DR. CRAIG LAMMERT (Orcid ID : 0000-0003-3809-640X)

DR. LAURA CRISTOFERI (Orcid ID : 0000-0001-9846-7474)

MR. ANDRES JOSE GOMEZ-ALDANA (Orcid ID : 0000-0002-7954-4910)

DR. SHALOM FRAGER (Orcid ID : 0000-0001-9313-3408)

DR. YASEMIN BALABAN (Orcid ID : 0000-0002-0901-9192)

DR. ALESSIO GERUSSI (Orcid ID : 0000-0002-5086-0514)

DR. MANUEL MENDIZABAL (Orcid ID : 0000-0002-7026-9908)

DR. EZEQUIEL RIDRUEJO (Orcid ID : 0000-0002-3321-0683)

DR. RENUMATHY DHANASEKARAN (Orcid ID : 0000-0001-8819-7511)

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Outcome of COVID-19 in Patients with Autoimmune Hepatitis: an International Multi-Centre Study.

Cumali Efe MD[1*], Renumathy Dhanasekaran MD[2*], Craig Lammert MD[3], Berat Ebik MD[4], Fatima Higuera-de la Tijera MD[5], Costica Aloman MD[6], Ali Rıza Calışkan MD[7], Mirta Peralta MD[8,9], Alessio Gerussi MD[10,11], Hatef Massoumi MD[12], Andreea M. Catana MD[13], Murat Torgutalp MD[14], Tugrul Purnak MD[15], Cristina Rigamonti MD[16], Andres Jose Gomez Aldana MD[17],Nidah Khakoo MD[18], Hüseyin Kacmaz MD[7], Leyla Nazal MD[19], Shalom Frager MD[12], Nurhan Demir MD[20], Kader

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Irak MD[21], Zeynep Melekoğlu Ellik MD[22], Yasemin Balaban MD[23], Kadri Atay MD[24], Fatih Eren MD[25], Laura Cristoferi, MD[10,11], Ersin Batıbay MD[1], Álvaro Urzua MD[26], Romee Snijders MD[27], Murat Kıyıcı MD[28], Murat Akyıldız MD[29], Nazım Ekin MD[4], Rotonya M Carr MD[30], Murat Harputoğlu MD[31], Ibrahim Hatemi MD[32], Manuel Mendizabal MD[9,33], Marcelo Silva MD[9,33], Ramazan Idilman MD[22], Marina Silveira MD[34], Joost P. H. Drenth MD[27], David N.Assis MD[34], Einar Björnsson MD[35,36], James L. Boyer MD[34], Pietro Invernizzi MD[10,11], Chyntia Levy MD[18], Thomas D. Schiano MD[37], Ezequiel Ridruejo MD[9,33,38&], Staffan Wahlin MD[39&].

[1]Department of Gastroenterology, Harran University Hospital, Şanlıurfa, Turkey.

[2]Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University, Stanford, CA, United States.

[3]Department of Medicine Indiana, University School of Medicine Indianapolis IN USA.

[4]Department of Gastroenterology, Gazi Yaşargil Education and Research Hospital, Diyarbakir, Turkey.

[5]Gastroenterology and Hepatology Unit. Hospital General de México,Ciudad de México, México.

[6]Rush University Medical Center, Section of Hepatology, Chicago, Illinois, USA.

[7]Department of Gastroenterology, Adıyaman University , Adıyaman, Turkey.

[8]Hepatology Section, Hospital Francisco J Muñiz, Ciudad Autónoma de Buenos Aires, Argentina.

[9]Latin American Liver Research Educational and Awareness Network (LALREAN), Pilar, Argentina.

[10]Division of Gastroenterology and Center for Autoimmune Liver Diseases Department of Medicine and Surgery University of Milano-Bicocca Monza Italy.

[11]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), San Gerardo Hospital, Monza, Italy.

[12]Department of Medicine, Montefiore Medical Center, Bronx, NY,USA.

[13]Division of Gastroenterology/Hepatology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

[14]Department of Gastroenterology, Infectious Diseases and Rheumatology, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Berlin, Germany.

[15]Division of Gastroenterology, Hepatology and Nutrition, McGovern Medical School, 6431 Fannin, MSB1.150, Houston, TX, 77030, USA.

[16]Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy and Division of Internal Medicine, "AOU Maggiore della Carità", Novara, Italy.

[17]Gastroenterology and Hepatology Unit. Fundación Santa Fe de Bogotá y universidad de Los Andes, Bogotá, Colombia.

[18]Division of Hepatology, University of Miami Miller School of Medicine, Miami, Florida, USA.

[19]Gastroenterology and Hepatology Unit. Clínica Las Condes, Santiago de Chile, Chile.

[20]Haseki Training and Research Hospital, Department of Gastroenterology, Istanbul, Turkey.

[21]Department of Gastroenterology, SBU Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey.

[22]Department of Gastroenterology, Ankara University Medical Faculty, Ankara, Turkey.

[23]Department of Gastroenterology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

[24]Departmant of Gastroenterology, Mardin State Hospital , Mardin, Turkey.

[25]Departmant of Gastroenterology, Ordu State Hospital , Ordu, Turkey.

[26]Gastroenterology and Hepatology Unit. Hospital Clínico Universidad de Chile, Santiago de Chile, Chile.

[27]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands.

[28]Department of Gastroenterology, Medical Faculty, Uludag University, Bursa 16059, Turkey.

[29]Department of Gastroenterology, Koc University School of Medicine, Istanbul, Turkey.

