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Autoantibodies are associated with worse outcomes in MASLD

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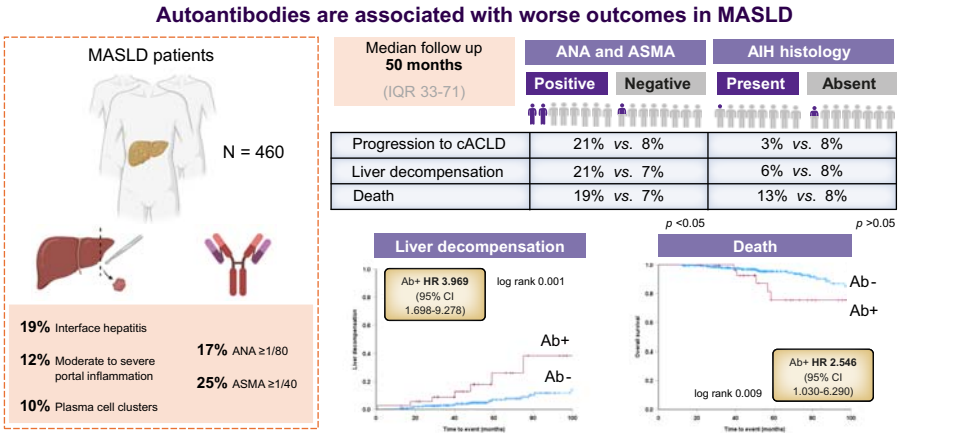
Graphical abstract



Ab: antibodies, AIH: autoinmune hepatitis, ANA: antinuclear antibodies, ASMA: anti-smooth muscle antibodies; cACLD: compensated advanced chronic liver disease

Highlights:

- Patients with MASLD and positive antibodies have a higher risk of liver-related outcomes and death.
- Histological autoimmune features in MASLD do not correlate with antibody positivity or outcomes.
- The presence of antibodies may serve as an inflammatory biomarker in MASLD.
- Further research is needed to explore the immune mechanisms involved and validate these findings.

Impact and implications:

Metabolic dysfunction-associated steatotic liver disease (MASLD) can coexist with other liver diseases, including autoimmune hepatitis. The role of autoantibodies and histological autoimmune features in MASLD progression remains controversial. Understanding the relationship between autoimmune characteristics and disease progression in MASLD may help physicians identify high-risk populations, enhance risk stratification, and personalize disease treatment.

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Autoantibodies are associated with worse outcomes in MASLD☆

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Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Autoantibodies (Ab), such as antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA), are frequently detected in MASLD, but their role in disease progression remains controversial. This study aimed to evaluate the prevalence of positive Ab and the histological features of autoimmune hepatitis (AIH) in MASLD and their association with liver-related outcomes.

Methods: We conducted a multicenter, retrospective, longitudinal study of patients with biopsy-proven MASLD from the HEPAmet Registry. Data on ANA (≥1/80), ASMA (≥1/40), and AIH histological features (portal inflammation, interface hepatitis, and plasma cell infiltration) were analyzed for their association with compensated advanced chronic liver disease (cACLD), liver decompensation, and death.

Results: Of the 460 patients (49% women, median age 58 years, median BMI 33 kg/m^2, and 45% with advanced fibrosis), 17% and 25% tested positive for ANA and ASMA, respectively. Histological features of AIH included interface hepatitis (19%), moderate/severe portal inflammation (12%), and plasma cell clusters (10%). Possible AIH based on histological criteria was present in 8% of patients. The presence of positive Ab was independently associated with cACLD development (odds ratio 2.890, p <0.030), liver decompensation (hazard ratio 3.969, p = 0.001), and death (hazard ratio 2.546, p = 0.036). In contrast, the presence of isolated histologic autoimmune features was not correlated with serological markers and did not affect the prognosis of MASLD.

Conclusions: ANA and ASMA are commonly found in patients with MASLD and are associated with poorer liver-related outcomes and reduced survival, whereas isolated histological autoimmune features provide no additional prognostic value.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease worldwide, with an increased prevalence tightly related to the rising incidence of obesity and type 2 diabetes.[1,2] Among all the histological characteristics that define MASLD, lobular inflammation is the main driver of fibrogenesis activation and fibrosis deposition. Fibrosis is recognized as the strongest risk factor for disease progression and is associated with MASLD prognosis.[3,4] Patients with MASLD and advanced fibrosis have an increased risk of developing cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC) and require liver transplantation. Moreover, the fibrosis stage in MASLD is associated with a significant increase in cardiovascular events, extrahepatic cancer, and mortality.[5–10]

It is known that other liver diseases can coexist in patients with MASLD, and the association of MASLD with autoimmune hepatitis (AIH) is particularly interesting. Different studies have reported that 20–35% of patients with MASLD present positive non-tissue-specific autoantibodies (Ab), such as antinuclear antibodies (ANA) or anti-smooth muscle antibodies (ASMA).[11–16] However, there are controversial data regarding the role of adaptive immunity and positive Ab in MASLD hepatic injury[14,15,17,18] or

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progression.[13,19,20] Interestingly, some data suggest that the presence of MASLD in patients with AIH is associated with a worse prognosis.[20–23] Similarly, experimental animal models have shown that the association between AIH and steatosis or steatohepatitis can lead to a more aggressive evolution of AIH and a higher presence of antigen-specific T cells.[24]

Previous studies suggest that patients with overlapping features of MASLD and AIH may have a distinct disease trajectory, potentially driven by a bidirectional synergistic interaction between both conditions, leading to a worse prognosis. However, the methodologies and findings of these studies are highly heterogeneous, and they fail to comprehensively integrate the impact of autoimmune serological and histological markers on liver-related prognosis, especially in MASLD. Therefore, this study aimed to evaluate the prevalence of positive Ab and AIH-related histological features in a multicenter MASLD cohort and to investigate their association with disease prognosis.

