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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.

KEYWORDS
(AILD), advanced liver disease, autoimmuneliver disease, chronic liver disease, COVID-19, Europe, incidence, online survey, prevalence, SARS-CoV-2

Key Summary

Summarize the established knowledge on this subject

- Registry studies show that patients with advanced stages of liver disease are at risk of mortality caused by COVID-19. But since data is entered by the treating physicians, there may be a bias towards reporting severe cases.
- Limited data is available on COVID-19 in patients with autoimmune liver disease (AILD). Immunosuppressive treatment required in patients with AIH and AILD patients after liver transplantation might represent an additional risk factor.

What are the significant and/or new findings of this study?

- In our patient-oriented survey we did not detect a higher frequency of COVID-19 cases in patients with AILD compared to the general population.
- These results suggest that patients with AILD are not at elevated risk of COVID-19. Our study is therefore an important addition to existing registry studies evaluating the risk of COVID-19 in patients with AILD.

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.[1,2] 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.[3–5] 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.[6] Most patients with AIH and 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.[7] 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.[8,9] 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.[10–12] 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.[13]

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.eurpa.eu/eusurvey) in Dutch, English, French, German, 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 (χ^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: Predniso(lo)ne 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%, PBC/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

TABLE 1 General characteristics of participants

	Total *n* = 1,779	
	n	**%**
Countries		
Austria	11	0.6
Belgium	59	3.3
Czechia	1	0.1
Denmark	3	0.2
Estonia	1	0.1
France	450	25.3
Germany	318	17.9
Greece	2	0.1
Hungary	1	0.1
Ireland	13	0.7
Italy	53	3
Luxembourg	4	0.2
Netherlands	267	15
Poland	59	3.3
Portugal	51	2.9
Romania	2	0.1
Slovenia	1	0.1
Spain	225	12.6
Sweden	48	2.7
United Kingdom	183	10.3
None of the above mentioned	26	1.5
Missing	1	0.1
Sex		
Male	378	18.1
Female	1382	77.7
Diverse	1	0.1
Missing	18	1
Age (y)		
10-19	54	3
20-29	99	5.6
30-39	207	11.6
40-49	346	19.4
50-59	518	29.1
60-69	368	20.7
70-79	161	9.1
80-100	17	1
Missing	9	0.5
AILD		
AIH	618	34.7
PBC	621	34.9
PSC	360	20.2
PBC/AIH	112	6.3
PSC/AIH	68	3.8
Cirrhosis		
No	1270	71.4
Yes	280	15.7
I don't know	217	12.2
Missing	12	0.7
Liver transplantation		
No	1651	92.8
Yes	125	7
Missing	3	0.2
Diagnosis of COVID-19		
No	1730	97.2
Yes	39	2.2
Missing	10	0.6

Note: Countries of residence and general characteristics of participants are displayed.

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.

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 predniso(lo)ne 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.

TABLE 2 Clinical differences among participants

	AIH Total *n* = 618	PBC Total *n* = 621	PSC Total *n* = 360	PBC/AIH Total *n* = 112	PSC/AIH Total *n* = 68	
Age	n (%)	n (%)	n (%)	n (%)	n (%)	*p*-value
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	601 (97.2)	606 (97.6)	347 (96.4)	109 (97.3)	67 (98.5)	0.288
Yes	14 (2.3)	12 (1.9)	12 (3.3)	0 (0)	1 (1.5)	
Missing	3 (0.5)	3 (0.5)	1 (0.3)	3 (2.7)	0 (0)	

Note: Statistical analyses were performed via χ^2 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 but not those with close contact to a SARS-CoV-2 positive individual 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).[8,9,14] 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	
Age	n (%)	n (%)	*p*-value	Medication AILD	n (%)	n (%)	*p*-value
10–19 years	53 (3.2)	1 (2.6)	0.98	Predniso(lo)ne	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				Active smoker			
Male	365 (21.1)	11 (28.2)	0.578	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)					
				Countries			
AILD				Austria	11 (0.6)	0 (0)	
AIH	601 (34.7)	14 (35.9)	0.288	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)	
				Germany	314 (18.2)	4 (10.3)	
Cirrhosis				Greece	1 (0.1)	1 (2.6)	
No	1232 (71.2)	31 (79.5)	0.171	Hungary	1 (0.1)	0 (0)	
Yes	277 (16)	2 (5.1)		Ireland	13 (0.8)	0 (0)	
I don't know	210 (12.1)	6 (15.4)		Italy	53 (3.1)	0 (0)	
Missing	11 (0.6)	0 (0)		Luxembourg	4 (0.2)	0 (0)	

