Prevalence of COVID-19 in patients with autoimmune liver disease in Europe: A patient-oriented online survey

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Abstract

Background: During the current SARS-CoV-2 pandemic it is important to identify risk factors for COVID-19. Registry studies are providing growing evidence on the elevated risk of mortality from COVID-19 in patients with chronic liver disease, especially in advanced stages. Results may, however, have a selection bias towards severe cases. Limited data is available on COVID-19 in patients with autoimmune liver disease (AILD).

Aim: To perform an online survey to capture the prevalence of COVID-19 and the state of medical care of patients with AILD in Europe during the pandemic.

Methods: Data was collected via an anonymous patient-oriented, online survey, which was available on the EUSurvey platform in nine European languages between 24th June 2020 and 14th October 2020. Of 1834 contributions, 51 were excluded because participants did not name an underlying AILD, and four were excluded because of duplicate data entry.

Results: Of 1,779 participants, 1,752 resided in 20 different countries of the European Union and the United Kingdom (UK). The five countries with the highest numbers of contributions were France (n = 450), Germany (n = 318), the Netherlands (n = 267), Spain (n = 225), and the UK (n = 183). 2.2% of participants (39/1779) had been diagnosed with COVID-19. There were no differences regarding age, sex, AILD, the status of liver cirrhosis, or status post liver transplantation between COVID-19 and non-COVID-19 cases. Of the 39 COVID-19 cases, five patients were admitted to a regular ward, one patient was admitted to ICU and required ventilation.

Conclusion: In our Europe-wide, patient-oriented survey on COVID-19 in patients with AILD, we detected a low rate of COVID-19, comparable to the period prevalence of the general population. These results suggest that patients with AILD are not at elevated risk of COVID-19.
INTRODUCTION

Arising from a cluster of pneumonia of unknown etiology in December 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19), has developed into a worldwide pandemic. Identifying patients at risk of severe courses of COVID-19 has gained major importance in order to protect vulnerable individuals, preserve the resources of health care systems, and guide patient counseling. Risk factors for a severe course of COVID-19 that have been identified in the past months include male sex, age over 65, smoking, diabetes, arterial hypertension, and chronic cardiovascular, renal, and respiratory disease. The role of autoimmune diseases and immunosuppressive treatment as potential risk factors is still under investigation. The three autoimmune liver diseases (AILD), autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are rare, but cause a notable disease burden accounting for about 11% of orthotopic liver transplantations in Europe between 1999 and 2009. Most patients with AIH and PSC, but not patients with AILD after liver transplantation, require lifelong immunosuppressive treatment. Furthermore, patients with liver cirrhosis independent of the kind of liver disease are regarded to be in a state of immune dysfunction. These patient groups may be at risk of severe COVID-19.

Data on patients with SARS-CoV-2 infection in patients with AILD is limited to regional observational studies driven by referral centers suggesting no increased risk of COVID-19 in patients with autoimmune hepatitis. However, patients with chronic liver disease, notably those with liver cirrhosis and a higher Child-Pugh score, seem to be at risk of decompensation of liver disease and death in the context of COVID-19. Furthermore, an international registry study on patients with COVID-19 and chronic liver disease in Europe identified liver cirrhosis and alcoholic liver disease to be risk factors for mortality from COVID-19.

Current registries on COVID-19 in patients with liver disease are based on data entry by treating physicians so reporting bias towards severe cases is likely. The primary aim of our study was to assess the incidence of COVID-19 in patients with AILD by directly addressing patients independent of their presentation to the health care system. We present the results of the first patient-oriented and Europe-wide survey on COVID-19 in patients with AILD.

PATIENTS & METHODS

Data was collected via a patient-oriented, browser-based online survey (Text S1). The survey was available on the EUSurvey platform (supported by the European Commission, ec.europa.eu/eusurvey) in Dutch, English, French, Italian, Polish, Portuguese, Spanish, and Swedish language between June 24, 2020 and October 14, 2020. No personal data of the participants were collected. The survey was supported by the patient representatives of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER) and locally at tertiary care centers associated with ERN RARE-LIVER. A first draft of the survey was developed by the physicians BFZ, CS, AWL, and MS. This version was then adapted by the patient representatives JW, MW, AT, and AL with regard to diction, the composition of questions, and also with regard to the relevance of questions from a patient’s perspective. The survey was circulated several times between all authors for feedback rounds until all authors agreed on the final version.

