Received: 21 December 2020 | Revised: 14 March 2021 | Accepted: 31 March 2021

DOI: 10.1111/liv.14900

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Autoimmune hepatitis in patients aged 70 years or older: Disease characteristics, treatment response and outcome

George N. Dalekos[1,2] | Kalliopi Azariadis[1] | Vasiliki Lygoura[1] | Pinelopi Arvaniti[1] | Stella Gampeta[1] | Nikolaos K. Gatselis[1,2]

[1]Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece

[2]Institute of Internal Medicine and Hepatology, Larissa, Greece

Correspondence
George N. Dalekos, Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa 41110, Greece.
Email: georgedalekos@gmail.com

Funding information
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Handling Editor: Ana Lleo

Abstract

Background & Aims: Autoimmune hepatitis (AIH) affects both sexes and all age groups. However, very few studies have focused specifically on the characteristics and outcome of AIH in patients aged 70 y or older.

Methods: 25/234 patients with well-established AIH and disease onset at ≥70-y (median: 73-y) were analysed and compared to the rest patients (median: 47 y). Treatment response was assessed in all patients from both groups who were eligible for treatment (n = 202).

Results: Disease presentation was mainly insidious in both groups (19/25, 76% vs. 134/209, 64.1%; $P = .313$). At diagnosis, older patients had lower alaninoaminotrasferase (101[433] vs. 199[441] IU/L, $P < .05$) but were more frequently cirrhotic (12/25, 48% vs. 57/209, 27.3%; $P = .03$). Importantly, similar rates of on-treatment response (16/18, 89% vs. 154/184, 84%; $P = .565$), corticosteroid withdrawal (10/16, 62.5% vs. 113/154, 73.4%; $P = .355$) and complete withdrawal of immunosuppression (1/16, 6.3% vs. 40/154, 26%; $P = .122$) were achieved in both groups. Treatment-related adverse events were evenly observed between groups (6/18, 33% vs. 54/184, 29%; $P = .724$). In treated patients, the age ≥70 y was only associated with the overall mortality (HR 8.3 [95% CI: 2.1-36.4], $P = .003$), but not with the liver-related mortality (HR 3.4 [95% CI: 0.4-30.0], $P = .268$).

Conclusion: AIH should be seriously considered in patients ≥70 y with unexplained impaired liver function tests as the disease is not infrequent in this group and seems to bear an increased risk for advanced disease stage at diagnosis. However, if immunosuppression is started promptly, it seems as safe and effective as in younger patients.

KEYWORDS

aged, autoimmune hepatitis, immunosuppression, older age

Abbreviations: AIH, Autoimmune hepatitis; ALT, alanine aminotransferase; anti-LC1, anti-liver cytosol type-1; anti-LKM1, anti-liver/kidney microsome type-1; anti-SLA/LP, anti-soluble liver antigen/liver pancreas; AZA, azathioprine; CR, complete response; EASL, European Association for the Study of the Liver; HASL, Hellenic Association for the Study of the Liver; HLA, human leucocyte antigens; IQR, interquartile range; MMF, mycophenolate mofetil; ULN, upper limit of normal.

Key Points

- AIH should be considered in patients aged ≥70 y with unexplained impaired liver tests.
- These patients have an increased risk for advanced disease stage at diagnosis.
- Immunosuppression should not be withheld as it seems as effective and safe as in younger patients.

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a progressive chronic liver disease of unknown etiology and female predominance.[1-5] Its manifestations range from asymptomatic to severe advanced disease that can rarely lead to fulminant hepatic failure. If left untreated, AIH usually exhibits a progressive course with poor prognosis.[3-9]

Since 1990s, it was documented that the disease has a bimodal distribution with one peak during childhood and adolescence and another between the fourth and sixth decade.[3-5] Today, it is well known that irrespective of ethnicity, AIH can affect both sexes and all ages with increasing prevalence in the aged.[10-16] Although the first reports of AIH diagnosed in patients ≥60-65 y, date more than two decades, relevant literature includes limited number of studies with a small series of patients, thus perpetuating the obscurity around AIH in this specific group of patients. The European Association for the Study of the Liver (EASL) and the Hellenic Association for the Study of the Liver (HASL) Clinical Practice Guidelines[3,4] categorize patients over 60-65 y as a special and difficult-to-manage patient population pointing out that the benefits of immunosuppression are not well established in terms of clinical endpoints because of the usually concurrent severe comorbidities.

