Behaviors, symptoms, and outcomes of North American patients with autoimmune hepatitis during the COVID-19 pandemic

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ABSTRACT

The management of patients with autoimmune hepatitis (AIH) in the era of SARS-CoV-2 is challenging given minimal published clinical data. We used a large cohort of patients with AIH across the USA to investigate the differences in known risk factors for severe SARS-CoV-2 and AIH characteristics among patients who experienced symptoms consistent with COVID-19 illness versus those who did not. Additionally, we explored the effect of living through the SARS-CoV-2 pandemic on the extrahepatic symptoms and behaviors of patients with AIH. An invitation to complete a COVID-19-specific questionnaire was publicized in well-established social media cohorts of patients with AIH. Eligibility criteria were age ≥18 years, US residency, and an AIH diagnosis by a physician. A total of 420 individuals were eligible for the study. Symptoms consistent with COVID-19 were reported in 11% (n=48) with 3 patients requiring hospitalizations. Body mass index (BMI) >40 kg/m^2 (23% vs 10%, p=0.01) and exposure to house (33% vs 3%, p=0.0001) or work (38% vs 17%, p=0.02) contacts with COVID-19 were factors found higher in those with symptoms. Cirrhosis or steroid use or immunosuppression was not significantly different between symptomatic and non-symptomatic groups. Worsening fatigue (45% vs 30%, p=0.06), anxiety (89% vs 70%, p=0.08), and itch (40% vs 18%, p=0.03) were more common among those reporting COVID-19 symptoms compared with those without. BMI >40 kg/m^2 and exposure to contacts with COVID-19 illness but not cirrhosis or immunosuppression were associated with increased risk of COVID-19 illness in patients with AIH.

Significance of this study

What is already known about this subject?
► Infection with SARS-CoV-2 virus is widespread and includes patients with autoimmune hepatitis (AIH) on chronic immunosuppression.
► Patients with AIH have not been shown to have increased risk of morbidity related to COVID-19; however, current studies are small and focused in Europe.
► Many patients with AIH have significant extrahepatic symptoms that impact quality of life and it is unclear how these have been impacted by the SARS-CoV-2 pandemic.

What are the new findings?
► Elevated body mass index and exposure to individuals with COVID-19 were significant factors observed in those with COVID-19 symptoms.
► Cirrhosis and immunosuppression patterns were not different among those patients with or without COVID-19 symptoms.
► Symptoms tied closely to quality of life in patients with AIH, fatigue, anxiety, and itch were increased among those reporting COVID-19 symptoms.

How might these results change the focus of research or clinical practice?
► Patients with AIH do not seem to be at increased risk of COVID-19-related morbidity, no matter their level of fibrosis or immunosuppressant regimen. However, clinical follow-up of patients beyond SARS-CoV-2 infection should focus on extrahepatic symptoms to improve quality of life.

INTRODUCTION

The world is currently dealing with COVID-19 illness caused by SARS-CoV-2.[1] The WHO escalated the epidemic to a pandemic state in March 2020 when person-to-person transmission led to rapid global spread. Although the primary clinical manifestations are related to pulmonary disease, it is now recognized that COVID-19 is a systemic illness associated with an unpredictable host immune response leading to activation of the coagulation cascade, multi-organ failure, and death.[2–4] Recent data suggest individuals of all ages are at risk for infection and severe disease.[3–6] However, the probability of fatal disease is highest in people aged ≥65 and those living in a nursing home or long-term care facility.[7–10] Other high-risk populations are those with underlying conditions including hypertension, cardiovascular disease,

diabetes mellitus type 2, chronic respiratory disease, cancer, renal disease, and obesity.[3 4 7–13]

