Internal and Emergency Medicine
https://doi.org/10.1007/s11739-024-03702-8

CE - LETTER TO THE EDITOR

The evolving landscape of autoimmune hepatitis: an ambispective cohort study

Cristina Rigamonti[1,2] · **Irene Giacone**[1,2] · **Giulia Francesca Manfredi**[1,2] · **Micol Giulia Cittone**[1,2] · **Mario Pirisi**[1,2]

Received: 17 February 2024 / Accepted: 30 June 2024

Abbreviations

AIH	Autoimmune hepatitis
ANA	Anti-nuclear antibodies
AO	Acute onset
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
AST	Aspartate aminotransferase
AZA	Azathioprine
BMI	Body mass index
CBR	Complete biochemical response
CI	Confidence interval
FU	Follow-up
IAIHG	International autoimmune hepatitis group
IgG	Immunoglobulin G
INR	International normalized ratio
IQR	Interquartile range
IST	Immunosuppressive therapy
kPa	Kilopascal
LKM1	Liver kidney microsome 1
LLN	Lower limit of normal
LSM	Liver stiffness measurement
LT	Liver transplantation
PBC	Primary biliary cholangitis
PC	Prospective cohort
PDN	Prednisone
RC	Retrospective cohort
SLA	Soluble liver antigen
SMA	Smooth muscle autoantibody
ULN	Upper limit of normal

✉ Cristina Rigamonti
cristina.rigamonti@uniupo.it

[1] Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy

[2] Division of Internal Medicine, AOU Maggiore Della Carità, Novara, Italy

Dear Editor,

Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease that has a wide spectrum of clinical presentation with insidious or acute onset (AO), potentially leading to cirrhosis and its complications [1, 2]. It affects people of all ages, gender, and ethnicities, with a female predominance estimated to be up to fivefold higher than that in males [1–3]. AIH incidence and prevalence landscape is progressively changing for both genders. A recent study highlighted an overall increase in the incidence rate and prevalence of AIH, confirming to be one of the highest ever reported in literature [4]. A potential change in clinical scenario of AIH in terms of increased proportion of patients with AO at diagnosis has also been described. A multicenter study reported an AO prevalence slightly under 50% [5].

The aim of our study was to investigate the clinical profile of a single-center cohort of patients diagnosed with AIH from 01/1995 to 03/2021, who were regularly followed up at the Liver Clinic of an academic hospital in Northwest Italy. The diagnosis of AIH, treatment, complete biochemical response (CBR) to therapy, and follow-up (FU) were established according to international guidelines [1, 2]. AO of disease was defined as presence of transaminase serum levels at diagnosis > 10 × upper limit of normal (ULN) and/or total bilirubin levels > 5 mg/dL. A retrospective collection of data including all patients who received AIH diagnosis from 01/1995 to 12/2017 (No. = 58), and a prospective data collection of all new AIH diagnoses from 01/2018 to 03/2021 (No. = 30) were performed. All clinical data at the time of diagnosis, then at 3–6–12–24 months after diagnosis, and at the last FU were collected. Since available, all patients underwent liver stiffness measurement (LSM) by vibration-controlled transient elastography at diagnosis and every 12–24 months during the FU. Endpoints of the study were death, liver transplantation (LT), and complications (ascites, variceal bleeding, hepatic encephalopathy,

Published online: 09 July 2024

hepatocellular carcinoma). FU time was censored at the date of death for deceased patients, at the date of LT for transplanted ones, and at last FU for alive patients.

Statistical analysis was carried out using SPPS software (v. 25.0). Comparisons between groups have been made using the Mann–Whitney *U* test or Kruskal–Wallis for continuous variables and the Fisher exact test for dichotomous variables. Survival was assessed by Kaplan–Meier analysis and stratified using the Log rank test. The statistical significance level considered was < 0.05.

The main characteristics of the 88 enrolled patients are shown in Table 1, stratified by time of diagnosis.