The aim of the present study was to shed light on the profile of AIH patients with advanced age (≥70 y) through a retrospective analysis of prospectively collected data extracted from a large series of AIH patients diagnosed and followed in our centre. Actually, we analysed the baseline, clinical, laboratory and histological characteristics as well as response to treatment, treatment-related adverse events and outcome as solid data in AIH patients ≥70 y is scarce.

2 | MATERIALS AND METHODS

2.1 | Study population

Two-hundred and thirty-four Caucasian patients (median [interquartile range, IQR] age: 58 [25] y; total follow-up 47.5 [81.3] mo) with well-established AIH[3-6] were included in the analysis. Patients were categorized in two groups according to age at onset using the 70 y as dichotomous value. Age onset was defined as the time of appearance of first symptoms or the first known abnormal transaminase test. Accordingly, 25/234 (10.7%) patients were ≥70 y at disease onset (median age: 73 [4] y).

Clinical presentation was defined as insidious when symptoms were vague and non-specific (eg, fatigue, arthralgia, malaise and anorexia) or when abnormal liver biochemistry was part of random check-up. Acute presentation refers to episode of acute icteric hepatitis [transaminases ≥10× upper limit of normal [ULN] plus clinically evident jaundice). The acute severe presentation was defined according to our previous publications as an acute symptomatic presentation of well-established newly diagnosed acute hepatitis without any sign of hepatic encephalopathy (time between symptoms and acute hepatitis presentation <24 wk) with international normalized ratio ≥1.5, elevated transaminases >10× ULN and total bilirubin ≥4 mg/dl, at any time during the acute course of the disease without lesions of chronic disease at the histological level.[7,8]

Patients eligible for treatment (n = 202; 18/25 patients with ≥70 y and 184/209 with <70 y) received prednisolone 0.5-1 mg/kg/d in combination mainly with mycophenolate mofetil (MMF 1.5-2 g/d; n = 157), according to the HASL guidelines and our published protocols[4,7,17-21] or azathioprine (AZA 1-2 mg/kg/d; n = 29). In brief, MMF was administered at 1 g/d, and after 3 wk, the dose was gradually increased to 1.5-2 g/d, which was maintained for at least 2 y after complete response (CR).[4,7,17-21] Prednisolone was started concurrently with MMF, followed by a gradual tapering (5 mg/wk up to 15 mg and then 2.5 mg/wk according to the biochemical and clinical response until withdrawal). After corticosteroid cessation and if the patient remained in CR for at least 6 mo, MMF was gradually reduced to 1-1.5 g/d in an attempt to achieve maintenance of remission at a minimal effective immunosuppression while minimizing the likelihood of its long-term side effects.[4,7,17-21] In case of no achievement of corticosteroids withdrawal, the maintenance dose of prednisolone was 5-7.5 mg/d. In a small subgroup of patients (n = 16), prednisolone at the same dose (0.5-1 mg/kg/d) was administered as monotherapy because of a recent (<5 y) or current history of malignancy (n = 3), mild disease (n = 7) or denial of the patients to receive combination treatment with AZA or MMF (n = 6). Additionally, 32 patients did not receive any treatment because they presented with burn-out decompensated or compensated cirrhosis with minimal or no necroinflammatory activity.

Follow-up was performed by periodic evaluation every 3-6 mo. Treatment endpoints were defined according to the EASL and HASL guidelines as well as our previous reports.[3,4,7,17,18] Treatment response was considered as CR when transaminases and IgG have normalized, symptoms improved or disappeared and liver histology, if performed, showed minimal or no inflammation. Partial response was defined as partial decrease of transaminases <2× ULN without achieving complete normalization and inability to withdraw or taper prednisolone. No response was defined as

persistently elevated transaminases ≥2-3× ULN and/or increased IgG despite intensive immunosuppression and confirmation of adherence to therapy. Relapse was defined as rise of transaminases ≥3× ULN and/or increase in IgG ≥2 000 mg/dl accompanied or not by reappearance of symptoms at any time during therapy following an initial CR. Treatment was withdrawn in accordance with EASL, HASL and our previous publications,[3,4,7,17,18] when immunosuppression had been administered for at least 4 y and for at least 2 y following CR.