[30]Division of Gastroenterology University of Pennsylvania, Philadelphia, Pennsylvania.

[31]Department of Gastroenterology, Inönü University School of Medicine, Malatya, Turkey.

[32]Department of Gastroenterology, Cerrahpaşa School of Medicine, İstanbul, Turkey.

[33]Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Pilar, Argentina.

[34]Department of Medicine, Section of Digestive Diseases Yale School of Medicine New Haven CT, USA.

[35]Department of Internal Medicine, Section of Gastroenterology, Landspitali University Hospital, Reykjavik, Iceland.

[36]Faculty of Medicine, University of Iceland, Reykjavik Iceland

[37]Division of Liver Diseases, the Mount Sinai Medical Center, New York, USA.

[38]Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas, CEMIC, Ciudad Autónoma de Buenos Aires, Argentina.

[39]Hepatology Division, Department of Upper GI, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden.

Corresponding author: Cumali Efe MD, **e-mail:** drcumi21@hotmail.com.

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[*]**Cumali Efe and Renumathy Dhanasekaran** contributed equally to this work as co-first authors.

[&]**Staffan Wahlin and Ezequiel Ridruejo** share senior authorship.

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ABSTRACT

Background: Data regarding outcome of Coronavirus disease 2019 (COVID-19) in patients with autoimmune hepatitis (AIH) are lacking.

Patients and methods: We performed a retrospective study on AIH patients with COVID-19 from 34 centres in Europe and the Americas. We analyzed factors associated with severe COVID-19 outcomes defined as the need for mechanical ventilation, intensive care admission, and/or death. The outcomes of patients with AIH were compared to a propensity-score matched cohort of non-AIH patients with chronic liver diseases (CLD) and COVID-19. The frequency and clinical significance of new-onset liver injury (alanine aminotransferase>2xupper limit of normal) during COVID-19 was also evaluated.

Results: We included 110 AIH patients (80%,female) with a median age of 49 (range:18–85) years at COVID-19 diagnosis. New-onset liver injury was observed in 37.1% (33/89) of the patients. Use of antivirals was associated with liver injury (p=0.041; odds ratio (OR) 3.36[1.05-10.78]) while continued immunosuppression during COVID-19 was associated with a lower rate of liver injury (p=0.009; OR 0.26[0.09-0.71]). The rates of severe COVID-19 (15.5% vs 20.2% p=0.231) and all-cause mortality (10% vs 11.5%; p=0.852) were not different between AIH and non-AIH CLD. Cirrhosis was an independent predictor of severe COVID-19 in patients with AIH (p<0.001; OR 17.46[4.22-72.13]). Continuation of immunosuppression or presence of liver injury during COVID-19 was not associated with severe COVID-19.

Conclusions: This international, multi-center study reveals that patients with AIH were not at risk for worse outcomes with COVID-19 than other causes of CLD. Cirrhosis was the strongest predictor for severe COVID-19 in AIH patients. Maintenance of immunosuppression during COVID-19 was not associated with increased risk for severe COVID-19, but did lower the risk for new-onset liver injury during COVID-19.

INTRODUCTION:

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), was first described in December 2019 in Wuhan, China [1]. Following this first report, it rapidly spread world-wide and caused an international pandemic. Most COVID-19 cases have mild symptoms but the disease can result in hospitalization, progression into respiratory failure and death [2-4]. Older age, cardiovascular diseases, chronic lung diseases, active cancer, obesity, and diabetes mellitus are risk factors for severe COVID-19 outcomes [5]. COVID-19 often affects the liver and individuals with underlying chronic liver diseases (CLD) have high rates of hospitalization and mortality [6-7].

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease [8]. Corticosteroids alone or in combination with azathioprine is the standard therapy in AIH. Several alternative immunosuppressive drugs, including tacrolimus, mycophenolate mofetil (MMF), methotrexate, 6-mercaptopurine, rituximab and infliximab are used in patients who do not respond or are intolerant to

standard therapy [8-9]. The majority of AIH patients require life-long immunosuppressive therapy, which may increase the risk of bacterial and viral infections [8]. Existing data regarding the clinical presentation and outcome of COVID-19 in patients with AIH is limited to small case series and expert opinions [10-11]. The stage of liver disease has been shown to be risk factor, but it is unclear whether the type of underlying liver disease is a major contributing factor to poor outcomes with COVID-19. Specifically for AIH, immunosuppressive therapy enhances the risk of severe COVID-19. On the other hand it may be argued that immunosuppression protects against the inappropriate immune response, or cytokine storm, which is a characteristic of severe COVID-19 [12].

The aims of this international multi-centre study, were to assess the clinical characteristics and outcomes of AIH patients infected with COVID-19 and to explore the frequency and factors associated with new-onset liver injury and severe COVID-19 outcome in these patients.

MATERIALS AND METHODS

Study design

We retrospectively evaluated data of AIH patients who were diagnosed with COVID-19 between March 11 and November 12, 2020 from 34 centres in 10 countries. All participants independently identified patients and collected data from electronic health records and patient's follow-up charts. Patients with AIH who were older >16 years at the time of COVID-19 with a diagnosis confirmed by a PCR based test were included in the study. Patients with typical radiological findings but with negative PCR tests were not included. All patients with AIH, or overlap with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), were diagnosed and treated according to international guidelines [8,13].