The study was announced by the following means: (1) Patient organizations drew the patients’ attention to the study by electronic flyers and/or posts on the respective webpages in the following...
countries: The Netherlands and Belgium (Dutch Liver Patients Association, Hoogland), United Kingdom (PSC Support, Oxford, and Children’s Liver disease Foundation, Birmingham), France (Association Pour la Lutte Contre les Maladies Inflammatoires du Foie et des Vois Biliaires, ALBI, Versailles) and Germany (Deutsche Leberhilfe e.V.). (2) All healthcare centers associated with ERN RARE-LIVER received a flyer announcing the study via the ERN RARE-LIVER electronic newsletter. The physicians of the ERN healthcare centers distributed this flyer manually to patients seen at the local outpatient clinic and/or by electronic media. Member centers are listed on the ERN RARE-LIVER webpage (https://rare-liver.eu/about/members-and-partners-of-the-network). (3) The study was also announced on the ERN RARE-LIVER webpage. In order to provide an estimation of response rate for this survey, the numbers of patients treated at ERN RARE-LIVER healthcare centers and being members of the above-mentioned patient organizations are provided in Table S1. In accordance with the local ethics committee, no ethical approval was necessary for this anonymous online survey.

Statistical analysis was performed using IBM SPSS Statistics 27. Chi squared ($\chi^2$) test was used to compare two or more groups. Statistical significance was considered for $p$-values <0.05.

RESULTS

General characteristics of participants

The inclusion and exclusion criteria of the survey are displayed in Figure S1. The survey included 1834 contributions. Fifty-one contributions were excluded because participants did not name an underlying AILD; four contributions were excluded because of duplicate data entry. Of the remaining 1,779 participants, 1,752 lived in 20 different countries of the European Union (EU) and the United Kingdom (UK), 26 lived in other countries (1 piece of missing data; Table 1). Most of the data were collected in five countries: France ($n = 450$), Germany ($n = 318$), the Netherlands ($n = 267$), Spain ($n = 225$), and the UK ($n = 183$). Most of the participants were of the female sex (77.7%). The largest group of participants was between 50 and 59 years old (29.1%), 8.6% of participants were younger than 30 years, 10.1% of participants were 70 years old or older (Table 1). The most common AILDs were PBC and AIH (34.9% and 34.7% resp.), followed by PSC (20.2%) and by the variant syndromes PBC/AIH (6.3%) and PSC/AIH (3.8%). About 29% of participants indicated having cirrhosis and 7% of participants had received liver transplantation (Table 1).

Clinical differences among patients with autoimmune liver diseases

There are known differences in the epidemiologic characteristics of the different AILDs, which may also lead to the differential distribution of risk factors for COVID-19. Therefore, we further characterized the cohort according to the underlying AILD. Age pattern was markedly different among the groups with 41.4% of participants diagnosed with PBC being 60 years old and older while only 18.9% of participants with PSC were 60 years old or older ($p < 0.001$ for differences in age pattern among the five AILD; Table 2). The rate of female participants was highest in the PBC group (90.8%) and lowest in the PSC group (51.4%). Patients with PSC/AIH variant syndrome showed the highest rate of cirrhosis, while the lowest rate of cirrhosis was in participants with PBC (PBC: 9.7%, AIH: 16.5%, PSC: 18.1%, PBC/AIH 21.4%, PSC/AIH 38.2%, $p < 0.001$). Previous liver transplantation was significantly more frequent in participants with PSC (16.9%) or PSC/AIH variant syndrome (16.2%) than in the other disease groups (AIH: 3.7, PBC: 4%, PBC/AIH: 4.5%, $p < 0.001$). The association with inflammatory bowel disease (IBD) was highest in the PSC patient groups (PBC: 2.7%, PBC/AIH: 4.5%, AIH: 4.9%, PSC/AIH: 27.9%, PSC: 54.7%, $p < 0.001$). Among other secondary diagnoses, only the percentage of patients diagnosed with arterial hypertension differed significantly between the AILD groups (PSC/AIH: 5.9%, PSC: 9.4%, PBC/AIH: 13.4%, AIH: 15.7%, PBC: 16.1%, $p = 0.008$).

The medical treatment regimens were analyzed, revealing significant differences among patients with AILD: Prednisolone was taken by 44.1% of AIH patients and by 3.9% of PBC patients (PSC: 8.9%, PBC/AIH: 32.1%, PSC/AIH: 52.9%, $p < 0.001$). About 56% of AIH patients received treatment with azathioprine or mercaptopurine. UDCA treatment was most frequent in PBC patients (PBC: 90%, PSC/AIH: 85.7%, PSC: 76.7%, PSC/AIH: 76.5%, AIH: 11.8 $p < 0.001$; Table 2).

Analysis of medical treatment of AILD (Table S2–S4) showed differences among the European countries. Furthermore, the kind of treatment of participants with concomitant IBD was analyzed (Table S5).

