HEPATOLOGY FORUM
doi: 10.14744/hf.2022.2022.0012

Coronavirus disease 2019 (COVID-19) in autoimmune hepatitis

Seyda Nur Dagli[1], Cumali Efe[2],

[1]Department of Physiology, Harran University Faculty of Medicine, Sanliurfa, Turkey; [2]Department of Gastroenterology, Harran University Faculty of Medicine, Sanliurfa, Turkey

Abstract

Severe acute respiratory syndrome coronavirus 2 is a highly transmissible and pathogenic virus that leads to coronavirus disease 2019 (COVID-19). The preexisting liver diseases alter the course of COVID-19. Therefore, specific management strategies must be considered in individuals with chronic liver diseases (CLDs) and COVID-19. Autoimmune hepatitis (AIH) is a rare immune-mediated liver disease. Patients with AIH require life-long treatment with immunosuppressive drugs that may increase the risk of poor COVID-19 outcomes. The stage of underlying liver disease is another factor that can affect the clinical outcomes of COVID-19 in patients with AIH. In this review, we aim to provide relevant issues that will be helpful to clinicians in understanding and improving the clinical care for patients with AIH during the pandemic.

Keywords: Autoimmunity; azathioprine; immunosuppression; liver failure; liver transplantation; steroids.

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in Wuhan, China.[1] COVID-19 has rapidly spread throughout the world and caused a global pandemic. COVID-19 generally has an asymptomatic course or can present with mild symptoms; however, it can also progress to respiratory failure and death, particularly in individuals with risk factors such as older age, cardiovascular disease, chronic lung disease, active cancer, and diabetes mellitus.[2] Several studies showed that patients with CLDs, especially those with cirrhosis, have higher hospitalization and mortality rates with COVID-19.[3,4]

Autoimmune hepatitis (AIH) is a rare chronic inflammatory liver disease.[5] Corticosteroids alone or in combination with azathioprine are the current standard therapy for AIH. Alternative drugs such as tacrolimus, mycophenolate mofetil (MMF), 6-mercaptopurine, rituximab, and infliximab can also be used in about 20%-30% of patients who do not respond or are intolerant to standard therapy.[5,6] AIH requires life-long immunosuppressive treatment, which also can enhance the risk of bacterial or viral infections in patients.[5]

The stage of the liver disease can be a contributing factor to adverse outcomes in AIH with COVID-19. In addition, immunosuppressive therapy for AIH may increase the risk of poor COVID-19 outcomes. On the other hand, immunosuppression could be protective against inappropriate immune response, or cytokine storm, which is characteristic of severe COVID-19.[7] Finally, SARS-CoV-2 infection may lead to a flare of underlying AIH. These factors render AIH a unique disease that should be managed with extra caution during the COVID-19 pandemic.

Here, we investigated the clinical characteristics and outcomes of COVID-19 in patients with AIH and discussed possible approaches that can be helpful to clinicians in the management of AIH with COVID-19.

Prevalence of COVID-19 in Patients with AIH

A multicenter Europe-wide patient-oriented survey on patients with AIH showed that the prevalence of COVID-19 in patients with AIH between June 24, 2020, and October 14, 2020, was not higher than in the general population. These results suggest that patients with AIH are not associated with an increased risk of COVID-19.[8]