Patients and methods

Study design and population

This multicenter, retrospective, longitudinal study included patients with a clinical and histological diagnosis of MASLD from the Spanish HEPAmet Registry. The present study enrolled patients from four tertiary centers in Spain (Hospital Clinic Barcelona, Hospital Marqués de Valdecilla, Hospital Vall d'Hebron, and Hospital Ramón y Cajal). The HEPAmet Registry is a nationally monitored registry governed by the Spanish Association for the Study of the Liver (AEEH). Demographic, clinical, biochemical, histological, elastography, and imaging data were recorded on an electronic REDCap platform. When the registry started, the new nomenclature for MASLD[25] was not yet accepted, and only patients meeting the non-alcoholic fatty liver disease (NAFLD) criteria and the exclusion of other concomitant chronic liver diseases were included. Subsequently, we confirmed that all patients included in the registry met the new MASLD criteria.[25] Therefore, the inclusion criteria for the present study were as follows: (1) patients aged 18–75 years, (2) histological and clinical diagnosis of MASLD, (3) exclusion of other chronic liver diseases, and (4) availability of serological Ab. The exclusion criteria were as follows: (1) follow-up shorter than 1 year, (2) high-risk alcohol use (defined as >20 g/day in women and >30 g/day in men), (3) HCC at inclusion, (4) previous liver transplant, and (5) extrahepatic malignancies with less than 2 years of life expectancy. We collected all information at the time of liver biopsy (inclusion in the registry) and longitudinal information on new-onset diseases, autoimmune features, treatment, and complementary tests during the follow-up period. All liver biopsies were re-read by expert liver pathologists at each center to assess the presence of autoimmune features that could have been overlooked during the first evaluation, including the following: (1) the presence of plasma cell clusters (defined as foci of ≥5 plasma cells), (2) moderate to severe interface hepatitis, and (3) the presence of portal inflammation. Moreover, they evaluated the presence of steatohepatitis using the non-alcoholic fatty liver disease activity score (NAS)[26] and liver fibrosis staged according to the METAVIR scoring system.[27] At the time of this analysis, pathologists were blind to clinical and serological data.

Autoimmunity evaluation

Ab were determined by indirect immunofluorescence in both rodent tissue sections and human epithelioma-2 (HEp-2) cells. Antibody titers were modified according to the recent recommendations of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER),[28] as shown in Table S1. Positive ANA and ASMA were considered at a titer of ≥1/80 and ≥1/40, respectively. Other titers were also assessed and analyzed for comparison.

The simplified AIH score established by the International AIH Group was calculated in all patients, giving 0–2 points according to the ANA and ASMA titers, IgG levels, the presence or absence of viral hepatitis, and compatible or typical histological features of AIH. However, it is important to consider that the presence of steatosis and/or steatohepatitis in the liver biopsy immediately gives 0 points to the histological category of the score. Therefore, the maximum score for the patients included in the study is 6, which is considered probable AIH. As per the definition, none of the patients included in the present study could have a definite AIH diagnosis using the simplified criteria.[29]

To address the histological limitations of the simplified score, the assessment of AIH characteristics in liver biopsy was performed according to the new consensus recommendations from the International AIH Pathology Group in 2022.[30] For practical reasons, we called this the '2022-AIH score'. This score divides patients into likely, possible, and unlikely AIH, depending on the histological findings. Using the '2022-AIH score' definition, patients with steatosis must present plasma cell clusters with portal inflammation or moderate lobular inflammation to be classified as having 'possible AIH'.

Clinical outcomes

The development of compensated advanced chronic liver disease (cACLD) at the end of follow-up, liver decompensation, HCC, death, and liver transplantation were the main clinical outcomes analyzed. cACLD at baseline was defined as the presence of F4 or F3 fibrosis and liver stiffness >15 kPa[31] and/or ultrasound signs of cirrhosis, such as nodular edges or portal hypertension signs. Progression to cACLD was defined as the absence of cACLD at inclusion and progression of liver stiffness >15 kPa and/or evidence of cirrhosis based on the clinical, biochemical, ultrasound, and/or histological criteria at the end of follow-up. Liver decompensation was defined as the occurrence of portal hypertension-related bleeding, ascites, overt encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome according to clinical guidelines.[32] The development of HCC and portal thrombosis and the need for liver transplantation were also analyzed. Patients were followed up until death, liver transplant, or the last visit. All clinical outcomes were assessed and confirmed by experienced hepatologists.

Ethics

This study complied with the principles of the Declaration of Helsinki and Istanbul. The protocol was approved by the institutional review board of the hospital, and all patients provided written informed consent to participate in the HEPAmet Registry (Reg. HCB/2016/0191). Confidentiality was preserved in agreement with current Spanish legislation on data protection (article 9 of the UE legislation 2016/679).