The ethical committee of the Larisa University Hospital approved the study which conforms to the guidelines of the 1975 Helsinki's Declaration as reflected in a priori approval by the institution's human research committee. All patients agreed to the use of their data after anonymous retrospective analysis by written consent at the time of initial evaluation.

2.2 | Autoantibody testing

Antinuclear antibodies, smooth muscle antibodies, anti-liver/kidney microsome type-1 (anti-LKM1) and anti-liver cytosol type-1 (anti-LC1) were initially detected by indirect immunofluorescence as we have described.[1,2,7,17-22] Anti-LKM1, anti-LC1 and anti-soluble liver antigen/liver pancreas (anti-SLA/LP) were also evaluated by Western immunoblotting using rat liver microsomal or cytosolic extracts.[1,2,19,20] Commercially available ELISA (INOVA, Diagnostics Inc San Diego, CA, USA) using recombinant SLA/LP/tRNP(Ser)Sec was also used for anti-SLA/LP determination according to the manufacturer's instructions.

2.3 | Determination of human leucocyte antigens

At the time of interview, 110 patients (47%) consented for human leucocyte antigens (HLA) haplotype determination by polymerase chain reaction-sequence-specific oligonucleotides.

2.4 | Liver histology

Liver biopsy was performed in 197 patients. In the rest patients, liver histology was not performed either because an acute-severe presentation with significant coagulation impairment or because patients refused the procedure. However, all these 37 patients fulfilled the rest criteria for a definite AIH diagnosis like positive liver autoimmune serology, increased IgG, exclusion of viral and other liver disorders and favorable response to immunosuppression. All biopsies were assessed by one experienced liver immunopathologist who was unaware of the clinical diagnosis of patients, using the Knodell histologic/activity index score.[23] According to our previous publications,[17-22] patients were divided into two groups according to inflammation: minimal-mild (score: 0-8) and moderate-severe (score: 9-18) and according to fibrosis: minimal/mild-moderate (score: 0-2) and severe fibrosis-cirrhosis (score: 3-4). For patients without available biopsy, diagnosis of cirrhosis was based on ultrasonography (coarse echo pattern of the liver parenchyma along with irregular hepatic margins, spleen >12cm, portal vein >16mm), and/or endoscopic findings of portal hypertension, and/or clinical findings of decompensation as we have reported recently.[24]

2.5 | Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of variables. Normally distributed values are expressed as mean ±standard deviation, while non-normally distributed as median (IQR). Data were analyzed by Pearson chi-square, Fisher's exact test and Mann-Whitney *U* test where applicable. To assess the association between age groups and mortality, Cox-proportional hazard analyses were used. Two-sided p values $< .05$ were considered significant.

3 | RESULTS

3.1 | Baseline characteristics

The parameters and histological findings at initial evaluation are shown in Table 1. No differences were found regarding presence and type of symptoms. Similar to the younger age group, insidious was the most prevalent mode of presentation in the aged population. The most commonly reported symptoms in older were mainly constitutional, like fatigue (20%), abdominal pain (12%) and polyarthralgias (12%), while 32% were completely asymptomatic. Jaundice at initial presentation was observed in 20% of older patients. However, alanine aminotransferase (ALT) was significantly lower ($P < .05$) in this group compared to the younger age group (Table 1).

As it was expected, older patients suffered more frequently from diabetes ($P < .05$) and cardiovascular diseases ($P = .001$) compared to the younger population (Table 1). No additional significant differences were found regarding comorbidities between the two groups (Table 1). Comorbidities did not influence the choice of treatment, except for patients with a previous or current history of neoplasia (n = 10). Actually, these patients received more often prednisolone monotherapy (3/10; 30%) compared to those without a cancer history (13/192; 6.8%; $P < .05$), even though malignancies were equally distributed in the two age-groups ($P = .220$; Table 1).