Characteristics of AIH Patients with COVID-19

To date, two international registry-based studies and a few case studies have evaluated the clinical presentation and outcome of COVID-19 in patients with AIH.[9-13] The general characteristics of published studies about COVID-19 outcomes in patients with AIH are presented in Table 1. The median age of AIH patients with COVID-19 was approximately 50 years, and most patients were females. In two studies,[9,10] 54% and 29% of patients with AIH had cirrhosis during COVID-19 diagnosis. Most patients with AIH presented with respiratory symptoms. Gastrointestinal symptoms were noted in 20%-30% of the patients. The majority of the patients (>83%) with AIH were under immunosuppression at the time of COVID-19. Prednis(ol)one and/or thiopurines (azathioprine/6-mercaptopurine) were the most commonly used immunosuppressive drugs. There were no changes in medications for 60%-65% of the patients during the COVID-19 diagnosis. Up to 40% of patients also had concomitant comorbid diseases such as arterial hypertension, diabetes mellitus, and coronary artery disease. New-onset liver injury was observed in 37% of the patients, with 18% moderate and 19% severe liver injury.[10] The use of antivirals was an independent predictor of liver injury (OR 3.36), while continued immunosuppression during COVID-19 lowered the risk of new-onset liver injury (OR 0.26).

How to cite this article: Dagli SN, Efe C. Coronavirus disease 2019 (COVID-19) in autoimmune hepatitis. Hepatology Forum 2022; 3(2):68–70.

Received: April 18, 2022; **Accepted:** April 18, 2022; **Available online:** May 05, 2022

Corresponding author: Seyda Nur Dagli; Harran Universitesi Tip Fakultesi, Fizyoloji Anabilim Dali, Sanliurfa, Turkey
Phone: +90 535 648 82 96; **e-mail:** seyda_dgl@hotmail.com

Table 1. Characteristics of published data about COVID-19 outcomes in patients with AIH

Study	Number of patients	Immunosuppressive therapy during COVID-19	Hospitalization	Mortality
Gerussi et al.[12]	10	100%	60%	10%
Marjot et al.[9]	70	83%	76%	23%
Efe et al.[10]	110	93%	46%	10%
Efe et al.[11]	254	92%	37%	7%

Outcomes of COVID-19 in Patients with AIH

In an international study,[9] COVID-19 outcomes of AIH (n=70) were compared with propensity score-matched (PSM) patients with non-AIH CLD (n=932) and healthy controls (n=769). The hospitalization rates, intensive care unit (ICU) admission rates, and all-cause mortality were not different between AIH and non-AIH CLDs. PSM analysis of patients with AIH versus healthy controls (n=769) revealed an increased risk of hospitalization in patients with AIH (+18.4%), but a similar risk of ICU admission and mortality in AIH and healthy controls. Another study compared the outcomes of AIH (n=110) with a PSM cohort of non-AIH CLD (n=220) and COVID-19.[10] The rates of hospitalization (46.4% vs 50.0%), need for supplemental oxygen (38.2% vs 42.2%), severe COVID-19 (15.5% vs 20.2%), and all-cause mortality (10% vs 11.5%) were similar in AIH and non-AIH CLDs.

In patients with AIH, age and comorbid conditions were predictors of severe COVID-19 outcomes, but cirrhosis was the strongest predictor of severe outcomes and mortality.[9,10] Overall mortality was 31% in AIH patients with baseline cirrhosis, while only 1.3% in those without.[10] The presence of liver injury and continued immunosuppression during COVID-19 were not associated with severe COVID-19. AIH activity (remission vs nonremission) was also not associated with the outcome.[10,11]

Immunosuppressive Drugs and COVID-19 Severity in AIH

The use of immunosuppression was not associated with outcomes in a previous study which included 58 immunosuppressive-treated AIH patients with COVID-19.[9] However, the small population size in this study did not allow for more powerful analyses. In another study,[10] dose reduction of immunosuppression during COVID-19 did not lower the risk of severe COVID-19 in AIH. Indeed, this outcome is not unexpected as the immunosuppressive effects of AIH medications continue 8-12 weeks after their discontinuation. In a follow-up study,[11] the authors included 254 patients with AIH, of whom 234 (92%) were taking immunosuppressive therapy during COVID-19 diagnosis. This study showed that patients with AIH on glucocorticoids (aOR 4.73) and patients receiving thiopurine treatment (aOR 4.78) were at an increased risk of increased COVID-19 severity compared with patients who did not receive treatment. Patients under both prednisolone-equivalent dose ≤5 mg/day (aOR 2.93) and >5 mg/day (aOR 8.30) were also at increased risk of poor outcomes. Patients who were using MMF (aOR 3.56) and tacrolimus (aOR 4.09) were also associated with poor COVID-19 outcomes.