Statistical analysis

Quantitative variables are expressed as median (IQR) or mean (SD), where appropriate. Categorical variables are expressed as absolute counts and percentages. Statistical significance between groups was assessed using the Chi-square test, Pearson's Chi-square, *t* test, or Mann–Whitney *U* test, where applicable. Univariate and multivariate analyses (MVA) using binary logistic regression or Cox regression were performed to determine the impact of autoimmune features on the clinical outcomes. Different combinations of variables were used to build the MVA according to the number of events. We included those with statistical significance in the univariate analysis, more clinical relevance (those reflecting advanced liver disease), and the variables of interest in our study (*e.g.* autoimmune features). When variables were collinear, we included only the most relevant in the MVA. Although type 2 diabetes and obesity, in most cases, were not significantly different between the two groups of comparison, we decided to add them to the MVA for their potential role as disease modifiers. Finally, center-adjusted analysis was also performed. Survival analysis was performed using Kaplan–Meier and log-rank tests. Statistical significance was defined as a two-sided *p* value <0.05. All statistical analyses were performed using SPSS Statistics software (version 29.0.0.0, IBM, Armonk, NY, USA).

Results

Baseline characteristics

Out of the 802 patients eligible for the study, 342 were excluded because of insufficient follow-up or incomplete availability of autoimmune serologies. Finally, 460 patients were included in the analysis. The study flowchart is presented in Fig. 1.

Baseline patient characteristics are summarized in Table 1. Briefly, 227 (49%) patients were women with a median age of 58 years (IQR 51–64 years). More than 50% of the population presented with comorbidities related to metabolic syndrome, such as obesity (n = 331, 72%) with a median BMI of 33 kg/m^2 (IQR 30–37 kg/m^2), arterial hypertension (n = 281, 61%), dyslipidemia (n = 273, 59%), and type 2 diabetes (n = 269, 58%). Almost one-quarter of the patients had immune-mediated diseases, with psoriasis being the most common (n = 42, 9%). Patients had slightly elevated liver tests, with a median aspartate aminotransferase (AST) of 43 IU/L (IQR 30–66 IU/L), alanine aminotransferase (ALT) of 55 IU/L (IQR 35–86 IU/L), and gamma-glutamyl transferase (GGT) of 74 IU/L (IQR 43–147 IU/L), and mostly had preserved liver function. At baseline, the median liver stiffness and controlled attenuation parameter (CAP) were 11.4 kPa (IQR 9–17 kPa) and 330 dB/m (IQR 299–361 dB/m), respectively. Regarding the histological findings, the median NAS score was 3 (IQR 2–4), and 45% of the patients had advanced fibrosis (113 [25%] F3 and 93 [20%] F4). At enrollment, 117 of 356 patients with available liver stiffness measurements (33%) fulfilled the cACLD criteria.

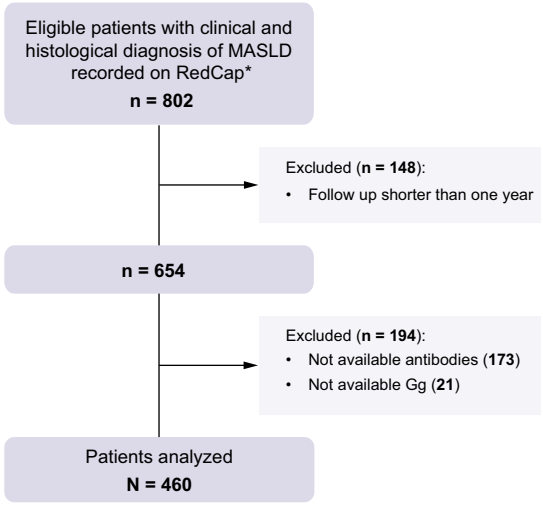

Fig. 1. Flowchart of the study. Ab, antibodies; Gg, gamma globulins; MASLD, metabolic dysfunction-associated steatosis liver disease.

Autoimmune characteristics

The autoimmune characteristics of the cohort are summarized in Table 1. ANA were positive at titers of ≥1/80 in 78 (17%) patients, and ASMA were positive at titers of ≥1/40 in 114 (25%). Moreover, only 36 (8%) patients were positive for both Ab. The median IgG and gamma globulin levels were 11 g/dl (IQR 9–13 g/dl) and 15.4% (IQR 13–17%), respectively. A total of 63 (14%) and 94 (20%) patients had IgG and gamma globulin levels above the upper limit of normal (ULN) for each center, respectively. Assessment of the liver biopsies showed that 87

Table 1. Baseline and autoimmune characteristics of the population.

Variables	Total (N = 460)
Demographics	
Female sex	227 (49)
Age (years)	58 (51–64)
BMI (kg/m^2)	33 (30–37)
Current low-risk alcohol use*	94 (20)
Current smoking	57 (12)
Comorbidities	
Arterial hypertension	281 (61)
Dyslipidemia	273 (59)
Type 2 diabetes mellitus	269 (58)
Obesity (BMI >30 kg/m^2)	331 (72)
Hypothyroidism	64 (14)
Extrahepatic malignancies†	56 (12)
Immune-mediated diseases‡	108 (23)
Bariatric surgery	55 (12)
Blood tests	
AST (IU/L)	43 (30–66)
ALT (IU/L)	55 (35–86)
GGT (IU/L)	74 (43–147)
ALP (IU/L)	89 (70–111)
Bilirubin (mg/dl)	0.65 (0.5–0.9)
Albumin (g/L)	44 (42–46)
Platelets (× 10^9)	211 (159–259)
INR	1.03 (0.97–1.09)
ANA	
≥1/40	135 (29)
≥1/80	78 (17)
≥1/160	49 (11)
ASMA	
≥1/40	114 (25)
≥1/80	45 (10)
≥1/160	20 (4)
Positive ANA or ASMA§	156 (34)
Positive ANA and ASMA	36 (8)