The presence of cirrhosis was diagnosed based on standard imaging studies (elastography, ultrasound, computerized tomography or magnetic resonance), liver tissue examination or clinical findings of portal hypertension or its complications. Complete biochemical response was defined as normal ALT, AST and immunoglobulin G (IgG) levels. Partial response was defined as a decrease of ALT or AST to below two times the upper normal limit (UNL) and non-response was defined as persistently elevated transaminase levels more than two times the UNL despite appropriate immunosuppressive

therapy [8,13]. High alcohol consumption was defined as a more than 2 drinks/day for men and more than 1 drink/day for women [14].

New-onset liver injury was defined as rising ALT values during COVID-19 and categorized as no or mild (<2xULN), moderate (2-5xULN) or severe (>5xULN). New-onset ALT >2xULN was used as definition of liver injury for the study. Patients who were non-responders to AIH therapy were excluded from new-onset liver injury analysis as they already had ALT >2xULN levels before the COVID-19 diagnosis. The cut offs for normal values of ALT were considered 25 U/L for women and 35 U/L for men [15]. Severe COVID-19 infection was defined as a composite of intensive care unit (ICU) admission, ventilator use and/or death in line with previously reported COVID-19 data [3]. The Harran University Hospital of Şanlıurfa was the coordinating centre (HRE ID 2020-00682) and local ethical review boards of participating centres approved the study.

Data collection

Collected patient data included general information of patients, autoimmune liver serology, types and doses of immunosuppression, patient's AIH response status at last follow-up before COVID-19 and presence of cirrhosis. At the time of COVID-19 diagnosis, body mass index (BMI), clinical features, and co-morbid conditions were recorded. Laboratory values at COVID-19 diagnosis and at peak/worst values any time in the first month of COVID-19 were used to evaluate liver injury. Any modification in the dose or type of immunosuppressive drugs during COVID-19, highest care level, hospitalization time, specific COVID-19 therapies and patient outcomes, providing a minimum of four weeks after COVID-19 were recorded.

In order to determine how AIH impacts clinical outcomes with COVID-19, we compared AIH patients to a control group of patients with non-AIH CLD and COVID-19. To identify a control group, we used data from a multi-center, observational study of adult patients with CLD and PCR-confirmed COVID-19. More details regarding the inclusion and exclusion criteria of this cohort have been previously published [7]. Only non-AIH patients from this cohort were included in the control group. None of the patients in the control group were on immunosuppression.

Statistical Analysis

Continuous variables were presented as mean with standard deviation, or as median with range. Student's t-test or the Mann-Whitney U test was used for comparisons, as appropriate depending on the distribution. Categorical variables were presented as numbers and percentages, and the chi-squared test was used for comparisons. Multivariable logistic regression analysis models were performed to predict the two major outcomes of the study (dependent variables): significant new-onset liver injury and severe COVID-19. According to the predefined statistical plan, we evaluated associations between each independent variable and outcome after having analysed the number of outcome events. In addition to predefined sex and age in terms of their clinical relevance for the outcomes, independent variables with a statistically significant relationship ($P < 0.1$) with dependent (outcome) variables in the univariate analysis were then included in the multivariable models. Hosmer–Lemeshow goodness-of-fit statistics were used to assess model fit. A p-value < 0.05 was considered to represent statistical significance.

We compared clinical outcomes of COVID-19 in patients with AIH and non-AIH CLD. We used propensity score analysis to identify a cohort of patients with non-AIH CLD and COVID-19 who were statistically matched on a 1:2 basis using the nearest neighbor approach. We matched the AIH and non-AIH for crucial variables which are known to impact clinical outcomes with COVID-19 including age, gender, presence of cirrhosis, diabetes mellitus hypertension and heart diseases.

RESULTS

General characteristics of the study population

Medical data of 115 patients AIH who acquired COVID-19 was analyzed. Five patients were excluded: three patients had previously undergone liver transplantation and two patients were concomitantly diagnosed with AIH and COVID-19 (Figure 1). The final study group included 110 AIH patients (80%, female) with a median age of 49 (range 18–85) years at COVID-19 infection. Four of these patients had been included in a previous study [11]. The general characteristics, clinical features and outcomes of the patients are presented in table 1. Twelve (10.9 %) patients had overlap with PBC and four (3.6%) with PSC. Co-existence of other immune mediated disorders were noted in 28 (25.5%) patients, including, autoimmune thyroid diseases in 17 (15.4%) patients, inflammatory

bowel diseases in three (2.7%), Sjögren syndrome in two (1.8%), systemic sclerosis in two (1.8%), rheumatoid arthritis in two (1.8%), systemic lupus erythematosus in one (0.9%), celiac disease in one (0.9%), ankylosing spondylitis in one (0.9 %) and anti-phospholipid syndrome in one (0.9%).

AIH characteristics before COVID-19

At last follow-up before COVİD-19 diagnosis, 88 (80%) patients were complete responders, 19 (17.3%) were partial responders and three (2.7%) were non-responders. Thirty-two (29.1%) patients with AIH had features of cirrhosis. A total of 53 (48.2%) patients had co-morbid conditions; diabetes mellitus (n=27, 24.5%) and hypertension (n=26, 23.6%) were the most common. Seven (6.4%) patients reported active smoking and two (1.8%) had high alcohol consumption. Five (4.5%) patients had a history of malignancy, two of which were active during COVID-19.

Most patients (92.7%) were on immunosuppressive therapy prior to the COVID-19 diagnosis. Eight patients (7.3%) were not on immunosuppressive therapy; six patients had withdrawn therapy (three by themselves and three by a physician), one patient was non-responder to available therapies and one had inactive ("burned-out") cirrhosis. At the time of COVID-19 diagnosis, 65 (59.1%) patients were on prednisone therapy (alone or in combination with other immunosuppressants) with median dose of 5 (range 2.5-60) mg/ day. Among them, 25 (22.7%) patients were on prednisone ≥10 mg/day therapy. The patients' immunosuppressive therapies are presented in table 1.