The frequency of autoantibodies was almost identical between the two groups (Table 1). HLA genotyping showed no differences concerning HLA-DR3 and DR4 presence. Overall, no differences were noted regarding the levels of γ-globulins, IgG, the simplified score and the co-incidence of other autoimmune diseases (Table 1). In contrast, older patients had significantly

TABLE 1 Baseline demographic, clinical, laboratory and histological characteristics of AIH patients according to age at disease onset (n = 234)

	≥70 y-old (n = 25)	<70 y old (n = 209)	*P* value
Age at disease onset (y)	73 (4)	47 (25)	<0.001
Female	18 (72%)	149 (71.3%)	NS
Time to diagnosis (mo)	8 (19.5)	12 (52.5)	NS
Comorbidities			
- Osteoporosis	2 (8%)	12 (5.7%)	NS
- Cardiovascular diseases	18 (72%)	64 (30.6%)	0.001
- Diabetes	8 (32%)	29 (13.9%)	<0.05
- COPD	0 (0%)	8 (3.8%)	NS
- Malignancy	2 (8%)	8 (3.8%)	NS
- IBD	0 (0%)	5 (2.4%)	NS
- Multiple sclerosis	2 (8%)	11 (5.3%)	NS
- Psychiatric disorders	0 (0%)	4 (1.9%)	NS
Disease duration till last follow-up (mo)	42 (55)	86 (130)	0.001
Follow up (mo)	33 (45)	49 (89.5)	NS
Type of presentation			
Insidious	19 (76%)	134 (64.1%)	NS
Acute	4 (16%)	32 (15.3%)	NS
Acute severe	2 (8%)	43 (20.6%)	NS
Presence of symptoms	17 (68%)	129 (61.7%)	NS
Concomitant other autoimmune disease	12 (48%)	81 (38.8%)	NS
AIH simplified score	6 (1.5)	6 (2)	NS
AST (IU/L, ULN: 35)	79 (321)	132 (366)	NS
ALT (IU/L, ULN: 40)	101 (433)	199 (441)	<0.05
γ-GT (IU/L, ULN: 37)	70 (134)	92 (150)	NS
ALP (IU/L, ULN: 120)	121 (106)	111 (93)	NS
Bilirubin (mg/dl, ULN: 1.1)	1.2 (2.1)	1.2 (3.7)	NS
Albumin (g/dl, normal range: 3.5-5.2)	3.8 (1.1)	4 (1)	NS
γ-globulin (g/dl, ULN: 3.5)	3.9 (1.1)	3.7 (1.1)	NS
IgG (mg/dl, ULN: 1400)	1810 (1015)	1780 (827)	NS
INR	1.2 (0.3)	1.1 (0.3)	NS
Platelets ($\times 10^3/mm^3$, normal range: 140-400)	172 (84.5)	200 (98)	NS
Positive antinuclear antibodies	18 (72%)	137 (66.5%)	NS
Positive smooth muscle antibodies	24 (96%)	199 (97.5%)	NS
anti-LKM positivity	0 (%)	16 (8.2%)	NS
anti-SLA/LP positivity	1 (4%)	24 (11.9%)	NS
HLA-typing	n = 7	n = 105	
HLADR3	2 (28.6%)	35 (33.3%)	NS
HLADR4	1 (14.3%)	17 (16.2%)	NS
Histology	n = 11	n = 186	
Grade Moderate or Severe	5 (45.5%)	114 (61.3%)	NS
Severe Fibrosis or Cirrhosis	7 (63.6%)	57 (30.6%)	<0.05
Presence of cirrhosis	12 (48%)	57 (27.3%)	0.03
Decompensation of cirrhosis[a]	2 (16.7%)	9 (15.8%)	NS
Not eligible for treatment	7 (28%)	25 (12%)	NS

Note: Abbreviations are same as in the text.

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; INR, international normalized ratio; n, number of patients in each respective group; NS, not significant; γ-GT, gamma-glutamyl transpeptidase.

[a]A history of variceal bleeding, ascites or hepatic encephalopathy among cirrhotic patients.

more frequently severe fibrosis or cirrhosis at the time of diagnosis compared to younger patients ($P = .03$) albeit no difference on disease activity (Table 1).

3.2 | Treatment and response

Age did not influence the drug choice and dosage, with most patients receiving prednisolone and MMF in both groups (Table 2). No differences were found between the older and younger group concerning the total duration of corticosteroids and overall treatment duration.

On-treatment CR was achieved in 16/18 (88.9%) patients with ≥70 y (154/184; 83.7% in <70 y group; $P = .565$). The rapidity of initial CR was 2 (5) months in older and 2 (3) months in the younger group ($P = .983$). Corticosteroid withdrawal was achieved in 10/16 (62.5%) older patients who achieved on-treatment CR and in 113/154 (73.4%) of the younger group ($P = .355$). At the time of this writing, complete cessation of immunosuppression according to the EASL and HASL guidelines[3,4] was possible in 1/16 (6.3%) of the older group with on-treatment CR and in 40/154 (26%) of the youngers ($P = .122$). Maintenance of response after treatment withdrawal did not differ between the two groups (Table 2).