(*continued on next page*)

Table 1. (*continued*)

Variables	Total (N = 460)
IgG ≥ULN[¶]	63 (14)
Gamma globulins ≥ ULN	94 (20)
Liver biopsy	
Steatosis	
No	25 (5)
Low	210 (46)
Moderate	159 (34)
Severe	66 (14)
Ballooning	
No	182 (40)
Moderate	190 (41)
Severe	88 (19)
Lobular inflammation	
No	117 (25)
≤2 foci	274 (60)
2–4 foci	66 (14)
≥4 foci	3 (1)
NAS score	3 (2–4)
Fibrosis	
F0	80 (17)
F1	104 (23)
F2	70 (15)
F3	113 (25)
F4	93 (20)
Interface hepatitis	87 (19)
Portal inflammation	
Low	270 (59)
Moderate to severe	53 (12)
Plasma cells	48 (10)
"2022-AIH score"**	
Unlikely AIH	423 (92)
Possible AIH	37 (8)
Baseline transient elastography	
Liver stiffness (kPa)	11.4 (9–17)
CAP (dB/m)	330 (299–361)
Liver assessment	
Baseline cACLD (n = 356)[††]	117 (33)

Qualitative variables are presented as n (%), and quantitative variables are presented as median (IQR).

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; NAS, non-alcoholic fatty liver disease activity score; ULN, upper limit of normal.

*Low-risk alcohol use was defined as <20 g/day in women and <30 g/day in men.

[†]Extrahepatic malignancies: 21 (4.5%) gynecological (uterus, breast, and prostate), 13 (2.8%) gastrointestinal, 7 (1.5%) urinary (kidney and bladder), 8 (1.7%) hematologic, 7 (1.5%) skin and bone, 1 (0.2%) central nervous system, and 1 (0.2%) upper airway.

[‡]Immune-mediated diseases: 42 (9%) psoriasis, 12 (2.6%) thyroidal disease, 11 (2.3%) extrinsic asthma, 11 (2.4%) inflammatory bowel disease, 9 (1.9%) hidradenitis, 5 (1%) spondyloarthropathies, 3 (0.6%) vitiligo, 1 (0.2%) rheumatoid arthritis, and 18 (4%) others.

[§]ANA ≥1/80 and ASMA ≥1/40 were considered positive.

[¶]The definition of ULN was different according to every center's threshold: Hospital Clinic Barcelona: IgG ≥15.3 g/L and gamma globulin ≥18.8%; Hospital Vall d'Hebron: IgG ≥16 g/L and gamma globulin ≥18.8%; Hospital Marqués de Valdecilla: IgG ≥14.8 g/L and gamma globulin ≥18.8%; and Hospital Ramón y Cajal: IgG ≥16 g/L and gamma globulin ≥17%.

**According to the consensus recommendations for histological criteria of AIH from the International AIH Pathology Group.[30]

[††]Baseline cACLD was defined based on liver biopsy when F4 or F3 with liver stiffness ≥15 kPa.

patients (19%) presented interface hepatitis, 53 (12%) had moderate to severe portal inflammation, and 48 (10%) presented plasma cell clusters. We calculated the simplified AIH score and found out that 14 (3%) patients had a simplified score of 6 based on clinical and serological characteristics. These patients were more frequently women, had a higher proportion of autoimmune comorbidities, and, as expected by the score definition, had a higher prevalence of ANA/ASMA positivity compared with those with a simplified score <6 (Table S2). None of these 14 patients had a compatible histological diagnosis of AIH because of the presence of steatosis, nor did they meet the histological criteria for a possible AIH using the new consensus.[30] As explained in the Patients and methods section, because of the disadvantages of the simplified AIH score in patients with MASLD, we also assessed the criteria of the International AIH Pathology Group for 2022. None of the patients fulfilled the criteria of 'likely AIH', and only 37 patients (8%) were classified as presenting a 'possible AIH' based on histology. None of these 37 patients were diagnosed by their referring clinicians or treated as AIH. Because our goal was to assess the relevance of serological and/or histological characteristics of AIH in MASLD progression, we decided to include all patients in the subsequent analysis.

We then compared patients with and without positive antibodies (Table 2), and no significant differences were found in baseline comorbidities, immune-mediated diseases, or autoimmune serological or histological features. Patients with both positive Ab had slightly lower levels of bilirubin (0.6 *vs*. 0.7 mg/dl; $p = 0.030$), lower CAP values (302 *vs*. 332 dB/m; $p < 0.001$), and lower liver stiffness (10 *vs*. 12 kPa; $p = 0.026$) than those with negative Ab. However, there were no significant

Table 2. Baseline characteristics according to the presence of both positive antibodies.