Management of AIH during COVID-19

Majority of patients (n=96, 87.3%) were symptomatic at the time of COVID-19 diagnosis; cough (n=68, 61.8%) and fever (n=65, 59.1%) were the most commonly reported symptoms. Gastrointestinal symptoms (abdominal pain, diarrhea, nausea and vomiting) were noted in 30 (27.2%) patients.

The dose or type of immunosuppression was modified in 33 (30%) patients during COVID-19, but remained unchanged in 69 (62.7%). General characteristics of the patients according to immunosuppressive therapy status are presented in table 2. Among patients on azathioprine/6-MP monotherapy (n=10), doses were reduced in three and discontinued in seven. Among patients on steroids monotherapy (n=2), the dose was reduced in one and discontinued in one. In patients treated

with a combination of azathioprine/6-MP and steroids (n=14), the dose of only azathioprine/6-MP was reduced in one and discontinued in five, and the dose of only steroids was reduced in five, while the doses of both azathioprine/6-MP and steroids were reduced in one patient and discontinued in two patients. Azathioprine was discontinued and tacrolimus reduced in a patient who was treated with both drugs. In one patient who was on triple immunosuppression, azathioprine was discontinued and both the steroid and tacrolimus doses were reduced. Among patients treated with MMF and steroids (n=4), only MMF was discontinued in three and both drugs were reduced in one patient. The dose was reduced in a patient on MMF monotherapy.

Antibiotics were given to 40 (36.4%) patients during COVID-19 infection. Sixty-seven (60.9%) patients received specific therapy for COVID-19. Hydroxychloroquine (n=29, 26.4%) and antivirals (n=22, 20%) were the most commonly used therapies. High dose steroids were given to 15 (13.6%) patients and plasma exchange was performed in three (2.7%) patients. Tocilizumab and rituximab were used in one (0.9%) patient each. The details of COVID-19 therapies are presented in Table 1.

Liver injury during COVID-19

New-onset liver injury was reported in 37.1% (33/89) of the patients: 16 (18%) had moderate and 17 (19.1%) had severe liver injury. New-onset liver injury was observed in 85.7% (6/7) of the patients who were not on immunosuppression, in 51.7% (15/29) of the patients whose immunosuppression was modified and in 22.6% (12/53) of the patients whose immunosuppression was unchanged during COVID-19. Predictors of liver injury are presented in Table 3. Multivariate regression analysis revealed that antivirals (defined in table 1) were associated with new-onset liver injury (p=0.041; odds ratio (OR) 3.36 [95% confidence interval (CI): 1.05-10.78]) and that continued immunosuppression during COVID-19 reduced the probability of liver injury (p= 0.009; OR 0.26 [0.09-0.71]).

Outcomes of COVID-19 in patients with AIH compared to non-AIH CLD

When the outcomes of patients with AIH (n=110) were compared to a cohort of non-AIH patients with CLD (n=220) and COVID-19 (supplementary table 1), no statistically significant differences were noted regarding the rates of all-cause mortality (10% vs. 11.5%; p=0.852), severe COVID-19

(15.5% vs. 20.2%; p=0.231), need for supplemental oxygen (38.2% vs. 42.2%; p=0.553) and hospitalization (46.4% vs 50.0%; p=0.560) (Figure 2).

Seventeen AIH patients had severe COVID-19 and 11 patients died due to COVID-19. Predictors of severe outcomes in patients with AIH are presented in Table 4. After adjusting for age, gender, co-existence of PBC/PSC or extrahepatic autoimmune diseases and AIH therapy response, the presence of cirrhosis was independently associated with severe COVID-19 ($p<0.001$; OR 17.46 [4.22-72.13]). AIH patients with comorbid conditions (defined in table 1) tended to have severe COVID-19 infection (p=0.06; OR 4.16 [0.94-18.36]). Presence of liver injury and continued immunosuppression during COVID-19 were not associated with severe COVID-19.

DISCUSSION

In this international multi-centre study, we evaluated the clinical presentation, laboratory features and outcomes of COVID-19 in patients with AIH. In our study population, 37.1% of the patients developed new-onset liver injury during COVID-19. Among 110 patients with AIH, 15.5% had severe COVID-19 and 10% of patients died. Our data show that i) the overall outcome of COVID-19 was favorable in patients without cirrhosis; ii) on-going immunosuppression was not associated with increased risk of severe COVID-19 and iii) maintenance of immunosuppression was associated with a lower risk for new-onset liver injury.

We found similar rates of severe COVID-19 outcome and mortality in patients with AIH and a matched control group of non-AIH CLD and COVID-19. Among patients with AIH, patients with cirrhosis had higher risk for severe COVID-19 outcomes (43.8% vs. 3.9%). Overall mortality was also significantly higher in patients with cirrhosis than those without (31.3% vs. 1.3%). In line with our results, other studies reported 30-34% mortality rates in patients with cirrhosis [16-17]. These results suggest that regardless of aetiology, cirrhosis is a strong predictor of worse prognosis in patients with COVID-19. Consistent with previous reports [5], AIH patients with comorbid conditions in our study tended to have severe COVID-19.