The SARS-CoV-2 virus is highly transmissible and is thought to be transmitted most readily by respiratory droplets from an infected person's cough or sneeze.[14] The Centers for Disease Control and Prevention currently defines a close contact as someone who has cared for or lived with a person with SARS-CoV-2 or a person having direct contact with respiratory secretions and/or body fluids of an infected patient with SARS-CoV-2.[14] Controlling the pandemic required governmental measures to decrease the spread and 'flatten the curve' (ie, reduce the number of symptomatic patients).[15] These measures were pursued through social distancing and lockdown through 'stay at home' orders.[15] In the USA, governors of 45 states issued 'stay at home' orders that closed all non-essential business operations, permitting employees of non-essential businesses to work only from home with few exceptions.[15] Governors also explicitly required citizens to stay home at all times unless engaging in essential activities, such as shopping for food and basic goods, commuting to perform essential work, seeking medical attention, or participating in outdoor activities.[15]

Liver injury in patients with COVID-19 illness is a concern for those with and without underlying chronic liver disease (CLD).[16–19] In patients with no underlying CLD, the liver injury may vary from direct viral cytopathic effect to ischemic hepatitis from the activation of inflammatory and coagulation cascades.[16–19] Besides, liver injury may be confounded with congestive hepatopathy from cardiac dysfunction, and drug-induced liver injury from therapies under investigation or drugs that are empirically used to treat COVID-19.[16–19] However, in patients with underlying CLD, notably cirrhosis, the effect of SARS-CoV-2 infection may be associated with higher mortality.[19–21] A recent report of COVID-19 outcomes in patients with CLD in 2 international reporting registries (COVID-Hep.net and COVID-Cirrhosis.org) between March 25 and April 20, 2020 found an overall mortality rate of 12% in CLD without cirrhosis, compared with 24% or higher in patients with cirrhosis depending on the Child-Turcotte-Pugh class and model for end-stage liver disease score.[21]

Patients with autoimmune hepatitis (AIH) may be at increased risk of COVID-19 illness and have poor outcomes due to ongoing therapy with immunosuppressive therapies and underlying CLD.[12] In a recent report from Italy, Rigamonti *et al* used a telephone survey and found COVID-19 incidence was 5–7 times higher in patients with AIH compared with the general population.[22] However, with a 3.6% incidence in a cohort of 138 patients comprising various autoimmune liver disorders, one must exercise caution in extrapolating these results.[22] Reassuringly, clinical outcomes of 70 patients with AIH and SARS-CoV-2 infection in Europe revealed there were no differences in proportions of major outcomes such as hospitalization, intensive care unit admission, and death.[23] Yet there remains a wide knowledge gap in the perceived impact of COVID-19 illness on patients with AIH in the USA. In this exploratory study, we survey a large cohort of patients with AIH across the USA to investigate the differences in known risk factors and AIH characteristics (immunosuppression and presence or absence of cirrhosis) in patients who experienced symptoms consistent with COVID-19 illness versus those who did not. Additionally, we examine the effect of living through these symptoms on the extrahepatic symptoms and behavior of patients with AIH.

METHODS

Recruitment

We invited members of the Autoimmune Hepatitis Association (AIHA) to complete a COVID-19 survey using the AIHA social media communities on Facebook and AIHA member email list. We have previously described this approach for collecting patient-reported disease attributes as well as recruitment to an ongoing AIH biorepository at Indiana University.[24–26] The collection of survey responses was completed via a weblink directed to an Institutional Review Board (IRB)-approved Research Electronic Data Capture (REDCap) survey (online supplemental table 1); a self-managed, secure, web-based platform for building and managing online surveys and databases. The study was electronically promoted 4 times between April 28 and May 16, 2020 (2 direct email messages to AIHA members and 2 electronic posts to the AIHA social media community). At the time of the study, these digital cohorts included 2875 members in the AIHA Facebook group and 1630 in the AIHA member email list with a significant overlap in membership.

COVID-19 survey

The survey included 64 discrete informational fields (online supplemental table 1) and collected information regarding respondent demographics, disease diagnosis, management and symptoms, employment, COVID-19 symptoms and exposures, and COVID-19 beliefs. Participants were required to be aged ≥18, US residents, and have previously received an AIH diagnosis from a physician. Survey respondents represented a wide array of local governments and differing timelines of stay at home order enforcement (figure 1).