AIH Triggered by COVID-19

AIH initially presentation following a bacterial or viral infection is a well-known phenomenon.[5,6] COVID-19 can alter immunological tolerance and lead to the new-onset or flare of a preexisting AIH. Few case studies suggested that AIH can be diagnosed for the first time during or a short time after COVID-19.[14,15] The diagnosis and treatment of AIH in active COVID-19 are challenging. Liver biopsy is not mandatory for AIH diagnosis in these patients if they have characteristic laboratory and serological findings.[16] Immunosuppressive therapy should be given during COVID-19 for patients with features of severe AIH, while it can be delayed in patients with mild hepatitis until recovery from COVID-19. These results also suggest that AIH should be considered among differential diagnoses in individuals who develop liver injury during or immediately after COVID-19.

Preventive Measures for Patients with AIH during COVID-19

The association between AIH and adverse COVID-19 outcomes supports the importance of preventive measures in this patient population. Vaccination against SARS-CoV-2 infection, mask-wearing, and social distancing should be strongly recommended for patients with AIH during the COVID-19 pandemic. These patients can also be managed remotely. Telemedicine has become particularly relevant in the management of patients with CLD during the current COVID-19 epidemic as it reduces hospital visits, which lowers the risk of SARS-CoV-2 contamination. Telemedicine was also evaluated for the management of AIH during the COVID-19 pandemic. Compared with the standard care group (in-person visit), adherence to therapy as well as the risk of disease relapse was lower in the telehealth group.[17] A recent study evaluated the immune response to SARS-CoV-2 vaccination in 96 patients with AIH.[18] Ten (10%) patients had low or no response to vaccination. Patients with AIH had significantly lower antibody levels than healthy controls, suggesting an early third booster dose is necessary for patients with AIH.