New-onset liver injury was observed in 37.1% during COVID-19. Other studies have reported the rate to be 27.4 % in a general population [18], 34.6 % in liver transplant recipients and 47.5% in patients

with CLD [19]. Liver injury was found to be predictor of poor outcome in these studies [7, 18-19]. In our AIH cohort, liver injury was not associated with adverse COVID-19 outcomes. There are several possible causes of liver injury in COVID-19 and all causes probably do not carry the same mortality risk [18, 20]. Patients who develop hepatocyte necrosis induced by systemic inflammatory response syndrome, or ischemic injury due to circulatory or respiratory failure, may have a higher mortality risk compared to those who have a drug induced liver injury or develop an AIH relapse. The similar outcomes of patients with and without liver injury in our study might be explained by the likely incidence of AIH relapse or drug-induced liver injury, both manageable causes of liver injury.

Relapse of AIH following infection is a well-known phenomenon [14]. COVID-19 can trigger hyperstimulation of the immune system, an event associated with high serum levels of inflammatory cytokines and chemokines [12]. Four patients with AIH and non-severe COVID-19 had new-onset liver injury along with high IgG levels, thus suggesting they experienced AIH relapse rather than COVID-19 induced liver injury (Table 5). Development of various inflammatory or autoimmune conditions has been reported during or shortly after COVID-19 [12, 21]. Some case reports suggested that AIH presents for the first time during COVID-19 [21-22]. In fact, two patients in our cohort (both excluded), did receive their initial diagnosis of AIH during COVID-19. Overall, our results suggest that COVID-19 may be associated with new onset or flare of AIH, especially in patients whose immunosuppression is reduced.

A lack of clear data has made it difficult to make definitive recommendations for management of immunosuppression during COVID-19. In our study, the doses and types of immunosuppression were continued unchanged in 62.7% of the patients when they acquired COVID-19, and this was not associated with adverse COVID-19 outcomes. Two previous studies [19,23] also reported that continued immunosuppression did not increase the risk of severe COVID-19 in liver transplant recipients, only MMF usage was linked to severe COVID-19 outcome [23]. In our study, MMF was discontinued or reduced in 62.5% (5/8) of the patients who were on this drug. Also, therapy with prednisone (≥10mg/day) was associated with higher hospitalization rates in a rheumatology setting [24] and similar results were also reported in patients with inflammatory bowel disease [25]**.** However, the rates of severe COVID-19 were not different in patients with AIH who were on

prednisone ≥10mg/day compared to patients on <10 mg/day (24 vs. 12.9%, p=0.211). Due to the low number of patients who were on ≥10 mg/day prednisone or MMF therapy, we cannot draw definitive conclusions about the associated risks. Of note, patients whose immunosuppressive therapy was modified during COVID-19 experienced higher rates of liver injury or AIH relapse than those in whom immunosuppressive therapy was not modified. Relapse of AIH due to reduction or withdrawal of immunosuppression during COVID-19 represents diagnostic and therapeutic challenges. Elevated aminotransferases may be misinterpreted as a marker for severe COVID-19 and lead to unnecessary hospitalizations. Induction therapy to achieve AIH remission requires higher doses of immunosuppression, which may adversely affect the outcome of COVID-19. Our results support maintaining immunosuppressive therapy during COVID-19.

We acknowledge that the retrospective nature of our study is a main limitation. However, given the unprecedented nature of the pandemic, and the low prevalence of AIH, we believe that our study offers valuable insights into the management of these patients. Another limitation is the possibility of selection bias since asymptomatic patients and those with mild disease were likely not included in our study. We have however included both out-patients and in-patients, and more than 50% our study population was out-patients. We also observed that some of the hospitalized patients had short hospital stay. Since patients with AIH were immunosuppressed, had concomitant co-morbid conditions and also due to lack information about appropriate use of immunosuppressive therapy during COVID-19, it is possible that patients were admitted out of caution and hospitalization may not necessarily reflect the severity of COVID-19. We also found that management and therapeutic strategies for COVID-19 vary significantly between centers and countries. To overcome these limitations, we used widely accepted clinical end-points of severe COVID-19 infection like ICU admission and need for mechanical ventilation [3,23,25].

Our study also has several strengths. We derived data from many hepatology centres across Europe and the Americas and this represents the largest cohort describing COVID-19 in AIH to date. Moreover, we collected detailed information on immunosuppression changes during the course of COVID-19 allowing to discern the effects of dose reductions and modifications on clinical outcomes.

Lastly, we have compared the AIH cohort with a matched non-AIH cohort which allows examining the impact of AIH itself on clinical outcomes of COVID-19.

In conclusion, this large multi-centre study of AIH patients with COVID-19 found overall mortality and severe COVID-19 rates of 10% and 15.5%, respectively. Patients with AIH, despite being immunosuppressed, did not experience worse clinical outcomes with COVID-19 than patients with non-AIH CLD. Presence of cirrhosis was the strongest predictor of severe COVID-19, and the overall outcome of COVID-19 was favorable in patients with non-cirrhotic AIH. Maintenance of immunosuppression was associated with lower risk of new-onset liver injury. We recommend that immunosuppression is not decreased or discontinued upon diagnosis of COVID-19.

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Author names in bold designate shared first authorship.