	Both positive antibodies* (N = 460)		
Variables	**Yes (n = 36)**	**No (n = 424)**	***p* value**
Demographics and comorbidities			
Age (years)	61 (55–67)	58 (51–64)	0.056
Female sex	19 (53)	208 (49)	0.668
Arterial hypertension	23 (64)	258 (61)	0.719
Dyslipidemia	23 (64)	250 (59)	0.563
Type 2 diabetes mellitus	21 (58)	248 (59)	0.985
Obesity (BMI >30 kg/m^2)	26 (72)	305 (74)	0.813
Immune-mediated diseases	6 (17)	102 (24)	0.315
Blood tests			
AST (IU/L)	41 (27–78)	43 (30–65)	0.949
ALT (IU/L)	41 (27–80)	56 (36–87)	0.138
GGT (IU/L)	74 (40–160)	75 (43–146)	0.995
ALP (IU/L)	98 (82–140)	88 (70–110)	0.052
Bilirubin (mg/dl)	0.6 (0.4–0.8)	0.7 (0.5–0.9)	**0.030**
Albumin (g/L)	45 (41–46)	44 (42–46)	0.577
Platelets (× 10^9)	222 (158–250)	211 (159–260)	0.956
INR	1.04 (0.97–1.10)	1.03 (0.97–1.09)	0.384
IgG ≥ULN[†]	5 (14)	58 (14)	0.566
Gamma globulins ≥ULN	10 (28)	84 (20)	0.255
Liver biopsy			
Steatosis			0.477
No	0 (0)	25 (6)	
Low	16 (44)	194 (46)	
Moderate	14 (39)	145 (34)	
Severe	6 (17)	60 (14)	
Ballooning			0.919
No	15 (42)	167 (36)	
Moderate	15 (42)	175 (41)	
Severe	6 (17)	82 (19)	
Lobular inflammation			0.132
No	8 (22)	109 (26)	
≤2 foci	25 (69)	249 (59)	
2–4 foci	2 (6)	64 (15)	

(*continued on next page*)

Table 2. (*continued*)

Variables	Both positive antibodies* (N = 460)		
	Yes (n = 36)	No (n = 424)	*p* value
≥4 foci	1 (3)	2 (1)	
NAS score	3.5 (2–4)	3 (2–4)	0.759
Advanced fibrosis (F3–F4)	14 (39)	192 (45)	0.459
Interface hepatitis	6 (17)	81 (19)	0.701
Portal inflammation			0.875
Low	20 (56)	250 (59)	
Moderate	4 (11)	50 (12)	
Plasma cells clusters	3 (8)	45 (11)	0.468
Possible AIH based on "2022-AIH score"‡	3 (8)	34 (8)	0.570
Baseline transient elastography			
Liver stiffness (kPa)	10 (7–14)	12 (9–17)	**0.026**
CAP (dB/m)	302 (259–340)	333 (302–363)	**<0.001**
Liver assessment			
Baseline cACLD (n = 356)§	6 (19)	111 (34)	0.075

Qualitative variables are presented as n (%), and quantitative variables are presented as median (IQR). The Chi-square test or Fisher's exact test was used for the comparison of qualitative variables, and the Mann–Whitney *U* test was used for the comparison of quantitative variables. Level of significance: p <0.05 (bold).

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; NAS, non-alcoholic fatty liver disease activity score; ULN, upper limit of normal.

*ANA ≥1/80 and ASMA ≥1/40 were considered positive.

†The definition of ULN was different according to every center's threshold: Hospital Clinic Barcelona: IgG ≥15.3 g/L and gamma globulin ≥18.8%; Hospital Vall d'Hebrón: IgG ≥16 g/L and gamma globulin ≥18.8%; Hospital Marqués de Valdecilla: IgG ≥14.8 g/L and gamma globulin ≥18.8%; and Hospital Ramón y Cajal: IgG ≥16 g/L and gamma globulin ≥17%.

‡According to the consensus recommendations for histological criteria of AIH from the International AIH Pathology Group.[30]

§Baseline cACLD was defined based on liver biopsy when F4 or F3 had liver stiffness of ≥15 kPa.

differences in the presence of histologically advanced fibrosis (F3–F4 39% *vs*. 45%; p = 0.459) at baseline. In contrast, patients who fulfilled the criteria for 'possible AIH' according to the '2022-AIH score' (n = 37, 8%) were significantly older (60 *vs*. 58 years old; p = 0.002), had higher AST levels (49 *vs*. 43 IU/L; p = 0.045), lower platelet count (148 × 10^9 *vs*. 213 × 10^9; p = 0.002), lower albumin levels (41 *vs*. 44 mg/dl), and more advanced liver disease (F3–F4, 62% *vs*. 43%; p = 0.011). However, there were no significant differences in the presence of positive Ab, gamma globulins, or IgG levels between patients with and without histological features of AIH (Table S3).

Outcomes

General evaluation

After a median follow-up of 50 (IQR 33–71) months, 34 patients (10%) progressed to cACLD and 33 (7%) had a liver decompensation, with ascites being the most frequent complication (n = 29, 6%) with a mean time until first decompensation of 40.3 months (SD 8.3 months, 95% CI 24.08–54.54 months). HCC was diagnosed in 16 patients (4%). Thirty-two patients (7%) died during follow-up, mostly because of extrahepatic reasons, and eight patients (2%) underwent liver transplantation (Table 3). Older age, worse liver function, and lower platelet count were associated with liver-related outcomes and survival (Table S4–S6).