Risk factors and prevalence of COVID-19 in autoimmune liver diseases

Out of 1,779 participants, 39 were diagnosed with COVID-19 (2.2%; Table 1). Most of the COVID-19 cases came from France (35.9%) and Spain (28.2%; Table 3). There were no significant differences in COVID-19 prevalence between the groups of AILD (PBC/AIH: 0%, PSC/AIH: 1.5%, PBC: 1.9%, AIH: 2.3%, PSC: 3.3%, $p = 0.288$, Table 2). Between COVID-19 cases ($n = 39$) and non-COVID-19 cases ($n = 1730$), there were no significant differences regarding age, sex, smoking, kind of AILD, status post liver transplantation, secondary diagnoses, or presence of liver cirrhosis (Table 3). Treatment of AILD did not differ significantly between COVID-19 and non-COVID-19 cases for most of the drugs. Only azathioprine or mercaptopurine was significantly more frequently taken by non-COVID-19 cases (26.4% vs. 10.3%, $p = 0.023$).

Diagnosis and severity of COVID-19 cases

Of the self-reported 39 COVID-19 cases, the diagnosis was confirmed by nasopharyngeal swab in 48.7% (19 cases; Table 4). The
majority of participants were diagnosed at the A&E department of a hospital (33.3%), followed by a general practitioners' office (30.8%). Five out of 39 cases were admitted to a regular ward of a hospital (12.8%) with a mean stay duration of 10.8 days (SEM 3.4 days). One participant was admitted to an intensive care unit and required mechanical ventilation. This participant was a 70–79-year-old woman with AIH, treated with prednisolone and azathioprine or mercaptopurine. She did not have liver cirrhosis or previous liver transplantation but had lung disease as comorbidity. Of the five patients, who had been admitted to a regular ward, three were treated with prednisolone, one with azathioprine or mercaptopurine, and three with UDCA (Table 5). None of them received changes regarding AILD treatment, while 6.3% of COVID-19 cases who were not admitted to hospital received dose reduction of their AILD treatment (Table 5).