Statistical analysis

Survey data were downloaded from REDCap and analyzed using SPSS (IBM SPSS Statistics, version 25) software.[26] Subgroup categorical analysis was completed to investigate the effects of age, gender, fibrosis, current immunologic therapy, prior liver transplant, other comorbid conditions, and other exposure hazards on the likelihood of developing COVID-19 symptoms during the SARS-CoV-2 pandemic (until May 2020). We further sought to describe the clinical factors of those patients reporting hospitalization related to severe COVID-19. Continuous variables were summarized as means with SDs (mean±SD). Data normality was not assumed; therefore, p values were obtained with the Wilcoxon rank-sum test. P values for discrete variables were obtained using the χ^2 test. Statistical significance was identified at $p < 0.05$.

RESULTS

Four hundred and seventy-eight surveys were completed over the 2-week study duration. Excluded surveys included those completed by individuals less than 18 years old, those outside the USA, or were incomplete (figure 2). In total,
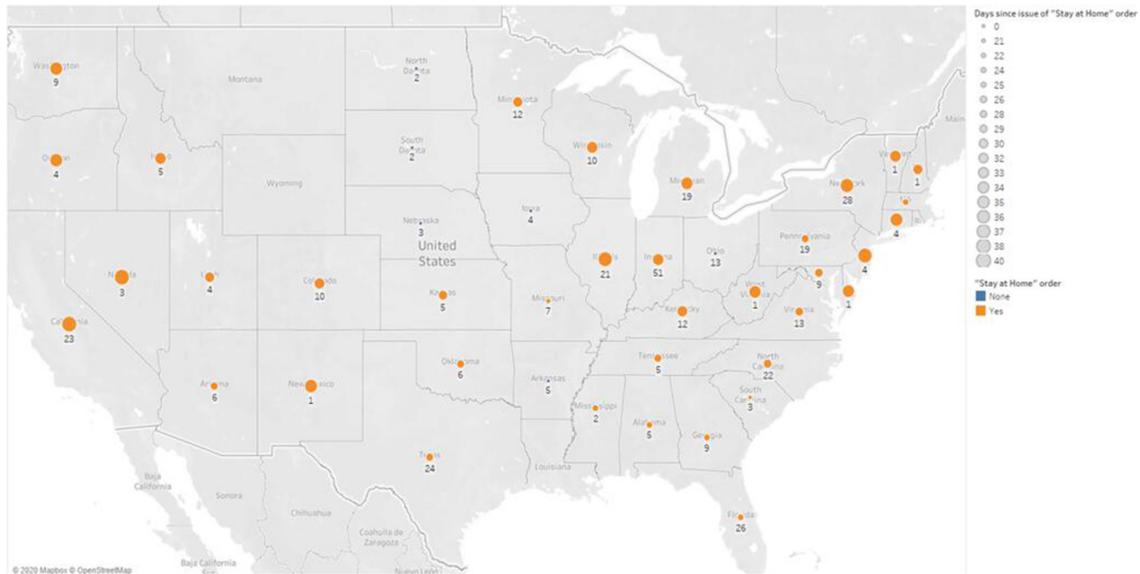
Figure 1 Survey responses from various states in the USA in relation to stay at home order and duration of stay at home order.

420 patients with AIH aged 52±13 years, representing 46 of the 50 (92%) states, completed the questionnaire. A majority of the respondents were female (91.7%) and Caucasian (91.2%) (table 1).

Underlying liver disease and risk factors for severe illness from COVID-19

The mean age of AIH diagnosis was 45±15 years, and in those who knew the degree of fibrosis through a liver biopsy (n=346), 78 patients (22.5%) reported cirrhosis. Purine analogs (azathioprine (AZA)/6-mercaptopurine) were the most common immunosuppressive agents used for AIH therapy (61.7%) followed by steroids in 40.7% (prednis(ol)one: 27.4%, budesonide: 13.4%). With the inclusion of immunosuppression medications (steroids and non-steroidal), 96% (403/420) had at least 1 risk factor associated with severe COVID-19 illness. Beyond medication risks, 60.5% (254/420) had at least 1 risk factor

associated with severe illness from COVID-19, 14.8% had 2 risk factors (62/420), 8.6% (36/420) had 3 or more risk factors. The most common risk factors included hypertension, increased age, and extreme obesity (body mass index (BMI) >40 kg/m^2).