Relationship between autoimmune features and outcomes

Next, we evaluated the relevance of the presence of autoimmune characteristics in our cohort by assessing their association with liver-related outcomes and survival. We analyzed both the presence of positive Ab and histological features of AIH, evaluated using the '2022-AIH score', and their relationship with outcomes (Tables 4 and 5 and Table S4–S6). Positive Ab, age, and elevated GGT levels were independently associated with cACLD development (Table S7 and Fig. 2A). Likewise, positivity for both Ab (ANA and ASMA) was independently associated with the development of liver decompensation (hazard ratio [HR] 3.969, 95% CI 1.698–9.278, p = 0.001) and death (HR 2.546, 95% CI 1.030–6.290, p = 0.043) (Fig. 2B and C). Moreover, we adjusted the MVA for the presence of type 2 diabetes and obesity and found that the presence of either of these comorbidities did not significantly affect the results.

A stratified analysis using different titers of ANA and ASMA was also performed (Table S9), highlighting the role of ASMA positivity alone with an HR of 3.615 for liver decompensation (95% CI 1.761–7.420, p <0.001), an HR of 2.215 for death (95% CI 1.057–4.643, p = 0.035), and an odds ratio (OR) of 2.560 for progression to cACLD (95% CI 1.248–5.249, p = 0.010). Kaplan–Meyer curves representing these results are shown in Fig. S1A–C.

The assessment of histological AIH features, based on the consensus recommendations for histological criteria of AIH, did not find a relevant association between the presence of isolated histological features of AIH and liver-related outcomes or survival (Table 4 and Table S3).

The main analysis was repeated, excluding the 37 patients with criteria of 'possible AIH' based on the '2022-AIH score' and found similar results (Table S9).

Sex perspective analysis

Because women have a higher probability of autoimmune disease, we decided to perform a specific analysis to assess if there were differences in baseline characteristics, autoimmune features, and outcomes between sexes. Women had a lower risk of alcohol (9% *vs*. 41%; p <0.001) and tobacco use (35%

Table 3. Clinical outcomes of the general population.

Clinical outcomes	Total (N = 460)
cACLD at the end of follow-up*	151 (43)
Progression to cACLD†	34 (10)
Liver decompensation‡	33 (7)
Hepatocellular carcinoma	16 (4)
Death	32 (7)
Non-liver-related§	21 (4–5)
Liver-related	11 (2–4)
Liver transplantation	8 (2)

Qualitative variables are presented as n (%), and quantitative variables are presented as median (IQR). Baseline and follow-up cACLD were assessed only in patients who underwent transient elastography (n = 356).

*This group includes patients with cACLD when liver biopsy was performed, plus patients with progression to cACLD from liver biopsy until the end of follow up.

†Progression to cACLD was defined as new clinical and radiologic criteria for liver cirrhosis or worsening of liver stiffness to ≥15 kPa.

‡Patients with decompensations at baseline (n = 8) were excluded from this analysis; from n = 452: 29 (6%) ascites, 9 (2%), portal hypertension-related bleeding, 10 (2%) overt encephalopathy, 5 (1%) bacterial spontaneous peritonitis, 4 (1%) portal thrombosis, and 2 (0.4%) hepatorenal syndrome.

§Non-liver-related death: infectious (10), cardiac (2), neoplastic (2), neurologic (2), and other (5). cACLD, compensated advanced chronic liver disease.

Table 4. Clinical outcomes according to autoimmune features.

	Progression to cACLD* (n = 356)			Liver decompensation (n = 452)			Death of any cause (n = 460)		
	Yes (n = 34)	No (n = 322)	*p*	Yes (n = 33)	No (n = 419)	*p*	Yes (n = 32)	No (n = 428)	*p*
Any positive antibody†	19 (56)	115 (36)	**0.021**	18 (55)	133 (32)	**0.007**	14 (44)	142 (33)	0.223
Both positive antibodies	7 (21)	25 (8)	**0.023**	7 (21)	29 (7)	**0.010**	6 (19)	30 (7)	**0.030**
Possible AIH based on "2022-AIH score"‡	1 (3)	25 (8)	0.264	2 (6)	35 (8)	0.480	4 (13)	33 (8)	0.250

Qualitative variables are presented as n (%). The Chi-square or Fisher's exact test was used for the comparison of qualitative variables. Level of significance: p <0.05 (bold).
AIH, autoimmune; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; cACLD, compensated advanced chronic liver disease.
*Progression to cACLD was defined as new clinical and radiologic criteria for liver cirrhosis or worsening of liver stiffness to ≥15 kPa without baseline cACLD.
†ANA and ASMA were considered positive at titles of ≥1/80 and ≥1/40, respectively.
‡According to the definition of the consensus recommendations for histological criteria of AIH from the International AIH Pathology Group.30

Table 5. Univariate and multivariate Cox regression.