SARS-CoV-2 and non-COVID 19 cases

At the preliminary peak of the COVID-19 pandemic in Europe, outpatient healthcare was not always maintained at regular levels.
|                          | AIH Total n = 618 | PBC Total n = 621 | PSC Total n = 360 | PBC/AIH Total n = 112 | PSC/AIH Total n = 68 | p-value |
|--------------------------|-------------------|-------------------|-------------------|-----------------------|---------------------|---------|
| Age                      |                   |                   |                   |                       |                     |         |
| 10–19 years              | 37 (6)            | 0 (0)             | 11 (3.1)          | 0 (0)                 | 6 (8.8)             | <0.001  |
| 20–29 years              | 54 (8.7)          | 1 (0.2)           | 31 (8.6)          | 4 (3.6)               | 9 (13.2)            |         |
| 30–39 years              | 75 (12.1)         | 31 (5)            | 72 (20)           | 11 (9.8)              | 18 (26.5)           |         |
| 40–49 years              | 100 (16.2)        | 122 (19.6)        | 83 (23.1)         | 25 (22.3)             | 16 (23.5)           |         |
| 50–59 years              | 166 (26.9)        | 207 (33.3)        | 93 (25.8)         | 39 (34.8)             | 13 (19.1)           |         |
| 60–69 years              | 125 (20.2)        | 170 (27.4)        | 46 (12.8)         | 21 (18.8)             | 6 (8.8)             |         |
| 70–79 years              | 53 (8.6)          | 78 (12.6)         | 19 (5.3)          | 11 (9.8)              | 0 (0)               |         |
| 80–100 years             | 5 (0.8)           | 9 (1.4)           | 3 (0.8)           | 0 (0)                 | 0 (0)               |         |
| Missing                  | 3 (0.5)           | 3 (0.5)           | 2 (0.6)           | 1 (0.9)               | 0 (0)               |         |
| Sex                      |                   |                   |                   |                       |                     |         |
| male                     | 121 (19.6)        | 51 (8.2)          | 171 (47.5)        | 12 (10.7)             | 23 (33.8)           | <0.001  |
| female                   | 491 (79.4)        | 564 (90.8)        | 185 (51.4)        | 98 (87.5)             | 44 (64.7)           |         |
| diverse                  | 1 (0.2)           | 0 (0)             | 0 (0)             | 0 (0)                 | 0 (0)               |         |
| Missing                  | 5 (0.8)           | 6 (1)             | 4 (1.1)           | 2 (1.8)               | 1 (1.5)             |         |
| Liver transplantation    |                   |                   |                   |                       |                     |         |
| No                       | 593 (96)          | 596 (96)          | 299 (83.1)        | 106 (94.6)            | 57 (83.8)           | <0.001  |
| Yes                      | 23 (3.7)          | 25 (4)            | 61 (16.9)         | 5 (4.5)               | 11 (16.2)           |         |
| Missing                  | 2 (0.3)           | 0 (0)             | 0 (0)             | 1 (0.9)               | 0 (0)               |         |
| Cirrhosis                |                   |                   |                   |                       |                     |         |
| No                       | 449 (72.7)        | 472 (76)          | 251 (69.7)        | 64 (57.1)             | 34 (50)             | <0.001  |
| Yes                      | 102 (16.5)        | 60 (9.7)          | 65 (18.1)         | 27 (24.1)             | 26 (38.2)           |         |
| I don't know             | 64 (10.4)         | 82 (13.2)         | 44 (12.1)         | 19 (17)               | 8 (11.8)            |         |
| Missing                  | 3 (0.5)           | 7 (1.1)           | 0 (0)             | 2 (1.8)               | 0 (0)               |         |
| Inflammatory bowel disease|                   |                   |                   |                       |                     |         |
| No                       | 579 (93.7)        | 590 (95)          | 160 (44.4)        | 107 (95.5)            | 48 (70.6)           | <0.001  |
| Yes                      | 30 (4.9)          | 17 (2.7)          | 197 (54.7)        | 5 (4.5)               | 19 (27.9)           |         |
| Missing                  | 9 (1.5)           | 14 (2.3)          | 3 (0.8)           | 0 (0)                 | 1 (1.5)             |         |
| Other conditions         |                   |                   |                   |                       |                     |         |
| Lung disease             | 44 (7.1)          | 52 (8.4)          | 20 (5.7)          | 11 (9.8)              | 2 (2.9)             | 0.233   |
| Diabetes                 | 37 (6)            | 40 (6.4)          | 18 (5)            | 6 (5.4)               | 5 (7.4)             | 0.885   |
| arterial hypertension    | 97 (15.7)         | 100 (16.1)        | 34 (9.4)          | 15 (13.4)             | 4 (5.9)             | 0.008   |
| Heart disease            | 20 (3.2)          | 23 (3.7)          | 11 (3.1)          | 8 (7.1)               | 0 (0)               | 0.12    |
| Kidney disease           | 9 (1.5)           | 17 (2.7)          | 6 (1.7)           | 6 (5.4)               | 3 (4.4)             | 0.058   |
| Other                    | 171 (27.7)        | 186 (30)          | 80 (22.2)         | 34 (30.4)             | 11 (16.2)           | 0.02    |
| None                     | 311 (50.3)        | 266 (42.8)        | 197 (54.7)        | 48 (42.9)             | 44 (64.7)           | <0.001  |
| Medication AILD          |                   |                   |                   |                       |                     |         |
| Predniso(lo)ne           | 276 (44.7)        | 24 (3.9)          | 32 (8.9)          | 36 (32.1)             | 36 (52.9)           | <0.001  |
| Budesonide               | 71 (11.5)         | 6 (1)             | 0 (0)             | 25 (22.3)             | 9 (13.2)            | <0.001  |

(Continues)
TABLE 2 (Continued)

|                    | AIH Total n = 618 | PBC Total n = 621 | PSC Total n = 360 | PBC/AIH Total n = 112 | PSC/AIH Total n = 68 |
|--------------------|-------------------|-------------------|-------------------|-----------------------|----------------------|
| Azathioprine/mercaptopurine | 347 (56.1) | 9 (1.4) | 31 (8.6) | 45 (40.2) | 30 (44.1) | <0.001 |
| Mycophenolate mofetil (MMF) | 70 (11.3) | 4 (0.6) | 11 (3.1) | 8 (7.1) | 11 (16.2) | <0.001 |
| Tacrolimus | 34 (5.5) | 19 (3.1) | 45 (12.5) | 8 (7.1) | 9 (13.2) | <0.001 |
| Cyclosporine | 4 (0.6) | 3 (0.5) | 4 (1.1) | 1 (0.9) | 0 (0) | 0.752 |
| Everolimus | 3 (0.5) | 2 (0.3) | 3 (0.8) | 0 (0) | 0 (0) | 0.692 |
| Ursodeoxycholic acid (UDCA) | 73 (11.8) | 559 (90) | 276 (76.7) | 96 (85.7) | 52 (76.5) | <0.001 |
| None | 69 (11.2) | 40 (6.4) | 45 (12.5) | 4 (3.6) | 2 (2.9) | <0.001 |

Diagnosis of COVID-19

|                  | No         | Yes        | Missing |
|------------------|------------|------------|---------|
|                  | 601 (97.2) | 14 (2.3)   | 3 (0.5) |
|                  | 606 (97.6) | 12 (1.9)   | 3 (0.5) |
|                  | 347 (96.4) | 12 (3.3)   | 1 (0.3) |
|                  | 109 (97.3) | 0 (0)      | 3 (2.7) |
|                  | 67 (98.5)  | 1 (1.5)    | 0 (0)   |

Note: Statistical analyses were performed via χ² test.
Abbreviations: AIH, autoimmune hepatitis; AILD: autoimmune liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PBC/AIH, variant syndrome AIH and PBC; PSC/AIH, variant syndrome AIH and PSC.