AIH Following COVID-19 Vaccine

Several case reports described AIH-like liver injury that developed after SARS-CoV-2 vaccination.[19] The laboratory and histological findings of most cases mimicked AIH. These patients responded well to corticosteroid therapy; however, one patient progressed to fulminant liver failure and underwent liver transplantation.[19,20] These results should not discourage patients from SARS-CoV-2 vaccination. Liver injury is a rare side effect of the COVID-19 vaccines, and the overall benefits of vaccination outweigh the risk of side effects during the pandemic.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SND, CE; Design – SND, CE; Supervision – SND, CE; Fundings – SND, CE; Materials – SND, CE; Data Collection and/or Processing – SND, CE; Analysis and/or Interpretation – SND, CE; Literature Search – SND, CE; Writing – SND, CE; Critical Reviews – SND, CE.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Morens DM, Daszak P, Taubenberger JK. Escaping Pandora's box-another novel coronavirus. N Engl J Med 2020;382(14):1293-1295. [CrossRef]
2. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020 12;323(18):1775-1776. [CrossRef]
3. Yapalı S. What hepatologists need to know about COVID-19? Hepatology Forum. 2020;2(1):41-43. [CrossRef]
4. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of Outcomes of COVID-19 in Patients with Chronic Liver Disease: US Multi-center Study. Clin Gastroenterol Hepatol 2021;19(7):1469-1479.e19.
5. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the american association for the study of liver diseases. Hepatology 2020;72(2):671-722. [CrossRef]
6. Wang G, Tanaka A, Zhao H, Jia J, Ma X, Harada K, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidance: the diagnosis and management of patients with autoimmune hepatitis. Hepatol Int 2021;15(2):223-257. [CrossRef]
7. Rodríguez Y, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, et al. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. J Autoimmun 2020;114:102506. [CrossRef]
8. Zecher BF, Buescher G, Willemse J, Walmsley M, Taylor A, Leburgue A, et al. Prevalence of COVID-19 in patients with autoimmune liver disease in Europe: A patient-oriented online survey. United European Gastroenterol J 2021;9(7):797-808. [CrossRef]
9. Marjot T, Buescher G, Sebode M, Barnes E, Barritt AS 4th, Armstrong MJ, et al; contributing Members and Collaborators of ERN RARE-LIVER/COVID-Hep/SECURE-Cirrhosis. SARS-CoV-2 infection in patients with autoimmune hepatitis. J Hepatol 2021;74(6):1335-1343. [CrossRef]
10. Efe C, Dhanasekaran R, Lammert C, Ebik B, Higuera-de la Tijera F, Aloman C, et al. Outcome of COVID-19 in patients with autoimmune hepatitis: An international multicenter study. Hepatology 2021 Jun;73(6):2099-2109.
11. Efe C, Lammert C, Taşçılar K, Dhanasekaran R, Ebik B, Higuera-de la Tijera F, et al. Effects of immunosuppressive drugs on COVID-19 severity in patients with autoimmune hepatitis. Liver Int 2022;42(3):607-614. [CrossRef]
12. Gerussi A, Rigamonti C, Elia C, Cazzagon N, Floreani A, Pozzi R, et al. Coronavirus Disease 2019 (COVID-19) in autoimmune hepatitis: a lesson from immunosuppressed patients. Hepatol Commun 2020;4(9):1257-1262.
13. Rigamonti C, Cittone MG, De Benedittis C, Rizzi E, Casciaro GF, Bellan M, et al. Rates of symptomatic SARS-CoV-2 infection in patients with autoimmune liver diseases in northern Italy: A telemedicine study. Clin Gastroenterol Hepatol 2020;18(10):2369-2371.e1 [CrossRef]
14. Kabaçam G, Wahlin S, Efe C. Autoimmune hepatitis triggered by COVID-19: A report of two cases. Liver Int 2021;41(10):2527-2528. [CrossRef]
15. Marabotto E, Ziola S, Sheijani AD, Giannini EG. COVID-19 and liver disease: Not all evil comes to harm. Liver Int 2021;41(1):237-238. [CrossRef]
16. Lleo A, Invernizzi P, Lohse AW, Aghemo A, Carbone M. Management of patients with autoimmune liver disease during COVID-19 pandemic. J Hepatol 2020;73(2):453-455. [CrossRef]
17. Efe C, Simşek C, Batıbay E, Calışkan AR, Wahlin S. Feasibility of telehealth in the management of autoimmune hepatitis before and during the COVID-19 pandemic. Expert Rev Gastroenterol Hepatol 2020;14(12):1215-1219. [CrossRef]
18. Duengelhoef P, Hartl J, Rüther D, Steinmann S, Brehm TT, Weltzsch JP, et al. SARS-CoV-2 vaccination response in patients with autoimmune hepatitis and autoimmune cholestatic liver disease. United European Gastroenterol J 2022;10(3):319-329. [CrossRef]
19. Lleo A, Cazzagon N, Rigamonti C, Cabibbo G, Lai Q, Muratori L, et al; Italian Association for the Study of the Liver. Clinical update on risks and efficacy of anti-SARS-CoV-2 vaccines in patients with autoimmune hepatitis and summary of reports on post-vaccination liver injury. Dig Liver Dis 2022 Mar 28:S1590-8658(22)00217-1. doi: 10.1016/j.dld.2022.03.014. [Epub ahead of print] [CrossRef]
20. Efe C, Harputluoğlu M, Soylu NK, Yilmaz S. Letter to the editor: Liver transplantation following severe acute respiratory syndrome-coronavirus-2 vaccination-induced liver failure. Hepatology 2022 Feb 17. doi: 10.1002/hep.32409. [Epub ahead of print] [CrossRef]