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Table-1. Demographics, clinical features and outcome of study population (n=110)	
Region	
North America, n (%)	34(30.9)
South America, n (%)	22(20)
Europe, n (%)	54(49.1)
Sex (female), n (%)	88 (80)
Overlap syndromes (PBC/PSC), n (%)	12/4(10.9)/(3.6)
Concomitant autoimmune diseases, n (%)	28(25.5)
ANA, n (%)[a]	77 (76.5)
SMA, n (%)[b]	46 (45.1)
LKM-1, n (%)[c]	3(3.8)
LC-1, n (%)[d]	3(6.2)
SLA, n (%)[e]	2(4.1)
AIH activity at last visit before COVID-19	
Complete response, n (%)	88(80)
Partial response, n (%)	19(17.3)
Non-response, n (%)	3(2.7)
Presence of Cirrhosis, n (%)	32(29.1)
Features of AIH patients at COVID-19 infection	
Age (years), mean (SD)	47.9 (15.8)
Time from AIH diagnosis, median (months)	60(1-480)
BMI, kg/m^2, mean (SD)	26.5 (5.3)
Co-morbidities, (%)	53(48.2)
Smoking	7(6.4)
Alcohol	2(1.8)
Hypertension	26(23.6)
Diabetes	27(24.5)
Coronary artery disease	5(4.5)
Atrial fibrillation	2(1.8)

Heart failure	2(1.8)
Respiratory disease	9(8.3)
Cancer history	5(4.5)
Kidney insufficiency	1(0.9)
Immunosuppressive therapy before COVID, n (%)	102(92.7)
Azathioprine/6-MP	27 (24.5)
Azathioprine/6-MP+Prednisolone/Budesonide	39 (35.4)
Azathioprine/6-MP +Tacrolimus	1 (0.9)
Azathioprine/6-MP+Prednisolone/Budesonide+ Tacrolimus	1 (0.9)
Azathioprine/6-MP+Prednisolone/Budesonide+ Infliximab	1 (0.9)
Azathioprine/6-MP+Prednisolone/Budesonide+ Vedolizumab	1 (0.9)
Prednisolone/Budesonide	20 (18.1)
Prednisolone/Budesonide+ Tacrolimus	2 (1.8)
Prednisolone/Budesonide+ MMF	4 (3.6)
Prednisolone/Budesonide+ Methotrexate	1 (0.9)
Prednisolone/Budesonide+ Tacrolimus +MMF	1 (0.9)
MMF	3 (2.7)
Sirolimus	1 (0.9)
Symptoms at presentation, n (%)	96 (87.3)
Fever	65 (59.1)
Cough	68 (61.8)
Dyspnoea	39 (35.5)
Headache	22 (20)
Fatigue and/or myalgia	65 (59.1)
Anosmia	19 (17.3)
Gastrointestinal symptoms, n (%)	30 (27.2)
Abdominal pain	11 (10)
Diarrhea	13 (11.8)
Nausea	7 (6.4)
Vomiting	11 (10)
Continued immunosuppression during COVID-19, n (%)	69 (62.7)

Antibiotic therapy during COVID-19, n (%)	40 (36.4)
Medical therapies for COVID-19, n (%)	67 (60.9)
Hydroxychloroquine	29 (26.4)
Antivirals	22(20)
Favipiravir	17(15.5)
Remdesivir	1 (0.9)
Lopinavir/Ritonavir	4 (3.6)
High dose steroids	15 (13.6)
Rituximab	1 (0.9)
Tocilizumab	1 (0.9)
Low molecular weight heparin	26 (23.6)
Plasma exchange	3 (2.7)
Oxygen therapy, n (%)	42 (38.2)
Nasal cannula	25 (22.7)
Non-invasive ventilation/mechanical ventilation	9(8.2)/8(7.3)
New-onset liver Injury during COVID-19, n (%)[f]	33 (37.1)
Outcome of study population	
Hospitalized, n (%)	51(46.4)
Intensive care admission, n (%)	15(13.6)
Death, n (%)	11(10)

ANA, antinuclear antibody; BMI, body mass index; LC-1, liver-cytosol type 1; LKM-1, liver kidney microsome type 1; MMF, mycophenolate mofetil; MP, mercaptopurine; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody. [a]ANA was available in 101 patients; BMI was available in 83 [b]SMA was available in 101 patients; [c]LKM-1 was available in 80 patients; [d]LC1-1 was available in 48 patients; [e]SLA was available in 48 patients; [f]Liver injury was evaluated in 89 patients.

Table-2. Characteristics of AIH patients according to immunosuppressive therapy status during COVID-19

	Immunosuppression unchanged (n=69, %)	Immunosuppression reduced/stopped (n=41, %)	*P* value
Age >65 (years)	13(18.8)	4(9.8)	0.278
Gender (female)	57(82.6)	31(75.6)	0.461
BMI>30	8(16.3)	8(23.5)	0.572
Co-morbidity	37(53.6)	18(43.9)	0.430
Cirrhosis	21(30.4)	11(26.8)	0.829
Remission before COVID-19	60(87)	28(68.3)	0.026
Symptoms at presentation	59(85.5)	37(90.2)	0.564
Treatment for COVID-19	43(62.3)	24(58.5)	0.840
*New-onset liver injury	12(22.6)	21(58.3)	0.001
Severe COVID-19	10(14.5)	7(17.1)	0.788
All-cause Mortality	4(5.8)	7(17.7)	0.096
*New-onset liver injury was evaluated in 89 patients.			