We assessed whether non-COVID-19 cases might have been in risk situations for SARS-CoV-2 infection and/or showed symptoms without receiving the diagnosis of COVID-19. Among participants who were not diagnosed with COVID-19 (n = 1730), about 16% reported to have suffered from cough, 11.5% from fever, 8.5% from shortness of breath, and 2.2% from smelling problems since January 2020. About 73% of participants did not report any of these symptoms (Figure 1a). Of the non-COVID-19 cases, 16.3% received a SARS-CoV-2 test since January 2020 (Figure 1b). Participants who reported fever or cough received a SARS-CoV-2 test significantly more often than participants without these symptoms (35.2% vs. 14.0% and 25.2 vs. 14.8%, p < 0.001, Table S6). Additionally, 1.3% of non-COVID 19 cases reported having had close contact with a SARS-CoV-2 positive individual who was living in the same household (Figure 1c). About 5% have had close contact with a SARS-CoV-2 positive individual who was not living in the same household (Figure 1d). Non-COVID 19 cases with close contact to a SARS-CoV-2 positive individual not living in the same household received a SARS-CoV-2 test significantly more often than cases without these contacts (Table S6).

Degree of information on COVID-19 of patients with autoimmune liver diseases

For most of the participants, medication was unchanged (85.4%), whereas medication was reduced in dosage or stopped for only a few participants (2.4% and 0.7% resp.; Figure 2a). About 57% of participants did not feel well informed about their personal risk of COVID-19 by their treating physician (Figure 2b). About 25% were told they were not at increased risk of COVID-19, while increased risk due to immunosuppressive treatment or the underlying liver disease was communicated to 19% and 8% of participants, respectively (Figure 2c).

DISCUSSION

Previous studies on SARS-CoV-2 infection in patients with AILD have been limited to smaller numbers of patients in distinct European regions such as Lombardy (Italy) and Flanders (Belgium).5,9,14 To our knowledge, our study is the first to document COVID-19 and the health status of patients with AILD in a Europe-wide, patient-oriented online survey including 1779 participants from 20 European countries.

The detected differences in demographics of participants with AIH, PBC, and PSC and the rate of concomitant IBD (Table 2) are in line with previous reports on the epidemiology of patients with AILD.15–17 The higher percentage of patients with comorbid arterial hypertension among AIH and PBC compared to PSC patients may be a result of the higher age of PBC patients and glucocorticoid treatment in AIH patients. PSC patients showed the highest frequency of status post liver transplant, which reflects limited therapeutic options for this AILD.17–19

COVID-19 was diagnosed in 2.2% of participants, which is in the same range as the reported 14,083 cases per million inhabitants for the European region.20 Comparing the period prevalence of the participants of our study in the five countries with the highest numbers of contributions to the reported SARS-CoV-2 infections in the general population, we see a mildly higher period prevalence for the participants from France (3.2% vs. 2.6%), Germany (1.3% vs. 0.78%) and Spain (4.9% vs. 2.84%), whereas in our cohort there were
### TABLE 3  Risk factors and prevalence of COVID-19 in participants