TABLE 2 Treatment manipulation, response and outcome according to age at disease onset (n = 202)

	≥70 y old (n = 18)	<70 y old (n = 184)	*P* value
Treatment regimen			
Prednisolone +MMF	13 (72.2%)	144 (78.3%)	NS
Prednisolone +AZA	3 (16.7%)	26 (14.1%)	NS
Prednisolone only	2 (11.1%)	14 (7.6%)	NS
Treatment duration (mo)	23 (41)	50 (65)	NS
Total duration of prednisolone (mo)	12 (44)	19 (55)	NS
Complete response on treatment	16 (88.9%)	154 (83.7%)	NS
Time to achieve initial complete response (mo)	2 (5)	2 (3)	NS
Corticosteroids withdrawal in patients with on treatment response	10/16 (62.5%)	113/154 (73.4%)	NS
Relapse during treatment after corticosteroids withdrawal	4/10 (40%)	55/113 (48.7%)	NS
Complete treatment withdrawal	1/16 (6.3%)	40/154 (26%)	NS
Maintenance of response after complete treatment withdrawal	1 (100%)	34/40 (85%)	NS

Note: Abbreviations are same as in the text.

Abbreviations: n, number of patients in each respective group; NS, not significant.

3.3 | Adverse events

The rate of at least one treatment-related adverse event was similar between the two groups with infections (27.8%) being the most common among aged (Table 3). Temporally modification of treatment regimen was not different between groups (11.1% in older vs. 6% in younger; $P = .326$). Treatment discontinuation was mandated in only three cirrhotic patients in the younger group (3/184, 1.6%; $P = 1.0$) due to one or more episodes of septicemia. Concerning treatment related adverse events in the whole group of treated patients (n = 202), only Cushing syndrome due to corticosteroids administration and development of neutropenia were associated with longer treatment duration (134 [104] months vs. 45 [60] months; $P = .003$ and 134 [123] months vs. 45 [60] months; $P < .02$, respectively). However, none of these events occurred in the older patients group (Table 3), while they were not associated with episodes of relapses, partial response or no response during treatment in both groups (data not shown).

3.4 | Outcome

Analysis of outcome was performed in the 202 treated AIH patients (51 cirrhotic and 151 non-cirrhotic at baseline). Two non-cirrhotic patients from the younger group progressed to cirrhosis (0/12 [0%] vs. 2/139 [1.4%]; $P = 1.000$). Development of at least one episode of decompenzation did not differ between the groups among cirrhotics at baseline or during follow-up (n = 53; Table 4). No difference was also found regarding the incidence of hepatocellular carcinoma. Overall mortality was 11/202 (5.4%), while liver-related mortality was 7/202 (3.5%). Overall mortality tended to be higher in the older patients ($P = .06$) although liver-related mortality was not different (Table 4).

TABLE 3 Treatment-related adverse events according to age at disease onset (n = 202)

	≥70 y old (n = 18)	<70 y old (n = 184)	*P* value
At least one adverse event	6 (33.3%)	54 (29.3%)	NS
Infection	5 (27.8%)	34 (18.5%)	NS
Myopathy	1 (5.6%)	3 (1.6%)	NS
Osteoporosis	1 (5.6%)	4 (2.2%)	NS
Abdominal pain	1 (5.6%)	6 (3.3%)	NS
Cushing	0 (0%)	7 (3.8%)	NS
Diabetes	0 (0%)	7 (3.8%)	NS
Acne	0 (0%)	3 (1.6%)	NS
Glaucoma	0 (0%)	2 (1.1%)	NS
Neutropenia	0 (0%)	7 (3.8%)	NS
Diarrhea	0 (0%)	1 (0.5%)	NS
Skin cancer	0 (0%)	1 (0.5%)	NS

Abbreviations: n, number of patients in each respective group; NS, not significant.

In treated patients, the Cox-regression analysis showed a significant high overall mortality in the ≥70 y group (HR 8.3 [95% CI: 2.1-36.4]; $P = .003$; Figure 1A) while liver-related mortality did not differ (HR 3.4 [95% CI: 0.4-30], $P = .268$; Figure 1B).