Table-3:Univariate and multivariate analyses of new-onset liver injury in AIH patients with COVID-19						
	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Sex (female)	1.21	0.37-3.93	0.742	1.85	0.42-8.05	0.407
Age (> 65 years)	0.56	0.16-1.94	0.364	0.76	0.18-3.10	0.704
BMI (>30)	2.05	0.62-6.75	0.235			
Complete response to therapy	0.27	0.09-0.85	0.025	0.27	0.06-1.15	0.077
Cirrhosis	1.05	0.42-2.63	0.908			
Co-morbidities	1.06	0.44-2.51	0.890			
Immunosuppression maintenance	0.20	0.08-0.52	0.001	0.26	0.09-0.71	0.009
Antibiotics	1.64	0.68-3.91	0.263			
Antivirals	3.00	1.06-8.49	0.039	3.36	1.05-10.78	0.041
Hydroxychloroquine	0.86	0.33-2.23	0.757			
High dose steroid	0.82	0.25-2.65	0.742			
O_2 therapy (any)	2.56	1.06-6.20	0.037	2.23	0.81-6.13	0.118
New-onset liver injury was analyzed in 89 patients. Co-morbidities and antivirals are presented in table-1.						

Table-4:Univariate and multivariate analyses for predictors of severe COVID-19 in AIH patients						
	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Sex (female)	1.19	0.31-4.59	0.792	2.20	0.44-10.82	0.330
Age (> 65 years)	2.81	0.84-9.40	0.093	1.03	0.23-4.48	0.964
Overlap of PBC/PSC	1.31	0.33-5.23	0.694			
Extrahepatic autoimmune diseases	1.26	0.40-3.98	0.684			
BMI (>30)	1.94	0.44-8.54	0.378			
Co-morbidities	6.46	1.73-24.02	0.005	4.16	0.94-18.36	0.060
Prednisolone (≥10 mg)	2.12	0.70-6.48	0.192			
Complete response to therapy	0.53	0.16-1.72	0.297			
Cirrhosis	19.44	5.04-74.92	<0.001	17.46	4.22-72.13	<0.001
Immunosuppression maintenance	0.82	0.28-2.36	0.718			
Acute liver injury	1.67	0.57-4.86	0.346			

Table-5.Characteristics of AIH patients with features of disease relapse during COVID-19

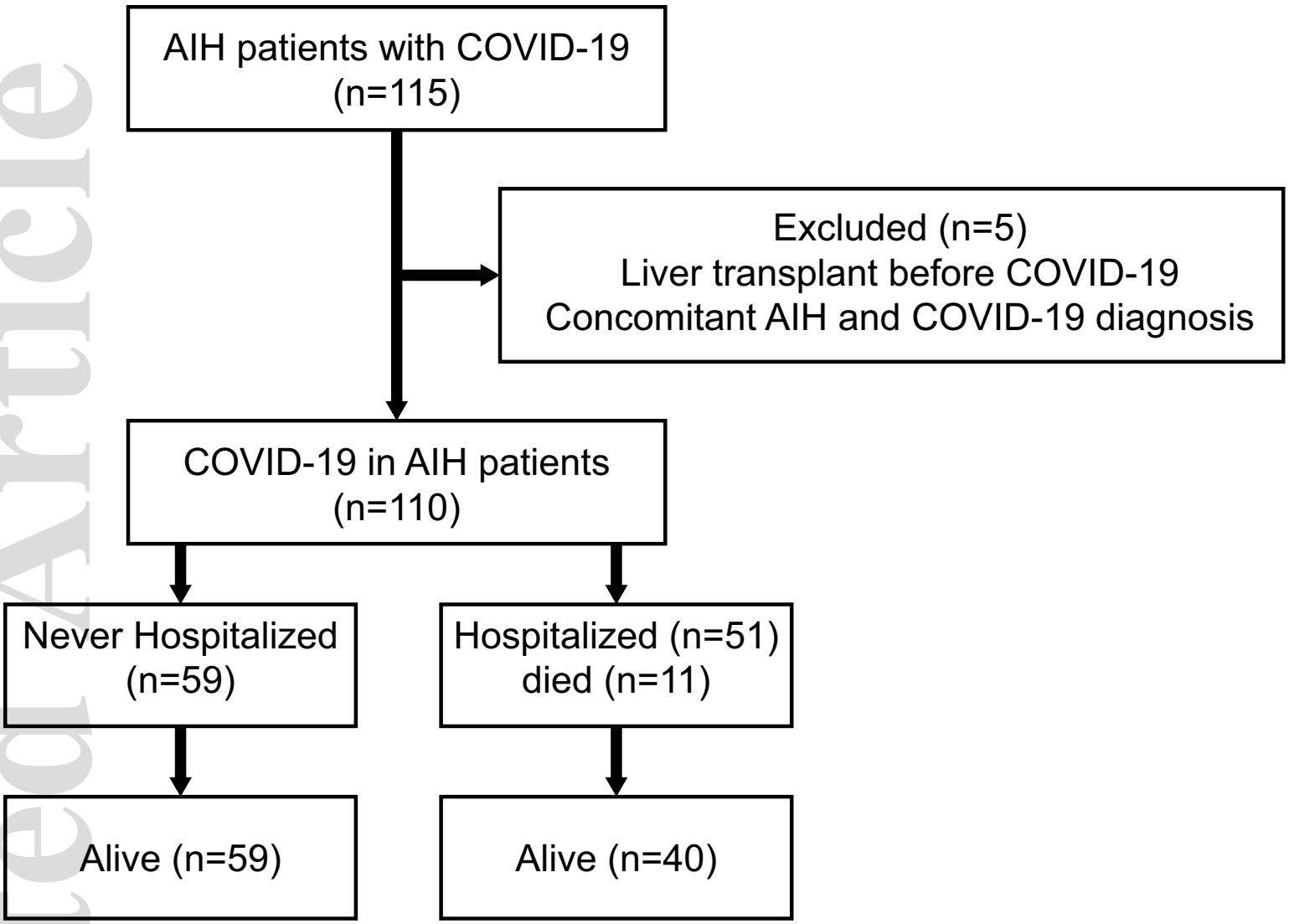
Case	Sex	Age at COVID-19	Diagnosis	Response at last visit	Therapy during COVID-19	Care for COVID-19	ALT/IgG (xUNL)	Management/ response
1	F	60	AIH	Complete	Azathioprine, 50 mg/day, Prednisolone, 5 mg/day	Home	6.9/1.1	Azathioprine and prednisolone increased /Yes
2	F	52	AIH	Complete	MMF, 1000 mg/day, Prednisolone, 10 mg/day	Hospital,5 day, no O_2 therapy	6.8/1.7	MMF switched to tacrolimus /Yes
3	F	44	AIH	Complete	In remission without therapy	Home	4.3/1.2	Azathioprine and prednisolone added /Yes
4	F	51	AIH/PBC	Complete	Prednisolone, 5 mg/day, UDCA, 750mg/day	Hospital, 6 days, nasal O_2	4.8/1.2	Prednisolone increased /Yes