SARS-CoV-2 exposures and subsequent testing

A majority of patients with AIH (96%) adhered to local state-mandated stay at home orders and social distancing all or most of the time. Despite compliance with these recommendations, some patients with AIH reported possible exposure to SARS-CoV-2 at work or home. Exposure to contacts at work which had symptoms suspicious for COVID-19 or a known positive SARS-CoV-2 test was reported in 14.9% of the study cohort or 10.5% of those who were working. Further, 6.4% (27/420) reported household contacts with symptoms consistent with COVID-19 or positive SARS-CoV-2 test. Among these 27 household
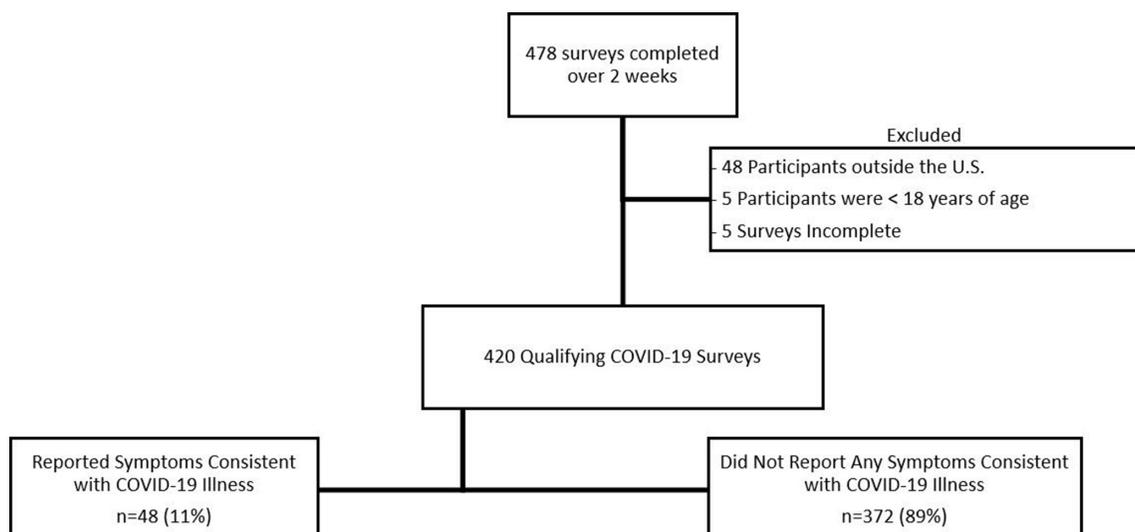
Figure 2 Survey completion and prevalence of symptoms consistent with COVID-19 among patients with autoimmune hepatitis (AIH).

3

Table 1 Demographics and selected characteristics of patients with autoimmune hepatitis (AIH) in the study cohort (n=420)

	Study participants (n=420)
Age at survey completion (years)	52±13
Age at diagnosis of AIH (years)	45±15
Female	92%
Race (%)	
Caucasian	91
African-American	2
Hispanic/Latino	3
Other	4
Fibrosis stage	
Cirrhosis	23% (78/346)
Non-cirrhotic	77% (268/346)
Unknown	15% (62/408)
Liver transplantation	3%
Current immunosuppressants (%)	
Predniso(lo)ne	27
Budesonide	13
AZA/6-MP	62
Mycophenolate mofetil	18
Tacrolimus	8
Sirolimus	1
None	6
Risk factors for severe COVID-19 illness (%)	
Hypertension	27
Over the age of 65 years	16
Asthma that requires the use of an inhaler	12
Severely overweight (BMI >40 kg/m^2)	12
Prior cancer diagnosis	9
Diabetes mellitus type 2	8
Chronic lung condition	5
Chronic kidney disease	2
Serious heart condition	1

AZA, azathioprine; BMI, body mass index; 6-MP, 6-mercaptopurine.

contacts, patients reported 59.3% (16/27) alerted their treating doctor and all were asked to self-quarantine. A majority (13/16) of those who informed their treating doctor underwent testing for SARS-CoV-2, and only 23.1% (3/13) had known positive results.