The proportion of males and AO disease was higher in prospective cohort (PC) than retrospective cohort (RC): 37% versus 17% ($p = 0.06$) and 77% versus 55% ($p = 0.06$), respectively. A significantly higher proportion of AO AIH

Table 1 Clinical features of patients at the diagnosis of AIH, stratified by time of diagnosis (retrospective cohort: AIH diagnosis until 12/2017; prospective cohort: AIH diagnosis from 01/2018)

Features	All cases (1995–2021) No. = 88	Retrospective cohort No. = 58	Prospective cohort No. = 30	*p**
Female gender, No	67 (76%)	48 (83%)	19 (63%)	0.06
Age, years	57 (45 – 67)	59 (45 – 67)	56 (45 – 67)	0.68
Caucasian ethnicity, No	81 (92%)	54 (93%)	27 (90%)	0.68
BMI, kg/m^2	24.9 (22.9 – 27.0)	25.1 (22.8 – 28.1)	24.2 (22.9 – 26.1)	0.70
ANA, No	59 (67%)	38 (65%)	21 (70%)	0.81
SMA, No	26 (29%)	22 (38%)	4 (13%)	0.01
LKM1, No	5 (6%)	5 (9%)	0	0.16
SLA, No	3 (3%)	1 (2%)	2 (7%)	0.26
AMA, No	12 (14%)	12 (21%)	0	0.07
Acute onset, No	55 (62%)	32 (55%)	23 (77%)	0.06
Histological diagnosis, No	75 (85%)	49 (84%)	26 (87%)	1.00
Fibrosis stage > 2 by Ishak, No	38 (43%)	26 (45%)	12 (40%)	0.82
Cirrhosis, No	19 (22%)	12 (14%)	7 (23%)	0.79
LSM, kPa	12.2 (7.2 – 22.5)	12.0 (7.3 – 27)	12.5 (7.2 – 18.5)	0.64
Liver complications, No	9 (10%)	4 (7%)	5 (17%)	0.26
Ascites, No	8 (9%)	3 (5%)	5 (17%)	0.11
Variceal bleeding, No	0	0	0	
Hepatic encephalopathy, No	3 (3%)	1 (2%)	2 (7%)	1.0
Hepatocellular carcinoma, No	0	0	0	
Hepatorenal syndrome, No	1 (1%)	1 (2%)	0	1.0
IAIHG score 10–15, No	45 (51%)	28 (48%)	17 (57%)	0.50
IAIHG score > 15, No	32 (36%)	23 (40%)	9 (30%)	0.48
AST, x ULN	14.1 (3.8 – 22.4)	8.6 (2.1 – 20.0)	19.6 (8.0 – 32.3)	0.006
ALT, x ULN	14.0 (3.9 – 27.0)	6.9 (2.1 – 23.3)	20.9 (8.8 – 37.5)	< 0.0001
ALP, x ULN	1.0 (0.7 – 1.3)	1.0 (0.7 – 1.6)	0.9 (0.6 – 1.2)	0.27
Total bilirubin, x ULN	1.4 (0.8 – 6.6)	1.2 (0.8 – 4.1)	2.5 (0.8 – 15.5)	0.01
Albumin, x LLN	1.1 (1 – 1.2)	1.2 (1.0 – 1.2)	1.1 (1.0 – 1.2)	1.00
IgG, x ULN	1.2 (1.0 – 1.6)	1.2 (0.9 – 1.6)	1.2 (1.0 – 1.6)	0.48
INR	1.1 (1.0 – 1.3)	1.12 (1.03 – 1.30)	1.5 (1.04 – 1.62)	0.32
Platelets, $\times 10^9$/l	201 (153 – 252)	190 (156 – 252)	220 (181 – 256)	0.19
Other autoimmune disease, No	31 (35%)	21(37%)	10 (33%)	0.81
Sjogren's syndrome, No	5 (6%)	4 (7%)	1 (3%)	0.65
Autoimmune thyroid disease, No	12 (14%)	8 (14%)	4 (13%)	1.00
Connectivitis, No	2 (2%)	1 (2%)	1 (3%)	1.00
Rheumatoid arthritis, No	2 (2%)	1 (2%)	1 (3%)	1.00
Others, No	10 (11%)	7 (12%)	3 (10%)	1.00