	UVA			MVA			MVA adjusted for T2DM			MVA adjusted for obesity		
Outcome/variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Liver decompensation												
Age (years)	1.04	1.003–1.079	**0.034**									
AST (IU/L)	1.001	0.992–1.010	0.832									
GGT (IU/L)	1.001	1.000–1.002	**0.004**									
ALP (IU/L)	1.007	1.004–1.010	**<0.001**	1.006	1.003–1.009	**<0.001**	1.006	1.003–1.009	**<0.001**	1.006	1.003–1.009	**<0.001**
Platelets (×10^9)	0.982	0.975–0.989	**<0.001**									
Any positive Ab	2.339	1.175–4.657	**0.016**									
Both positive Ab	3.598	1.551–8.346	**0.003**	3.969	1.698–9.278	**0.001**	4.007	1.698–9.456	**0.002**	3.753	1.594–8.834	**0.002**
Advanced fibrosis	10.550	3.215–34.622	**<0.001**	7.213	2.040–25.500	**<0.001**	10.782	3.261–35.649	**<0.001**	10.163	3.075–33.588	**<0.001**
CAP (dB/m)	0.987	0.979–0.996	**0.004**									
Baseline cACLD	7.280	2.443–21.691	**<0.001**									
Death of any cause												
Age (years)	1.072	1.030–1.115	**0.001**	1.071	1.028–1.116	**0.001**	1.072	1.027–1.119	**0.008**	1.011	1.006–1.017	**<0.001**
GGT (IU/L)	1.002	1.000–1.003	**0.015**	1.002	1.000–1.003	**0.001**	1.002	1.000–1.003	**0.008**	5.166	2.189–12.191	**<0.001**
Platelets (×10^9)	0.995	0.990–1.000	0.075									
Both positive Ab	3.125	1.271–7.688	**0.013**	2.546	1.030–6.290	**0.043**	2.531	1.021–6.277	**0.045**	18.250	4.987–66.787	**<0.001**
Portal inflammation	2.218	1.017–4.837	**0.045**	–	–	–						
Advanced fibrosis	2.154	0.993–4.672	0.052	–	–	–						
Baseline cACLD	1.677	0.695–4.045	0.250	–	–	–						

A univariate and multivariate Cox regression with a level of significance of p <0.05 (bold) was used to assess factors independently related to the development of liver decompensation and death. Adjustment for the presence of T2DM and obesity was performed separately. Advanced fibrosis was defined as F3–F4 in liver biopsy. Moderate to severe portal inflammation was considered significant. Ab, antibodies; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; HR, hazard ratio; MVA, multivariate analysis; T2DM, type 2 diabetes; UVA, univariate analysis.

vs. 49%; p = 0.003) than men but a higher prevalence of extrahepatic malignancies (15% *vs*. 9%; p = 0.049) and thyroid disease (21% *vs*. 7%; p = 0.001). Women had more severe lobular inflammation on liver biopsy, as measured by the NAS score (4 *vs*. 3; p <0.005). No differences in autoimmune serological or histological features were observed between sexes, except for a higher prevalence of ANA ≥1/40 in women (35% *vs*. 24%; p = 0.006). The observed differences did not have a significant impact on the presence of advanced fibrosis at baseline, liver-related outcomes, or survival. Table S10 shows a detailed analysis comparing both sexes.

Discussion

The present study evaluated the prevalence of serological and histological autoimmune characteristics in a multicenter cohort of 460 patients with MASLD and their association with liver-related outcomes and survival. Our results showed that the presence of positive Ab (ANA and ASMA) was associated with worse liver-related outcomes, including progression to cACLD, liver decompensation, and death. In contrast, the presence of histological features of AIH was not associated with the presence of Ab and did not have a significant impact on liver outcomes.

The prevalence of positive Ab reported in MASLD, in both adults[12–14,19,34–37] and children,[15,16,38,33] ranges from 13% to 46%. Similarly, in our cohort, 17% of patients presented with positive ANA and 25% with positive ASMA, whereas only 8% were positive for both Ab. Whether Ab play a specific role in MASLD progression or have prognostic implications remains unclear, largely because of the heterogeneity of previous studies and the potential influence of confounding factors. A systematic review assessing biopsy-proven MASLD found that patients with positive ANA did not have more advanced fibrosis or lobular inflammation in liver biopsy.[34] Another study involving 401 patients with MASLD indicated that those with positive Ab did not have a higher presence of liver cirrhosis.[18] In contrast, a recent retrospective study of 2,285 patients with MASLD found that the odds of advanced fibrosis increased by 28% in the presence of positive Ab. However, the assessment of advanced fibrosis was inconsistent, relying primarily on serum-based non-invasive tests, with 49% of patients having an FIB-4 score ≥2.67 and 75% having an AST to platelet ratio index (APRI) ≥0.7. Only a small subset of patients underwent liver biopsy, and among these, a low proportion (13%) had advanced fibrosis.[37] Likewise, another study involving 388 patients with histology-proven MASLD showed that positive Ab, present in 13% of the cohort, were associated with advanced fibrosis (stages F3 and F4). However, the proportion of patients with advanced fibrosis in this cohort had a higher percentage of the genotype *PNPLA3* rs738409 GG or CG,[13]