COVID-19 illness and SARS-CoV-2 infection

A total of 48 (11%) patients with AIH reported symptoms consistent with COVID-19 illness during the stay at home orders (figure 1). There were no demographic differences between the 2 groups of patients with AIH with or without symptoms suspicious for COVID-19 illness (table 2). Further, there was no difference between AIH treatment regimens among these 2 groups (table 2).

Risk factors that have been associated with a higher risk of severe illness from COVID-19 were compared as well, and only BMI >40 kg/m^2 was more likely to be observed in patients with AIH with symptoms consistent with COVID-19 illness (23% vs 10%, p=0.01). The only other significant factor associated with COVID-19 symptoms included exposure to work contacts with COVID-19 illness,

but not the number of coworkers, customers, or healthcare occupation. Close and frequent interaction with customers or coworkers appeared to be a risk factor for COVID-19 symptoms but was not statistically significant (p=0.09). Among patients with AIH reporting symptoms consistent with COVID-19 illness, 25% (12/48) had no identifiable home or work contacts with COVID-19 symptoms. Eight patients with AIH with COVID-19 symptoms either worked from home or did not work and had no symptomatic home contacts, 4 worked outside the house and had no symptomatic work or home contacts. Among these working outside the home, 50% were healthcare workers.

Stratification of COVID-19 symptoms according to fibrosis level (cirrhosis, n=78; non-cirrhotic, n=268) did not reveal statistically significant differences in demographic, treatment, or job status/exposures between the 2 groups (table 3). However, in both groups with cirrhosis and no cirrhosis, patients with household contacts with COVID-19 symptoms were more likely to report COVID-19 symptoms themselves.

AIH management by treating physician

Eight patients with AIH reported that their treating doctors pre-emptively adjusted immunosuppressant regimens in anticipation of pandemic across the USA (adjustment was made to steroids (50%), AZA (37%), mycophenolate mofetil (MMF) (12%)). A majority of patients with AIH (67%) also reported routine laboratory testing or procedural appointments were scheduled to be due during the local stay at home orders (282/420) and only 57% were rescheduled (160/282).

Among patients with AIH with symptoms consistent with COVID-19, 58% (28/48) alerted their treating doctor, 82% (23/28) were told to self-quarantine, 50% (14/28) were provided a SARS-CoV-2 test, and 43% (6/14) tested positive. Among those with a positive SARS-CoV-2 test, 33% (2/6) had medications adjusted after positive results (medications adjusted for patient 1: prednisone/tacrolimus/AZA and patient 2: tacrolimus/MMF), and 50% (3/6) were hospitalized. Individual descriptions of hospitalized patients are reported in online supplemental table 2. Hospitalized patients were all women, Caucasian (2 of 3), non-cirrhotic (2 of 3), on immunosuppression (2 of 3 prednisone), and had at least 1 comorbidity associated with severe COVID-19 illness.

Extrahepatic AIH symptoms and the pandemic

Extrahepatic symptoms related to AIH were present before the pandemic in 84% of patients with AIH including 69% (288/420) with fatigue, 44% (187) poor sleep, 23% (97) depression, 32% with anxiety (135), 50% (79) joint pain, 19% (79) with itch, and 28% (118) right upper quadrant (RUQ) pain. Many patients (55% reported worsening of at least 1 extrahepatic symptom) reported multiple pre-existing extrahepatic symptoms worsened during the pandemic including 32% (91/288) with fatigue, 45% (85/187) sleep, 59% (57/97) depression, 73% anxiety (98/135), 10% (21/209) joint pain, 33% (26/79) itch, and 9% (11/118) RUQ pain. Worsening fatigue (45% vs 30%, p=0.06), anxiety (89% vs 70%, p=0.08), and itch (40% vs 18%, p=0.03) tended to be more common among patients