Categorical variables are reported as percentages, continuous variables as medians, with interquartile ranges in brackets

*Comparison of variables between retrospective and perspective cohorts by Mann–Whitney *U* test for continuous variables and Fisher exact test for categorical variables

was observed among males in the PC versus RC (30% versus 10%, respectively; $p=0.01$). Proportion of AO progressively increased over time in males, but not in females (Fig. 1). AO was observed in 59% and in 69% of patients < 60 and ≥ 60 years, respectively ($p=0.49$), confirming a similar presentation independently from age at diagnosis [6].

Overall, 83 patients (94%) underwent immunosuppressive therapy (IST) within 6 months from the diagnosis: 27 patients (31%) were treated with prednisone (PDN), 3 (3%) with azathioprine (AZA), 53 (60%) with a combination therapy of PDN-AZA. In this group, seven patients developed side effects due to AZA; four patients underwent mycophenolate mofetil as second-line therapy plus PDN. LT has been indicated as first-line treatment within 2 weeks of diagnosis in one patient with acute liver failure at the onset. In five patients (6%), IST start was delayed over 6 months after diagnosis: in one patient due to breastfeeding, in two for initial refusal, in two with mild liver disease (grading inflammatory < 4). CBR was achieved in 77%, 81%, 74%, 76%, and 82% of patients at 6, 12, 24, 36 months