|                      | Non-COVID-19 Total n = 1,730 | COVID-19 Total n = 39 | Non-COVID-19 Total n = 1,730 | COVID-19 Total n = 39 | p-value |
|----------------------|-------------------------------|-----------------------|-------------------------------|-----------------------|---------|
| **Age**              |                               |                       |                               |                       |         |
| 10–19 years          | 53 (3.2)                      | 1 (2.6)               | 0.98                          | Prednisolone          | 393 (22.7) | 7 (17.9) | 0.481 |
| 20–29 years          | 97 (5.6)                      | 2 (5.1)               | Budesonide                    | 109 (6.3)             | 0 (0)    | 0.106   |
| 30–39 years          | 201 (11.6)                    | 5 (12.8)              | Azathioprine/mercaptopurine   | 456 (26.4)            | 4 (10.3) | 0.023   |
| 40–49 years          | 337 (19.5)                    | 8 (20.5)              | Mycophenolate mofetil (MMF)   | 103 (6)               | 1 (2.6)  | 0.374   |
| 50–59 years          | 509 (29.2)                    | 10 (25.6)             | Tacrolimus                    | 112 (6.5)             | 2 (5.1)  | 0.735   |
| 60–69 years          | 357 (20.6)                    | 7 (17.9)              | Cyclosporine                  | 12 (0.7)              | 0 (0)    | 0.602   |
| 70–79 years          | 155 (9)                       | 4 (10.3)              | Everolimus                    | 8 (0.5)               | 0 (0)    | 0.67    |
| 80–100 years         | 16 (0.9)                      | 1 (2.6)               | Ursodeoxycholic acid (UDCA)   | 1025 (59.2)           | 24 (64.1)| 0.542   |
| Missing              | 8 (0.5)                       | 1 (2.6)               | None                          | 153 (8.8)             | 7 (17.9) | 0.05    |
| **Sex**              |                               |                       |                               |                       |         |
| Male                 | 365 (21.1)                    | 11 (28.2)             | No                            | 1559 (90.1)           | 37 (94.9)| 0.392   |
| Female               | 1347 (77.9)                   | 28 (71.8)             | Yes                           | 156 (9)               | 2 (5.1)  |         |
| Diverse              | 1 (0.1)                       | 0 (0)                 | Missing                       | 15 (0.9)              | 0 (0)    |         |
| Missing              | 17 (1)                        | 0 (0)                 |                                | 0 (0)                 |         |         |
| **Countries**        |                               |                       |                               |                       |         |
| AILD                 |                               |                       | Austria                       | 11 (0.6)              | 0 (0)    |         |
| AIH                  | 601 (34.7)                    | 14 (35.9)             | Belgium                       | 54 (3.1)              | 4 (10.3) |         |
| PBC                  | 606 (35)                      | 12 (30.8)             | Czechia                       | 0 (0)                 | 1 (2.6)  |         |
| PSC                  | 347 (20.1)                    | 12 (30.8)             | Denmark                       | 3 (0.2)               | 0 (0)    |         |
| PBC/AIH              | 109 (6.3)                     | 0 (0)                 | Estonia                       | 1 (0.1)               | 0 (0)    |         |
| PSC/AIH              | 67 (3.9)                      | 1 (2.6)               | France                        | 433 (25)              | 14 (35.9)|         |
| **Cirrhosis**        |                               |                       |                               |                       |         |
| No                   | 1232 (71.2)                   | 31 (79.5)             | Greece                        | 1 (0.1)               | 1 (2.6)  |         |
| Yes                  | 277 (16)                      | 2 (5.1)               | Hungary                       | 1 (0.1)               | 0 (0)    |         |
| I don't know         | 210 (12.1)                    | 6 (15.4)              | Ireland                       | 13 (0.8)              | 0 (0)    |         |
| Missing              | 11 (0.6)                      | 0 (0)                 | Italy                         | 53 (3.1)              | 0 (0)    |         |
| Luxembourg           | 4 (0.2)                       | 0 (0)                 |                               |                       |         |         |

(Continues)
| Condition                          | Non-COVID-19 | COVID-19 | Non-COVID-19 | COVID-19 |
|-----------------------------------|--------------|----------|--------------|----------|
|                                   | Total n = 1,730 | Total n = 39 | Total n = 1,730 | Total n = 39 |
| Liver transplantation             |              |          |              |          |
| No                                | 1605 (92.8)  | 37 (94.9) | 265 (15.3)   | 0 (0)    |
| Yes                               | 122 (7.1)    | 2 (5.1)   | 57 (3.3)     | 2 (5.1)  |
| Missing                           | 3 (0.2)      | 0 (0)     | 50 (2.9)     | 0 (0)    |
|                                   |              |          |              |          |
| Inflammatory bowel disease        |              |          |              |          |
| No                                | 1445 (83.5)  | 30 (76.9) | 46 (2.7)     | 1 (2.6)  |
| Yes                               | 259 (15)     | 8 (20.5)  | 183 (10.6)   | 0 (0)    |
| Missing                           | 26 (1.5)     | 1 (2.6)   | 25 (1.4)     | 1 (2.6)  |
|                                   |              |          |              |          |
| Other conditions                  |              |          |              |          |
| Lung disease                      | 124 (7.2)    | 5 (12.8)  | 1 (0.1)      | 0 (0)    |
| Diabetes                          | 104 (6)      | 1 (2.6)   | 194 (11.3)   | 0 (0)    |
| arterial hypertension             | 244 (14.1)   | 4 (10.3)  | 19 (1.1)     | 0 (0)    |
| Heart disease                     | 60 (3.5)     | 2 (5.1)   | 45 (2.6)     | 0 (0)    |
| Kidney disease                    | 40 (2.3)     | 1 (2.6)   | 19 (1.1)     | 0 (0)    |
| Other                             | 466 (26.9)   | 13 (33.3) | 6 (0.3)      | 0 (0)    |
| None                              | 842 (48.7)   | 19 (48.7) | 39 (2.3)     | 0 (0)    |

Note: Statistical analyses were performed via $\chi^2$ test.