Table 2 Differences in characteristics among patients with AIH with and without symptoms consistent with COVID-19 illness (n=420)

	Symptoms consistent with COVID-19 illness		
	Yes (n=48)	No (n=372)	P value
Age at survey completion (years) (mean, SD)	50±12	52±13	0.57
Age at AIH diagnosis (years) (mean, SD)	42±15	45±15	0.89
Female	95.8%	91%	0.27
Cirrhosis	33%	21%	0.12
Liver transplantation for AIH	0%	3%	0.23
Tested for SARS-CoV-2	29%	0%	**0.0001**
Rate of positivity (among those who underwent testing)	43%	Not applicable	
Current immunosuppression (%)			
Any steroids	44	40	0.60
Other immunosuppression beyond steroids*	87	83	0.44
No medications	6	6	0.87
Risk factors for severe COVID-19 illness (%)			
Over the age of 65	8	17	0.11
Asthma that requires the use of an inhaler	17	12	0.34
Chronic lung condition	8	5	0.31
Serious heart condition	0	1	0.42
Chronic kidney disease	4	2	0.39
Hypertension	25	27	0.75
Diabetes mellitus	12	7	0.20
Severely overweight (BMI >40 kg/m^2)	23	10	**0.01**
African descent	4	2	0.22
Prior cancer diagnosis	8	9	0.90
Doctor adjusted immunosuppressive medication in anticipation of pandemic	2%	2%	0.92
House contacts with COVID-19 symptoms	33%	3%	**0.0001**
Occupational factors among those with jobs during stay at home orders (n=192)			
	n=21	n=171	P value
Close, frequent contact with coworkers or customers	48%	29%	0.09
Interaction with more than 5 customers per day	48%	50%	0.41
Interaction with more than 5 coworkers per day	71%	76%	0.16
Work contacts with COVID-19 symptoms	38%	17%	**0.02**
Worked in healthcare setting	29%	16%	0.17

Bold values are considered signficant (p<0.05).

*No significant differences according to individual immunosuppressant agents.

AIH, autoimmune hepatitis; BMI, body mass index.

with AIH reporting COVID-19 symptoms compared with those without.

Employment during the pandemic and stay at home orders

Two hundred and sixty-two (62%) of respondents were actively working in the month before the local 'stay at home' orders. Among these, 93% (242/262) had a job that involved close interactions with coworkers and/or customers (45% >10 coworkers/day; 42% >10 customers/day). A majority (73%) (192/262) maintained their pre-existing employment through the 'stay at home' orders until the time of the survey. Among these, 24 (12.5%) were able to work remotely. Unfortunately, the remaining 27% (70/262) lost their jobs during the stay at home order with 80% fired, furloughed, or placed on extended leave. Surprisingly, 3% quit because of health risks during the coronavirus pandemic.

Among all participants working before initiation of stay at home orders, 23% (60/262) held a job in a healthcare setting with the risk of close interaction with patients with COVID-19. Among those employed in healthcare, 22 patients (37%) requested a change in job function because of their underlying AIH diagnosis or ongoing treatment with immunosuppression medications. The employer supported this change in 73% (16/22).

Future behaviors of patients with AIH

Participants reported they would make changes in behaviors when stay at home orders are relaxed. They planned to increase handwashing/sanitizing (90%), limit entertainment outside the home (88%), wear a mask in public (82%), limit interactions with friends (55%), limit interactions with family (34%), reduce hours worked (7%), change jobs (3%), and seek AIH medication change (2%). Participants who had symptoms consistent with COVID-19 were

Table 3 Selected demographics and risk factors for COVID-19 in patients with AIH stratified by fibrosis level (n=346) according to symptoms consistent with COVID-19