4 | DISCUSSION

This study specifically describes a series of consecutive AIH patients aged 70 y or older and compares disease characteristics, treatment efficacy, safety and outcome with younger patients followed in our tertiary referral center, as data focused especially on this age-group are missing. To the best of our knowledge, this is the first report where patients older than 70 y were treated with prednisolone and MMF as front-line therapy. Three main findings arose from our study: (a) AIH can affect not infrequently patients ≥70 y, as 1 out of 10 in our large series of AIH patients was diagnosed after the age of 70 y. (b) There was no influence of age on disease progression and liver-related survival, and most importantly, (c) immunosuppressive treatment according to the guidelines should not be withheld, as it was proved as effective and safe as in younger patients even though this specific group bears an increased risk for advanced disease stage at diagnosis.

As AIH may occur in any age, it has become clear that the affected older patients are now on the rise.[16,25,26] This increase may reflect the general aging of the population and be related to increasing medical awareness of this entity not only among specialists but also among general practitioners. Another explanation might be the immunosenescence of the geriatric population leading to autoimmunity and emergence of genuine novel AIH cases.[27] Therefore, physicians should keep in mind AIH in the differential diagnosis of unexplained impaired liver biochemistry in patients ≥70 y although because of polypharmacy, careful history of medications is also essential for detecting drug-induced liver injury.[28] The simplified criteria for AIH diagnosis aid in the diagnosis as they can easily be applied in everyday clinical practice, and this proved valid also in our older patients.[6]

An issue of major concern is the profile of AIH patients ≥70 y. We showed that 76% of aged had an insidious presentation and the symptoms were constitutional. This finding is of particular importance as fatigue and polyarthralgias without arthritis in an older patient, possibly with more than one comorbidity, will not necessarily prompt a primary care physician to order liver biochemistry tests. Indeed, previous studies have shown that characteristics of AIH in aged population are different compared to younger patients, with older been less symptomatic at presentation.[12,13,29,30]

Despite the insidious presentation of the disease, our older patients had significantly higher frequency of cirrhosis at diagnosis. Our results are in accordance with a meta-analysis which showed that the aged are more likely to be cirrhotic and asymptomatic at presentation.[28] This could be attributed to a more aggressive disease which progresses to cirrhosis rapidly or a subclinical course that escapes recognition in earlier stages.[10,29,31] In contrast, younger patients were characterized by significantly higher ALT at presentation. Therefore, physicians should carry a high degree of suspicion when encountering aged patients with non-specific symptoms and abnormal liver function tests. HLA haplotype did not confirm HLA-DR4 predominance in older Greek patients, a finding that was supported by previous studies,[12,32] indicating variances in genetic background of patients from different geographical areas.

Another relevant question is the issue of treatment, with controversy regarding benefits in this group of patients.[10,11,15,29,31] Treating aged with high doses or lengthy intervals of immunosuppression remains a matter of concern for many physicians which is not sufficiently addressed so far, as patients aged ≥70 y are often excluded from trials.[15,29] From a clinical point of view, most hepatologists, internists and general practitioners will be reluctant to administer corticosteroids to older patients, especially when comorbidities

TABLE 4 Outcome of autoimmune hepatitis in treated patients (n = 202)

	≥70 y old	<70 y old	*P* value
Development of cirrhosis during follow-up, yes/no (n = 151)	0/12	2/137	NS
Decompensation during follow-up, yes/no (n = 53)	2/4	15/32	NS
Development of HCC, yes/no (n = 202)	0/18	5/179	NS
Death of any cause, yes/no (n = 202)	3/15	8/176	0.062
Liver-related death, yes/no (n = 202)	1/17	6/178	NS

Abbreviations: HCC, hepatocellular carcinoma; n, number of patients in each respective group; NS, not significant.