(Continues)

TABLE 3 (Continued)

	Non-COVID-19 Total *n* = 1,730	COVID-19 Total *n* = 39			Non-COVID-19 Total *n* = 1,730	COVID-19 Total *n* = 39
				Netherlands	265 (15.3)	0 (0)
Liver transplantation				Poland	57 (3.3)	2 (5.1)
No	1605 (92.8)	37 (94.9)	0.64	Portugal	50 (2.9)	0 (0)
Yes	122 (7.1)	2 (5.1)		Romania	2 (0.1)	0 (0)
Missing	3 (0.2)	0 (0)		Slovenia	1 (0.1)	0 (0)
				Spain	212 (12.3)	11 (28.2)
Inflammatory bowel disease				Sweden	46 (2.7)	1 (2.6)
No	1445 (83.5)	30 (76.9)	0.322	United Kingdom	183 (10.6)	0 (0)
Yes	259 (15)	8 (20.5)		None of the above mentioned	25 (1.4)	1 (2.6)
Missing	26 (1.5)	1 (2.6)		Missing	1 (0.1)	0 (0)
Other conditions						
Lung disease	124 (7.2)	5 (12.8)	0.179			
Diabetes	104 (6)	1 (2.6)	0.368			
arterial hypertension	244 (14.1)	4 (10.3)	0.494			
Heart disease	60 (3.5)	2 (5.1)	0.577			
Kidney disease	40 (2.3)	1 (2.6)	0.918			
Other	466 (26.9)	13 (33.3)	0.374			
None	842 (48.7)	19 (48.7)	0.955			

Note: Statistical analyses were performed via χ^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.

TABLE 4 Characteristics of COVID-19 cases

	Total *n* = 39	
	n	%
Diagnosis of COVID-19 was confirmed by swab of your nose and throat area		
No	18	46.2
Yes	19	48.7
Missing	2	5.1
Diagnosis of COVID-19 was made by/at		
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		
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		
No	37	94.9
Yes	1	2.6
Missing	1	2.6
I required ventilation		
No	0	0
Yes	1	2.6
Missing	38	97.4
I stayed at home during COVID-19		
No	3	7.7
Yes	32	82.1
Missing	4	10.3
I had the following symptoms during COVID-19		
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)		
mean (SEM)	10.8 (3.38)	

Abbreviations: A&E, ambulance and emergency; COVID-19, coronavirus disease 2019; SEM, standard error of the mean.

TABLE 5 AILD treatment and treatment changes of COVID-19 cases according to status of hospital admission

	Admitted to regular ward	
	No Total *n* = 32	Yes Total *n* = 5
Treatment changes	n (%)	n (%)
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	n (%)	n (%)
Predniso(lo)ne	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.

no reported COVID-19 cases from the Netherlands (0.0% vs. 2.35%) and the UK (0.0% vs. 1.7%).[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.[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).[3,4] Chronic liver disease and liver cirrhosis have been described as risk factors for mortality of COVID-19.[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,[22,23] larger studies did not reveal higher mortality for patients with previous liver transplantation.[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.