Abbreviations: AIH, autoimmune hepatitis; AILD, autoimmune liver disease; COVID-19, coronavirus disease 2019; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PBC/AIH, variant syndrome AIH and PBC; PSC/AIH, variant syndrome AIH and PSC.
no reported COVID-19 cases from the Netherlands (0.0% vs. 2.35%) and the UK (0.0% vs. 1.7%).\textsuperscript{20} However, compared to the seroprevalence of SARS-CoV-2 in different European countries such as Spain, Italy, and the UK (5.4%, 2.5%, and 6.0% seroprevalence, resp.), the rate of COVID-19 based on self-reports in our study cohort was similar or even lower than those rates of the general national populations.\textsuperscript{21} The comparison of COVID-19 versus non-COVID-19 cases among the participants did not show significant differences regarding previously described risk factors such as age, male sex, lung disease, arterial hypertension which is probably due to the small number of COVID-19 cases in our cohort (\(n = 39\), 2.2% of participants)\textsuperscript{3,4}. Chronic liver disease and liver cirrhosis have been described as risk factors for mortality of COVID-19.\textsuperscript{10–12} In our study, only one patient was treated in an intensive care unit. Due to the limited number of severe COVID-19 cases in our survey, the stage of liver disease could not be analyzed as a risk factor. Despite reports of higher mortality due to COVID-19 of patients postliver transplantation at the beginning of the pandemic,\textsuperscript{22,23} larger studies did not reveal higher mortality for patients with previous liver transplantation.\textsuperscript{24–26} Our survey included 125 patients post liver transplantation. We did not detect a significant difference of COVID-19 cases between AILD patients post liver transplantation and those without liver transplantation.

### Table 4: Characteristics of COVID-19 cases

| Diagnosis of COVID-19 was confirmed by swab of your nose and throat area | Total n = 39 |  |
|---|---|---|
| No | 18 | 46.2 |
| Yes | 19 | 48.7 |
| Missing | 2 | 5.1 |

| Diagnosis of COVID-19 was made by/at | Total n = 39 |  |
|---|---|---|
| General practitioner | 12 | 30.8 |
| Outpatient healthcare service | 3 | 7.7 |
| A&E department of a hospital | 13 | 33.3 |
| Other | 10 | 25.6 |
| Missing | 1 | 2.6 |

| I was admitted to a regular ward of a hospital for COVID-19 | Total n = 39 |  |
|---|---|---|
| No | 32 | 82.1 |
| Yes | 5 | 12.8 |
| Missing | 2 | 5.1 |

| I was admitted to an intensive care unit of a hospital for COVID-19 | Total n = 39 |  |
|---|---|---|
| No | 37 | 94.9 |
| Yes | 1 | 2.6 |
| Missing | 1 | 2.6 |

| I required ventilation | Total n = 39 |  |
|---|---|---|
| No | 0 | 0 |
| Yes | 1 | 2.6 |
| Missing | 38 | 97.4 |

| I stayed at home during COVID-19 | Total n = 39 |  |
|---|---|---|
| No | 3 | 7.7 |
| Yes | 32 | 82.1 |
| Missing | 4 | 10.3 |

| I had the following symptoms during COVID-19 | Total n = 39 |  |
|---|---|---|
| Fever | 20 | 51.3 |
| Cough | 20 | 51.3 |
| Shortness of breath | 16 | 41 |
| Smelling problems | 10 | 25.6 |
| None | 7 | 17.9 |
| Other | 18 | 46.2 |

| Duration of stay on a regular ward (in days) | Total n = 39 |  |
|---|---|---|
| Mean (SEM) | 10.8 (3.38) |

### Table 5: AILD treatment and treatment changes of COVID-19 cases according to status of hospital admission

| Treatment changes | Admitted to regular ward | Total n = 32 | Admitted to intensive care unit | Total n = 5 |
|---|---|---|---|---|
| Unchanged | 24 (75) | 5 (100) |
| Reduced in dosage | 2 (6.3) | 0 (0) |
| Not applicable | 5 (15.6) | 0 (0) |
| Missing | 1 (3.1) | 0 (0) |

| Medication AILD | Admitted to regular ward | Total n = 32 | Admitted to intensive care unit | Total n = 5 |
|---|---|---|---|---|
| Prednisolone | 4 (12.5) | 3 (60) |
| Budesonide | 0 (0) | 0 (0) |
| Azathioprine/mercaptopurine | 4 (12.5) | 0 (0) |
| Mycophenolate mofetil (MMF) | 0 (0) | 1 (20) |
| Tacrolimus | 2 (6.3) | 0 (0) |
| Cyclosporine | 0 (0) | 0 (0) |
| Everolimus | 0 (0) | 0 (0) |
| Ursodeoxycholic acid (UDCA) | 21 (65.6) | 3 (60) |
| None | 6 (18.8) | 0 (0) |