IgG; Immunoglobulin G, MMF; Mycophenolate mofetil, UDCA;Ursodeoxycholic acid, UNL;xupper normal limit.

Figure legends:

Figure 1: Study flow chart for patient inclusion.

Figure 2: Clinical outcomes of COVID-19 in patients with AIH compared to non-AIH chronic liver disease. All-cause mortality (10% vs 11.5%), severe COVID-19 (15.5% vs 20.2%), need for supplemental oxygen (38.2% vs 42.2%) and hospitalization (46.4% vs 50%). P=ns for all comparisions.



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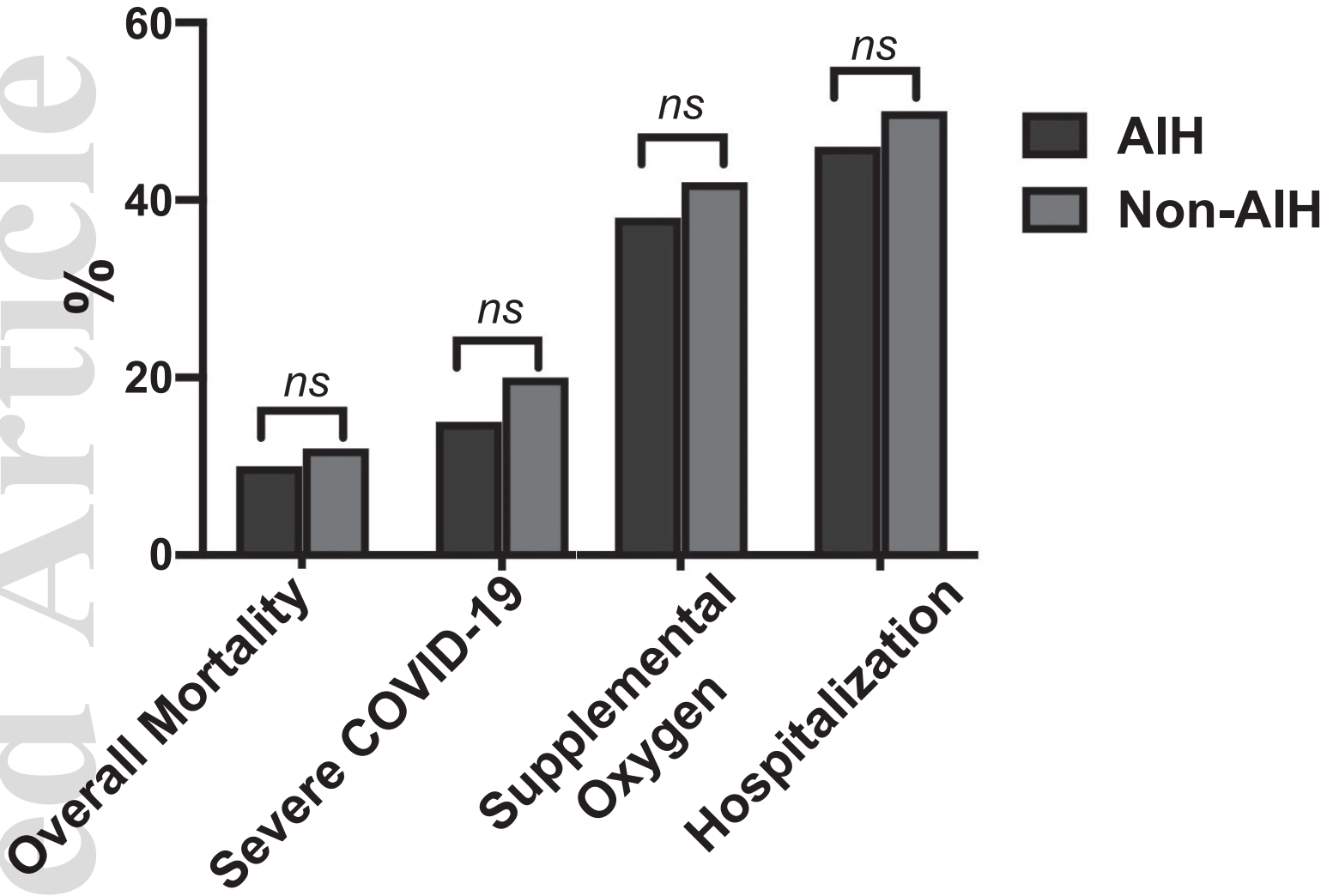

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