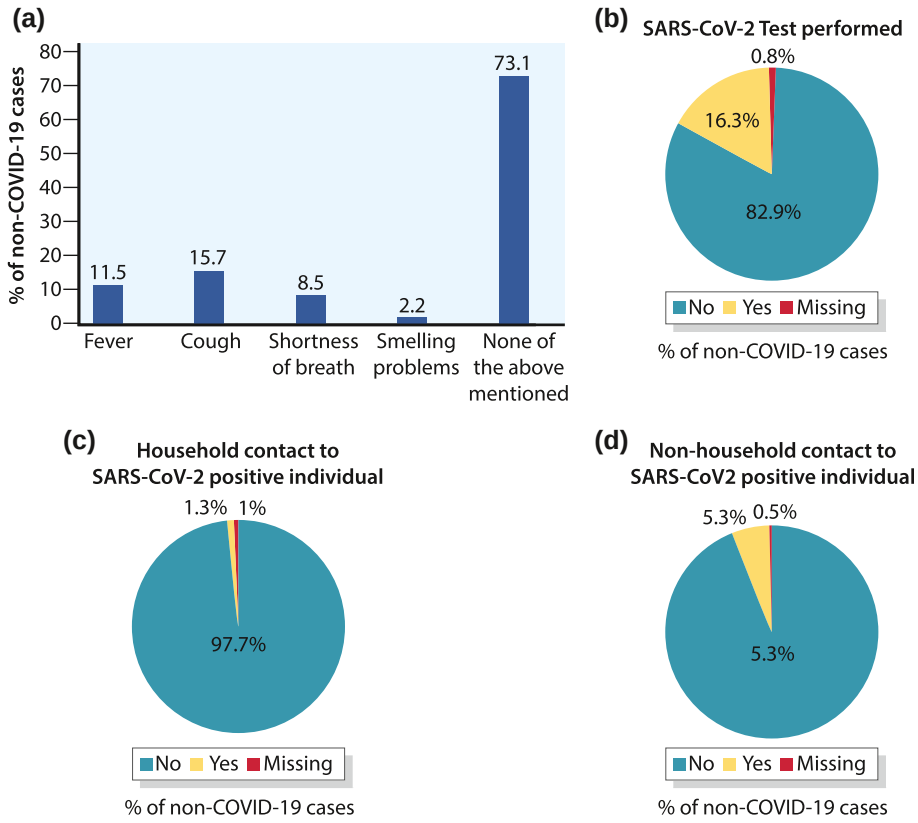

FIGURE 1 Symptoms, testing, and contacts of non-COVID-19 cases. (a) Reported symptoms since January 2020. (b) SARS-CoV-2 test since January 2020 until participation in this study. (c) Close contact with a SARS-CoV-2 positive individual living in the same household as the participant. (d) Close contact with a SARS-CoV-2 positive individual not living in the same household as the participant. Answers in the percentage of non-COVID-19 cases (n = 1,730). COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

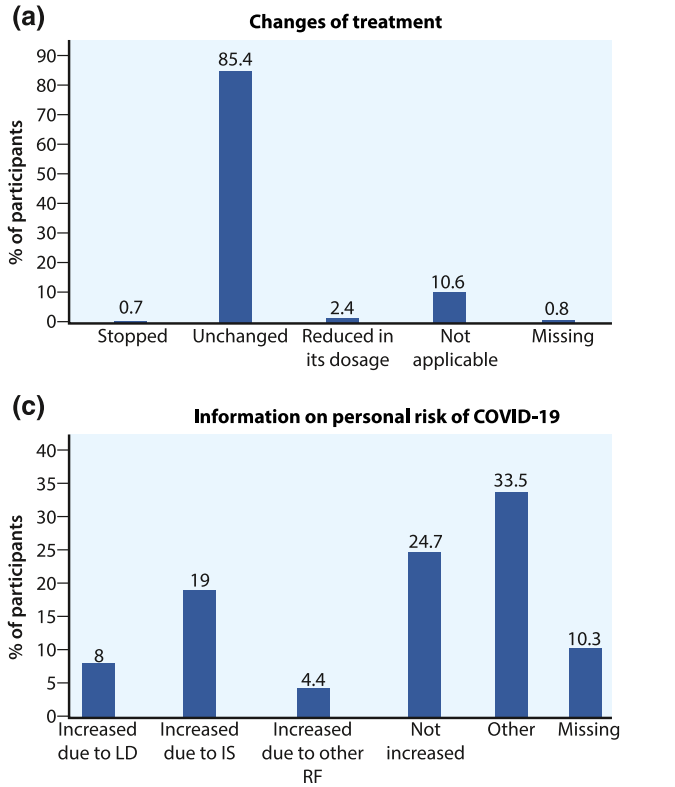

FIGURE 2 Changes of medication and information on COVID-19. (a) Changes in AILD medication during the SARS-CoV-2 pandemic. (b) Participants felt well informed about their personal risk of COVID-19. (c) Information of the participants on their personal risk of COVID-19 by the treating physician. (a–c) Answers in the percentage of participants (n = 1,779). AILD, autoimmune liver disease; COVID-19, coronavirus disease 2019; LD, liver disease; IS, immunosuppression; RF, risk factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

As registry studies did not show higher mortality from COVID-19 in liver transplant recipients,[24,25] 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.[24,26] Association of systemic glucocorticoids and hospitalization or adverse events in patients with IBD or rheumatic disease and COVID-19 was reported.[27,28] However, the use of dexamethasone seems to be beneficial in hospitalized COVID-19 patients requiring respiratory support.[29] 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.[30]

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 underreporting. 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 Willemse, Martine Walmsley, Alison Taylor, Christoph Schramm, and Marcial Sebode designed the survey. José Willemse, Martine Walmsley, Alison Taylor, and Angela Leburgue distributed the survey. José Willemse 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 online in the Supporting Information section at the end of this article.

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