	Symptoms consistent with COVID-19 illness					
	Cirrhosis (n=78)			No cirrhosis (n=268)		
	Yes (n=14)	No (n=64)	P value	Yes (n=29)	No (n=239)	P value
Age at survey completion (years) (mean, SD)	48±12	52±13	0.28	51±13	53±12	0.39
Age at AIH diagnosis (years) (mean, SD)	39±14	42±15	0.48	43±15	46±13	0.31
Female gender	93%	86%	0.48	97%	93%	0.42
Caucasian	93%	95%	0.40	86%	91%	0.23
Income (<$50,000/year)	42%	28%	0.10	21%	20%	0.98
Current immunosuppression						
Any steroids	64%	52%	0.39	34%	37%	0.81
Other than steroids	79%	87%	0.39	93%	82%	0.13
No medications	0%	5%	0.41	7%	6%	0.83
Doctor adjusted immunosuppressive medications in anticipation of pandemic	0%	0%	n/a	3%	2%	0.77
House contacts with COVID-19 symptoms	29%	0%	**0.0001**	41%	3%	**0.0001**
Stay at home orders followed (most of the time)	93%	94%	0.13	100%	96%	0.74
Occupational factors among those with jobs during stay at home orders						
	n=4	n=26		n=13	n=113	
Close, frequent contact with coworkers or customers	75%	31%	0.09	38%	30%	0.54
Interaction with more than 5 customers per day	50%	54%	0.67	51%	46%	0.84
Interaction with more than 5 coworkers per day	50%	71%	0.43	77%	76%	0.47
Work contacts with COVID-19 symptoms	25%	75%	0.63	31%	18%	0.26
Worked in healthcare setting	25%	11%	0.46	31%	17%	0.22
Stay at home orders followed (most of the time or more)	75%	88%	0.30	100%	92%	0.52

Bold values are considered signficant (P value < 0.05)
AIH, autoimmune hepatitis; n/a, not applicable.

Table 4 Attitudes and preferences of patients with AIH with and without symptoms consistent with COVID-19 illness

	Symptoms consistent with COVID-19 illness		
	Yes (n=48)	No (n=372)	P value
Adhering to state's guidelines (%)			
All of the time	68.8	70.4	0.32
Most of the time	29.2	25.3	
Some of the time	0	3.8	
Never	2.1	0.5	
When state guidelines are relaxed, plans for protection (%)			
Change in medications or dosage	4	2	0.39
Use of a facemask in public	81	83	0.79
Increase handwashing or use of hand sanitizer	83	92	**0.06**
Cut down the number of working hours	4	7	0.4
Change job	2	3	0.61
Limit interactions with friends	48	56	0.31
Limit interactions with family	35	34	0.83
Limit entertainment outside of the home	77	89	**0.02**
COVID-19 test that detects active viral infection without physician order would make it easier to return to physical community.	50%	50%	1.00
COVID-19 test that shows exposure and immunity without physician order would make it easier for return to physical community.	85.4%	82.5%	0.62

Bold values are considered signficant (P value < 0.05)
AIH, autoimmune hepatitis.

less likely to report plans to increase handwashing or use of hand sanitizer and limit entertainment outside of their home compared with participants who did not have symptoms consistent with COVID-19 (table 4).

In order to alleviate concerns about returning to public domains, 50% (210/420) of respondents believed that SARS-CoV-2 testing without the need for a physician's order would be needed: 54% (114/210) would require it performed monthly, 42% (89/210) weekly, and 3% (7/210) daily. In the cohort, 83% (348/420) believed that SARS-CoV-2 antibody tests, without physician order, would increase the return to public domains. There was no difference in these beliefs between patients with AIH who did and did not have COVID-19 symptoms (table 4).

DISCUSSION

The COVID-19 pandemic has not left any facet of humanity untouched. The current study sheds light on the consequences of COVID-19 illness in patients with AIH and its potential impact on other disease attributes.