Abbreviation: AILD, autoimmune liver disease.
As registry studies did not show higher mortality from COVID-19 in liver transplant recipients, immunosuppressive treatment per se does not seem to be a risk factor for severe courses of COVID-19. Webb et al. described no significant associations between the use of different classes of immunosuppressants and the outcome of COVID-19 in liver transplant recipients, while Colmereo et al.
suggested an increased risk of severe courses of COVID-19 for mycophenolate in a dose dependant manner. Association of systemic glucocorticoids and hospitalization or adverse events in patients with IBD or rheumatic disease and COVID-19 was reported. However, the use of dexamethasone seems to be beneficial in hospitalized COVID-19 patients requiring respiratory support. In our cohort, there were no significant differences in the usage of glucocorticoids, calcineurin inhibitors, or mycophenolate mofetil between the COVID-19 and non-COVID-19 groups. For most of the survey participants, medication for AILD was unchanged during the pandemic. However, in the COVID-19 group, significantly fewer patients were treated with azathioprine or mercaptopurine (10.3%) than in the non-COVID-19 group (26.4%, p = 0.023). To further analyze the influence of immunosuppressive medication and especially of azathioprine on the course of COVID-19 and to make clear recommendations on the continuation of immunosuppression during the COVID-19 pandemic, further studies with larger patient numbers are needed. As mentioned above, due to the small number of COVID-19 cases in our survey, we were not able to perform analyses determining risk factors for adverse outcomes. However, a recent publication based on registry data of a large cohort of patients with AIH and SARS-CoV-2 infection supports that immunosuppressive treatment is not a risk factor for mortality from COVID-19.

Of the 39 COVID-19 cases, the diagnosis was confirmed by nasopharyngeal swab in only 48.7% of cases. Of those patients who received confirmation of COVID-19 diagnosis by nasopharyngeal swab, a higher percentage was admitted to the hospital (Table S7). This may reflect the health care systems’ challenges in providing sufficient resources for testing of patients with mild courses of COVID-19 at the high point of the pandemic. It does, however, need to be taken into consideration that some of the COVID-19 cases in our cohort may have suffered from respiratory tract infection caused by other pathogens than SARS-CoV-2. Unfortunately, questions on whether the diagnosis was confirmed by serology were not included in the survey.

Of the non-COVID-19 cases, 26.9% had one or more symptoms that are potentially compatible with COVID-19 (fever, cough, shortness of breath, smelling problems) whereas only 16.3% received a SARS-CoV-2 test. The reasons for not testing are not known but could refer to avoidance of contact to the health care system in the context of the pandemic, limited access to tests, or unwillingness. It is therefore possible, that not all COVID-19 cases were detected.

Due to the patient-oriented approach, our study has inevitable limitations. First, we are not able to validate the participants’ data. This limitation includes potential bias and false data. Second, since the study was announced by different channels (e.g., by patients’ organizations and/or by treating physicians from healthcare centers) and due to the entry of non-personal data, we are not able to report an exact response rate for this survey. Third, questions of the survey needed to be comprehensible in order to avoid too many details and thus sources of errors. Therefore, we did not include questions on the dosage of medication, laboratory data, etc. Inherent to our study design, we were not able to analyze the mortality of COVID-19 in patients with AILD. This represents a potential bias of under-reporting. Nevertheless, we are convinced that our patient-oriented survey is an important contribution to capture the situation of AILD patients in Europe during the COVID-19 pandemic since it may better reflect mild cases and those not being infected with SARS-CoV-2. Therefore, our survey adds relevant information to data from previous registry studies which focus more on severe courses of COVID-19.

In summary, in our multinational Europe-wide, patient-oriented survey on COVID-19 in patients with AILD, we detected only a low rate of COVID-19 (39 of 1,779 participants, 2.2%) which is comparable to the general population. These results suggest that patients with AILD seem not to be at elevated risk of COVID-19.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interests that could be perceived as prejudicing the impartiality of the research reported.

AUTHORS CONTRIBUTIONS
Britta Franziska Zecher, Gustav Buescher, José Willems, Martine Walmsley, Alison Taylor, Christoph Schramm, and Marcial Sebode designed the survey. José Willems, Martine Walmsley, Alison Taylor, and Angela Leburgue distributed the survey. José Willems translated the survey into Dutch. Angela Leburgue translated the survey into French. Britta Franziska Zecher analyzed the data. Britta Franziska Zecher, Christoph Schramm, Ansgar W. Lohse, and Marcial Sebode interpreted the data. Britta Franziska Zecher and Marcial Sebode wrote the manuscript. All authors revised the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found in the Supporting Information section at the end of this article.

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