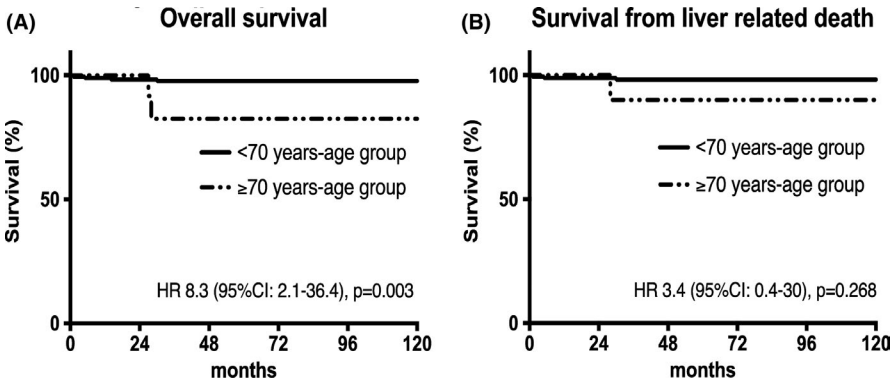

FIGURE 1 Overall survival and survival free from liver related death analysis in AIH-treated patients (n = 202) according to age group. The age ≥70 y was related only with the overall survival (HR 8.3 [95% CI: 2.1-36.4], $P = .003$], while survival free from liver related death was similar between the two age groups (HR 3.4 [95% CI: 0.4-30.0], $P = .268$)

such as osteopenia or diabetes and polypharmacy may be present. However, the response rates as shown by our study suggest that even AIH patients ≥70 y can be candidates for immunosuppression. In this context, a recent meta-analysis showed that standard therapy was effective in inducing remission in the older, while treatment failure and relapses were less often compared to younger patients.[15] Our results further support the existing data, although it should be emphasized that this is the first report specifically designed in AIH patients ≥70 y who were treated with prednisolone and MMF as front-line therapy. Actually, in parallel with our previous findings,[7,17-21] the present study showed that at least in our hands, this kind of first-line treatment was equally effective in terms of achieving and maintaining CR in both patient-groups.

Bone density monitoring and intervention to prevent steroid-related bone disease should be implemented throughout the course of the disease in all patients but especially in ≥70 y and during the induction therapy.[1,3-5,11,28] It must be noted that all of our aged patients were treated with bisphosphonates, calcium intake and vitamin D supplements accordingly, in order to prevent development or worsening of existing osteopenia/osteoporosis. In addition, treatment with corticosteroids alone should not be preferred in older patients due to the high risk of corticosteroid-related complications. Despite the indisputable comorbidity that accompanies the mature age, our results were in parallel with other studies,[11,13,32] indicating that treatment-related adverse events did not increase with age and overall immunosuppression was equivalently safe between <70 and ≥70 y. It is also important to point out that the severity of encountered adverse events was not life-threatening and seldom led to permanent drug discontinuation or treatment modification in both age groups.

In conclusion, clinicians should consider AIH in the differential diagnosis of patients ≥70 y presenting with constitutional symptoms and unexplained impaired liver biochemistry. Though AIH patients ≥70 y may frequently present with advanced hepatic fibrosis and/or cirrhosis, their natural history, treatment efficacy and safety seem similar with the younger patients. Taking into consideration our findings and also that AIH bears a poor prognosis if left untreated, there is no evidence to support treatment deferment or deviation in patients ≥70 y and, therefore, appropriate immunosuppression therapy should be started promptly.