In our study, most patients with AIH adhered to local 'stay at home' orders; despite this, 11% of patients with AIH had symptoms consistent with COVID-19 illness. This is nearly twice as high as the prevalence observed in a recent Italian telephone interview study, including 73 patients with AIH (5.6%).[22] Our study further showed that notable risk factors associated with symptoms consistent with COVID-19 illness included BMI >40 kg/m^2, exposure to work or home contacts with COVID-19 symptoms and working in a healthcare setting. AIH-related factors, such as type of immunosuppression and the presence of cirrhosis, were not associated with increased risk of COVID-19 illness. Notably, the type of immunosuppression with steroids or others did not differ in either cirrhosis or non-cirrhotic group in those with symptoms. Together, it appears that immune suppressants used for the AIH treatment do not appear to increase the risk of severe COVID-19 illness and are consistent with observations of prior coronavirus epidemics[27][28] (Middle East respiratory syndrome and severe acute respiratory syndrome), as these viruses did not cause more severe disease in immunocompromised patients.[29] A similar observation was found among a group of 70 European patients with AIH.[23]

We observed that exposure to work and household contacts with COVID-19 symptoms and working in a healthcare setting were associated with the report of symptoms consistent with COVID-19 illness. It is also reassuring there were only 3 hospitalizations (6%) among the 48 patients (11%) who reported symptoms.

Despite the release of a clinical insight paper by the American Association for Study of Liver Disease providing guidelines to managing physicians cautioning against preemptive adjustment to immunosuppression regimens, we observed 5% of patients without cirrhosis with adjustments completed before the pandemic.[30] The short-term and long-term impacts of these decisions on managing patients' chronic immunosuppression are unknown, yet we believe the inherent risk of AIH relapse could outweigh the small risk of severe COVID-19 disease in patients with AIH on immunosuppression. The current study also highlights the pandemic's likely toll on routine care of liver disease, with 43% of patients who did not reschedule their laboratory, imaging, or procedural appointments.

The impact of the COVID-19 pandemic extended beyond the liver with many patients with AIH reporting worsening of extrahepatic symptoms, notably depression and anxiety, associated with reduced quality of life.[31] However, in those with symptoms consistent with COVID-19 illness, itching was statistically significantly higher. This finding is novel and it is likely mediated through the virus's binding to the host angiotensin I converting enzyme 2, which is significantly higher in cholangiocytes than hepatocytes.[32] Future studies should examine if new onset or worsening of the itch is a manifestation of SARS-CoV-2 infection, particularly in those with underlying liver disease.

The current study dwells on the behavioral changes associated with the pandemic. Many see themselves adjusting their behaviors beyond the 'stay at home' orders to protect themselves from SARS-CoV-2 infection irrespective of having experienced symptoms consistent with COVID-19 illness. However, patients with AIH with a history of symptoms consistent with COVID-19 illness may be more confident in their possible immunity, as they seemed less likely to increase handwashing or limit their engagement of entertainment outside the home when 'stay at home' orders are relaxed.

Certain aspects of the current study merit further clarification. We admit a limitation is the absence of confirmatory testing among patients with AIH reporting symptoms consistent with COVID-19 (fever, dry cough, shortness of breath, etc). However, in the USA, a system-wide shortage of SARS-CoV-2 tests during most of the 'stay at home' orders prevented routine testing and necessitated doctors to manage patients as likely positive. Another limitation associated with a study based on a survey is the response rate. The present research leverages our prior experience to conduct research in rare diseases such as AIH through digital cohorts within the social 'mediome'.[26] We are confident the current study is less likely to be biased by the response rate, as the response rate to the current survey is consistent with our previously published work using a similar approach.[26] Further, a dedicated chart review of previously recruited patients using this framework has provided 'high confidence' in patients' ability to precisely report on aspects of their disease.[2] Furthermore, one could argue that those who may have died would not respond to the survey. Unfortunately, this is an inherent limitation with the current study design. It is reassuring that there were only 3 hospitalizations among the 48 patients who reported symptoms.

We provide a relatively large cross-sectional assessment of patients with AIH from the USA and their symptoms, behaviors, and beliefs regarding the SARS-CoV-2 infection. Among the previously reported risk factors, only BMI >40 kg/m^2 in participants with AIH appears to be associated with symptoms consistent with COVID-19 illness. The severity of liver disease and the use of immune suppressants were not associated with an increased risk of COVID-19 illness. Worsening of itching appears to be a symptom related to COVID-19 illness, and perhaps the ongoing multicenter registries will shed more light on this novel observation.

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