twenty-six per cent (n = 39) developed mild/moderate respiratory symptoms likely due to an underlying SARS-CoV-2 infection; however, since the NPS was not carried out, they were classified as suspected cases of COVID-19. Only 4 patients (3%, all female older than 18 years) were diagnosed as confirmed COVID-19 cases; the majority of them (3/4 patients, 75%) presented with a mild or moderate clinical phenotype (1 was asymptomatic) whilst 1 patient died; this patient had risk factors for complicated COVID-19 described in the general population, including old age and associated comorbidities.

Interestingly, we found that the observed incidence of cases in our cohort of patients was not different from the estimated incidence in the general population, suggesting that patients with AILD are not more susceptible to COVID-19 than the general population.[7]

We previously reported our review of past outbreaks of coronavirus infections and our preliminary experience with these patients followed in our centre, and we suggested that immunocompromised patients (adults and children) are not at increased risk of severe COVID-19 compared to the general population.[3] There is growing evidence confirming this finding, including some reports suggesting that immunosuppression may even provide some protection from lung damage in patients with COVID-19. However different immunosuppressive drugs have a different effector pathway, therefore a generalization of this concept seems unwise. Immunosuppressive medications have effects on humoral immunity, cell-mediated immunity and neutrophil function, potentially increasing the risk of severe infections caused by many viral agents. Nonetheless, in previous coronavirus epidemics, immunosuppressive treatments have not been shown to favour a complicated course, and this study confirms it.

Patients with AILD are mainly treated with steroids and antimetabolites. The NIH COVID-19 treatment guidelines report that oral corticosteroid therapy, used prior to COVID-19 diagnosis for another underlying conditions, should not be discontinued, but they recommend against the routine use of systemic corticosteroids in hospitalised patients with COVID-19.[10] However, it should be remembered that patients with autoimmune disorders under chronic steroid treatment are at risk of developing adrenal crises under any physical stress, due to secondary adrenal insufficiency. Therefore, patients with AILD developing severe COVID-19 should be administered steroids for adrenal replacement.

The experience with antimetabolites (such as azathioprine or mycophenolate mofetil) is scarce. However we recently reported the uneventful course of patients with inflammatory bowel disease who were under immunosuppressive or immunomodulating drugs, including antimetabolites, during the SARS-CoV-2 epidemic.[4]

In conclusion, during the SARS-CoV-2 outbreak in northern Italy, children and adults with AILD maintained a good health status. COVID-19 was diagnosed in a similar percentage of patients as in the general population, and the outcome was favourable in most cases. The absence of major complications related to COVID-19 in patients with AILD living in a highly endemic area suggests that, in these patients, during the SARS-CoV-2 global pandemic, tapering or withdrawing immunosuppressive treatment is not required.

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Supplementary data

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High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry

To the Editor:

Chronic liver disease (CLD) and cirrhosis are common conditions[1] associated with immune dysregulation,[2] leading to concerns that these patients are at increased risk of complications from COVID-19 resulting from infection with SARS-CoV-2.[3] However, the effects of COVID-19 among patients with pre-existing liver disease are currently undefined.

We report the outcomes of the first 152 consecutive submissions of clinician-reported cases of laboratory-confirmed COVID-19 in patients with CLD to two international reporting registries (COVID-Hep.net and COVIDCirrhosis.org) between 25 March 2020 and 20 April 2020. Our combined database includes 103 patients with cirrhosis and 49 with non-cirrhotic CLD from 21 countries across 4 continents (59.9% male, median age 61 years, aetiology: 22.4% non-alcoholic fatty liver disease, 19.7% alcohol, 11.8% hepatitis B, 10.5% hepatitis C, 35.6% other/combination).

Contributors were encouraged to enter data at the end of the patient's disease course. For patients admitted to hospital, cases were only included in the analysis if a definitive outcome of death or discharge was reported. 95.2% of patients with cirrhosis were hospitalised with a median length of hospital stay until discharge or death of 10 days (IQR 5–14 days). Outcomes for patients with cirrhosis included admission to intensive care unit (ICU) in 23.3%, invasive ventilation in 17.5%, non-invasive ventilatory support in 18.6%, renal replacement therapy in 4.9% and death in 39.8%. Mortality far exceeded that reported in

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