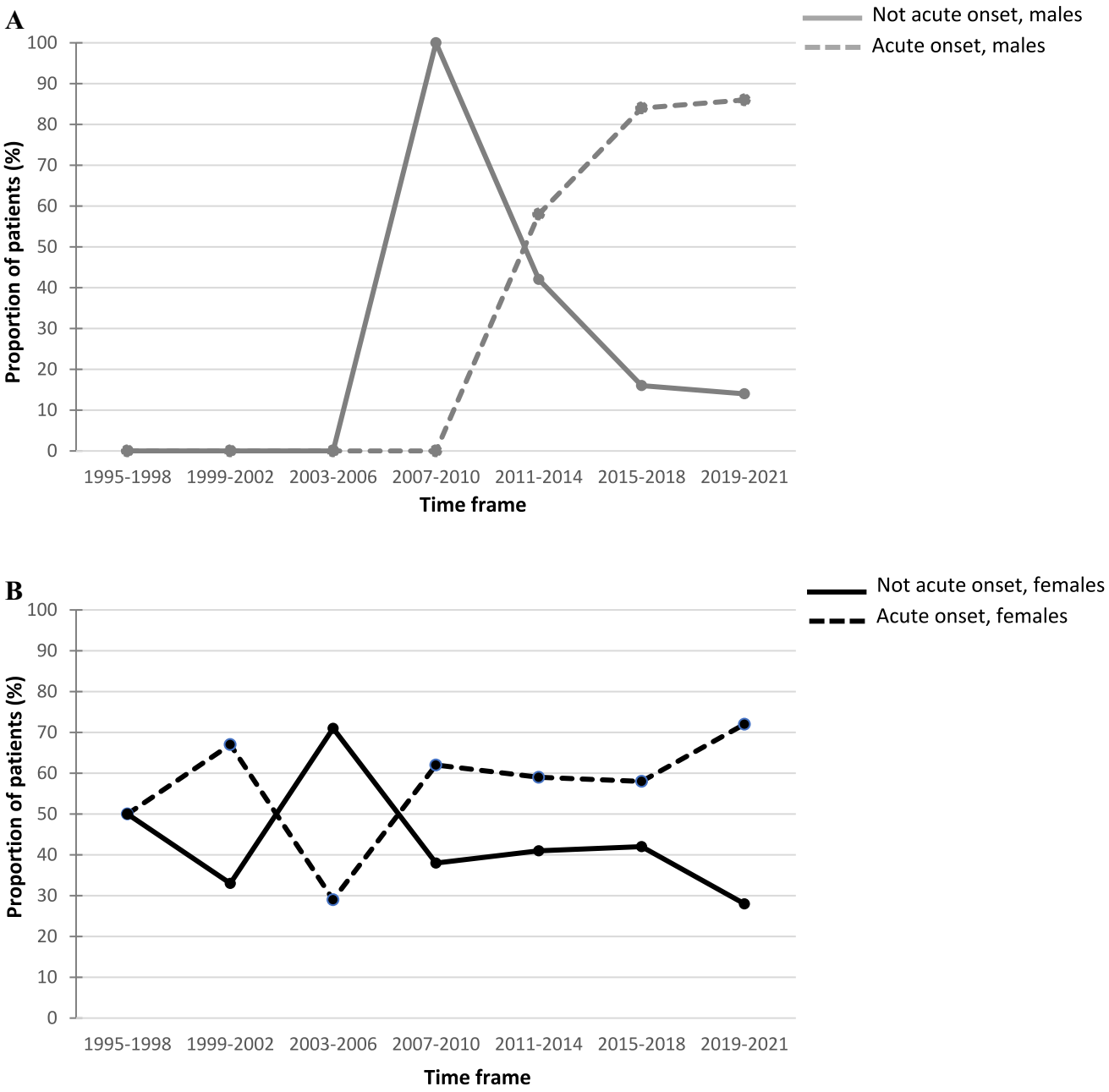

Fig. 1 Panel A: Proportion of acute and non-acute onset of AIH in 21 male patients, stratified by diagnosis time frames of three years each. Panel B: Proportion of acute and non-acute onset of AIH in 67 female patients, stratified by diagnosis time frames of 3 years each

after diagnosis, and at the last FU, with a similar proportion observed both in RC and PC.

In a median time of 66 months (IQR 29 – 103), 239 LSM were performed. A median reduction in LSM of – 45% (IQR – 66 to – 20%) was observed at the last FU compared to the diagnosis, with a median annual reduction of – 9% (IQR – 14–0). In patients with CBR, the median annual LSM reduction was slightly higher (median – 10%, IQR 19 to – 3%) than that in patients without CBR (median – 5%, IQR – 10 to + 1%, $p = 0.22$). The main reduction in LSM was observed during the first 12 months from the diagnosis (median – 41%, IQR -56 to – 20%).

During FU, two patients in the RC experienced progression of liver fibrosis on biopsy, both initially refusing IST at diagnosis. Three patients developed hepatic complications (one esophageal varices, one esophageal varices and ascites, one ascites). Two patients had been diagnosed simultaneously AIH and cancer (one breast carcinoma and one uterus adenocarcinoma). Nine patients developed tumors during IST (two basalioma, two breast cancer, two intraepithelial cervix tumors, one colon cancer, one endometrial adenocarcinoma, one melanoma). A patient with associated connective tissue disease developed pulmonary hypertension. Four patients died during FU: one patient for decompensated cirrhosis, one for breast cancer skeletal metastasis, one for metastatic endometrial carcinoma, and one for pulmonary hypertension complications. An AO patient underwent LT for acute liver failure within 2 weeks after diagnosis. Mean overall survival was 22 years (95% CI, 19 – 26). LT-free survival probability at 5, 10, and 15 years from diagnosis was, respectively, 97%, 91%, and 78%.

CBR proportion and LSM longitudinal variations were similar in patients with and without AO, although the formers had significantly higher LSM and transaminase levels at diagnosis. Mean survival was similar whatever disease onset: 16 years (95% CI, 15–17) in AO patients and 19 years (95% CI, 12–26) in non-AO patients ($p = 0.43$). Estimated LT-free survival probability at 5, 10, and 15 years from diagnosis was 95% in AO patients versus 100%, 87%, and 58% in non-AO patients.