CONFLICT OF INTEREST

The authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

George N. Dalekos https://orcid.org/0000-0001-7075-8464

REFERENCES

1. Zachou K, Muratori P, Koukoulis GK, et al. Review article: autoimmune hepatitis – current management and challenges. *Aliment Pharmacol Ther*. 2013;38:887-913.
2. Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: etiopathogenetic, clinico-laboratory and histological characteristics. *World J Gastroenterol*. 2015;21:60-83.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol*. 2015;63:971-1004.
4. Dalekos GN, Koskinas J, Papatheodoridis GV. Hellenic association for the study of the liver clinical practice guidelines: autoimmune hepatitis. *Ann Gastroenterol*. 2019;32:1-23.
5. Mack CL, Adams D, Assis DN, 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;72:671-722.
6. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169-176.
7. Zachou K, Arvaniti P, Azariadis K, et al. Prompt initiation of high-dose i.v. corticosteroids seems to prevent progression to liver failure in patients with original acute severe autoimmune hepatitis. *Hepatol Res*. 2019;49:96-104.
8. Dalekos GN, Gatselis NK, Zachou K. Acute severe autoimmune hepatitis: corticosteroids or liver transplantation? *Liver Transpl*. 2019;25:1588-1589.
9. Trivedi PJ, Hubscher SG, Heneghan M, Gleeson D, Hirschfield GM. Grand round: autoimmune hepatitis. *J Hepatol*. 2019;70:773-784.
10. Newton JL, Burt AD, Park JB, Mathew J, Bassendine MF, James OF. Autoimmune hepatitis in older patients. *Age Ageing*. 1997;26:441-444.
11. Schramm C, Kanzler S, Meyer zum Büschenfelde K-H, Galle PR, Lohse AW. Autoimmune hepatitis in the elderly. *Am J Gastroenterol*. 2001;96:1587-1591.
12. Granito A, Muratori L, Pappas G, et al. Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. *Aliment Pharmacol Ther*. 2005;21:1273-1277.
13. Al-Chalabi T, Boccato S, Portmann BC, McFarlane IG, Heneghan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. *J Hepatol*. 2006;45:575-583.
14. Verslype C, George C, Buchel E, Nevens F, van Steenbergen W, Fevery J. Diagnosis and treatment of autoimmune hepatitis at age 65 and older. *Aliment Pharmacol Ther*. 2005;21:695-699.
15. Durazzo M, Lupi G, Scandella M, Ferro A, Gruden G. Autoimmune hepatitis treatment in the elderly: a systematic review. *World J Gastroenterol*. 2019;25:2809-2818.
16. Ngu JH, Bechly K, Chapman BA, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? *J Gastroenterol Hepatol*. 2010;25:1681-1686.
17. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naive patients. *J Hepatol*. 2011;55:636-646.
18. Zachou K, Gatselis NK, Arvaniti P, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. *Aliment Pharmacol Ther*. 2016;43:1035-1047.
19. Zachou K, Gampeta S, Gatselis NK, et al. Anti-SLA/LP alone or in combination with anti-Ro52 and fine specificity of anti-Ro52 antibodies in patients with autoimmune hepatitis. *Liver Int*. 2015;35:660-672.
20. Zachou K, Weiler-Normann C, Muratori L, Muratori P, Lohse AW, Dalekos GN. Permanent immunosuppression in SLA/LP-positive autoimmune hepatitis is required although overall response and survival are similar. *Liver Int*. 2020;40:368-376.

21. Rigopoulou EI, Gatselis N, Arvaniti P, Koukoulis GK, Dalekos GN. Alcoholic liver disease and autoimmune hepatitis: sometimes a closer look under the surface is needed. *Eur J Intern Med*. 2021;85:86-91.
22. Gatselis NK, Vakrakou AG, Zachou K, et al. Decreased serum DNase1-activity in patients with autoimmune liver diseases. *Autoimmunity*. 2017;50:125-132.
23. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1981;1:431-435.
24. Gatselis NK, Tornai T, Shums Z, et al. Golgi protein-73: A biomarker for assessing cirrhosis and prognosis of liver disease patients. *World J Gastroenterol*. 2020;26:5130-5135.
25. Lv T, Li M, Zeng NA, et al. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. *J Gastroenterol Hepatol*. 2019;34:1676-1684.
26. Morii K, Nagano Y, Yamamoto T, Nakamura S, Okushin H. Increasing incidence of elderly-onset autoimmune hepatitis. *Geriatr Gerontol Int*. 2017;17:1722-1728.
27. Ongradi J, Kovesdi V. Factors that may impact on immunosenescence: an appraisal. *Immun Ageing*. 2010;7:7.
28. Rizvi S, Gawrieh S. Autoimmune hepatitis in the elderly: diagnosis and pharmacologic management. *Drugs Aging*. 2018;35:589-602.
29. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. *Aliment Pharmacol Ther*. 2014;39:117-124.
30. Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. *Drugs Aging*. 2008;25:219-239.
31. Sonthalia N, Jain S, Thanage R, et al. Clinical, serological, histopathological and treatment profile of autoimmune hepatitis in the elderly. *Clin Exp Hepatol*. 2020;6:13-19.
32. Baven-Pronk MAMC, Biewenga M, van Silfhout JJ, et al. Role of age in presentation, response to therapy and outcome of autoimmune hepatitis. *Clin Transl Gastroenterol*. 2018;9:165.

How to cite this article: Dalekos GN, Azariadis K, Lygoura V, Arvaniti P, Gampeta S, Gatselis NK. Autoimmune hepatitis in patients aged 70 years or older: Disease characteristics, treatment response and outcome. *Liver Int*. 2021;41:1592–1599. https://doi.org/10.1111/liv.14900