While overall median age at diagnosis in our study was consistent with previous literature data [1, 2], overall proportion of AO AIH was greater than ones former reported [1, 2, 5]; the net increase was observed in the PC (23 out of 30 patients). In a previous multicentric Italian study, AO frequency was 43% [5]. These data support the hypothesis that an increased abruption of AO is to be seen in recent years, especially in males. In our series, proportion of AO among males was significantly higher in PC versus RC ($p = 0.01$), whereas it was similar in the two cohorts among females. The overall rate of AO in males was 66%. The overall female:male ratio was 3.2:1, being 4.8:1 in the RC, which is comparable to available data [1–3], and 1.7:1 in the PC, underlying a probable trend of growing incidence in males. Thus, our analysis pictures a trend of increasing proportion of males and AO presentation that needs further investigation in multicenter studies.

The CBR rate was excellent, in line with data previously reported [1], and it was similar in AO and non-AO patients. Longitudinal dynamics of LSM during FU were consistent with a progressive decline over time, which was more pronounced in patients with CBR than in those without CBR.

Indeed, survival was similar on AO and non-AO patients. This slightly contrasts with previous data, which showed a better long-term prognosis outcome in patients with an AO [5]. However, our AO patients had a significantly shorter median FU time than the non-AO patients, limiting definitive conclusions on this issue.

Similarly, our cohort has shown a trend toward improved LT-free survival for patients with AO compared to those with non-AO. Overall, the outcome in our patients was favorable, as shown by 10- and 15-year survival rates.

In conclusion, our single-center study documented an increasing trend in the proportion of males and AO cases among AIH patients in recent years. This trend might reflect a potential shift in the clinical-epidemiological landscape of AIH, possibly linked to yet unknown environmental triggers; however, it requires further confirmation in larger prospective studies. Finally, our data confirm a favorable prognosis in terms of CBR and survival for AIH patients undergoing treatment, with no significant differences observed after stratifying patients according to the type of disease onset.

Author contributions C.R. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: C.R., M.P. Acquisition of data: C.R., M.G.C. Drafting of the manuscript: C.R., I.G., G.F.M., M.G.C. Critical revision of the manuscript for important intellectual content: all the authors. Statistical analysis: C.R. Study supervision: M.P.

Funding This study had no financial support.

Data availability The data underlying this article will be shared upon reasonable request to the corresponding author.

Declarations

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

Human and animal rights statement The study was conducted in full accordance with the Declaration of Helsinki and has been approved by the local Ethical Committee.

Informed consent Each patient signed an informed consent.

References

1. EASL Clinical Practice Guidelines (2015) Autoimmune hepatitis. J Hepatol 63(4):971–1004. https://doi.org/10.1016/j.jhep.2015.06.030
2. Mack CL, Adams D, Assis DN et al (2020) 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 72(2):671–722. https://doi.org/10.1002/hep.31065
3. Lv T, Li M, Zeng N et al (2019) Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. J Gastroenterol Hepatol 34(10):1676–1684. https://doi.org/10.1111/jgh.14746
4. Lamba M, Ngu JH, Stedman CAM (2021) Trends in incidence of autoimmune liver diseases and increasing incidence of autoimmune hepatitis. Clin Gastroenterol Hepatol 19(3):573-579.e1. https://doi.org/10.1016/j.cgh.2020.05.061
5. Muratori P, Carbone M, Stangos G et al (2018) Clinical and prognostic implications of acute onset of autoimmune hepatitis: an Italian multicentre study. Dig Liver Dis 50(7):698–702. https://doi.org/10.1016/j.dld.2018.02.015
6. Granito A, Muratori L, Pappas G et al (2005) Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. Aliment Pharmacol Ther 21(10):1273–1277. https://doi.org/10.1111/j.1365-2036.2005.02488.x