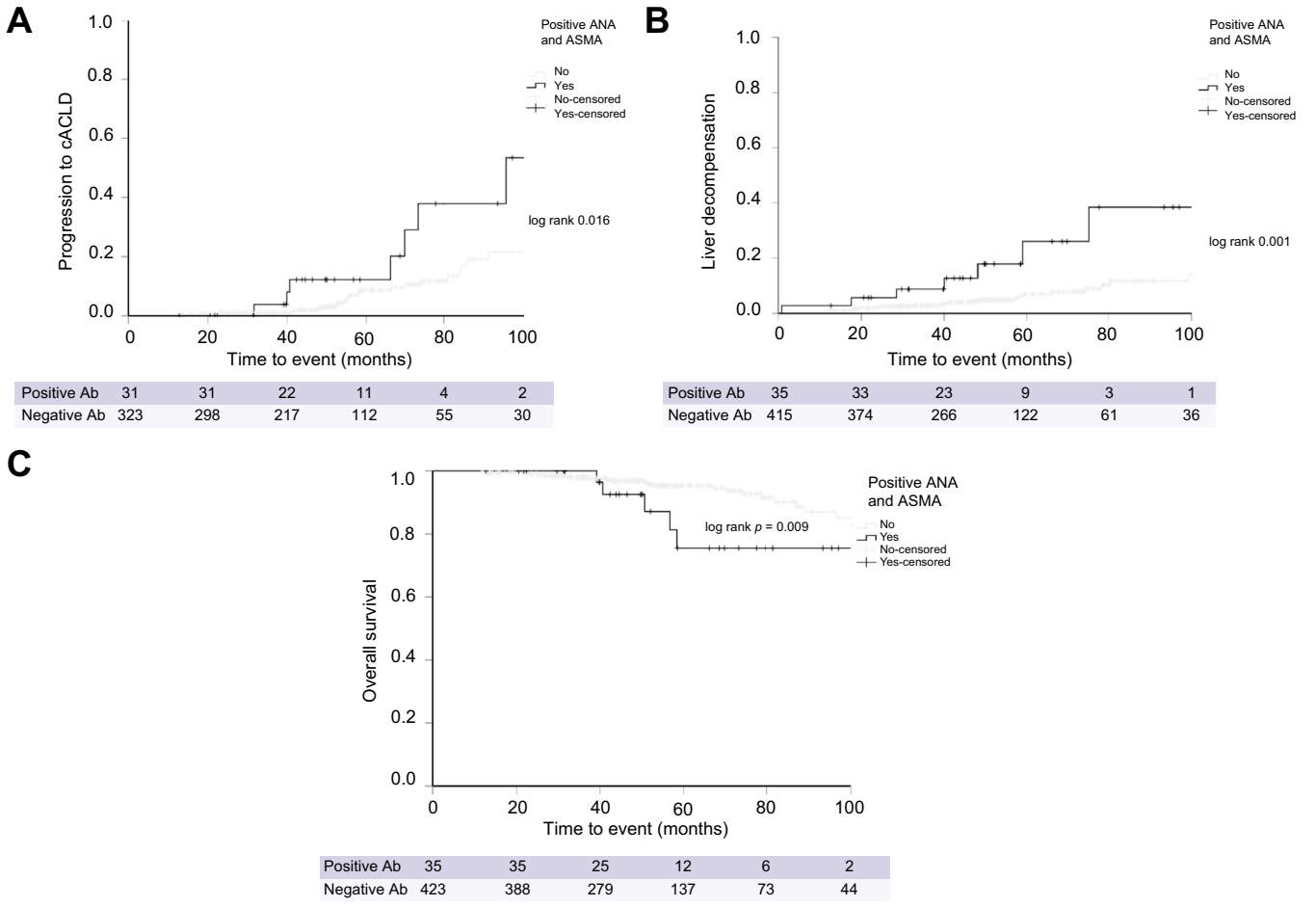

Fig. 2. Outcomes were represented in Kaplan–Meier curves based on the positivity of autoantibodies. (A) Progression to cACLD and both positive antibodies. (B) Liver decompensation and both positive antibodies. (C) Survival and both positive antibodies. Ab, autoantibodies; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; cACLD, compensated advanced chronic liver disease.

which is known to be associated with more severe disease[14,39] and thus could be an important confounding factor. In our study, we reported a large cohort of biopsy-proven MASLD with longitudinal assessment of liver outcomes and found that the presence of positive Ab was not associated with more advanced liver disease at baseline (F3–F4 48% *vs*. 43%; p = 0.31) but had an impact on future outcomes.

The association between Ab and liver-related outcomes in MASLD has been explored in only a few studies. One of the largest longitudinal studies involving 900 patients with biopsy-proven MASLD reported that none of the patients with positive ANA (17% of the cohort) exhibited histological features of AIH or had higher rates of liver-related complications compared with those with negative Ab, even after a median follow-up of 106 months.[19] In contrast, our study is among the first to demonstrate an independent association between Ab positivity and increased risk of liver-related outcomes and mortality. These differences could be attributed to the higher baseline prevalence of advanced liver disease in our cohort (45%) compared with the 23% reported in the study by Younes *et al.*,[19] making our population more suitable for evaluating liver-related outcomes. Moreover, Younes *et al.*[19] only assessed ANA, which is the most extensively studied autoantibody in the literature, but it is non-specific and can be found in various systemic diseases and even in the normal population.[40] In our study, we also analyzed ASMA, a liver-specific antibody, and we found that the presence of ASMA was associated with both liver-related outcomes and survival.

Surprisingly, in our study, Ab positivity did not translate into a higher prevalence of histological features suggestive of AIH. Conversely, patients with histological features of AIH did not exhibit a higher prevalence of positive Ab. In the literature, only a few studies with fewer than 50 patients have addressed and correlated histological and serological autoimmune findings and have achieved similar results.[18,19] Therefore, our results suggest that Ab in patients with MASLD may not reflect histological AIH characteristics but could instead be an indirect sign of systemic chronic inflammation and may have their own toxicity mechanisms to promote disease progression.[41]

Interestingly, previous reports have shown that ANA positivity in non-immune diseases could be linked to worse prognosis. For example, in a large cohort of 1,143 obese patients, ANA positivity was associated with a higher prevalence of cardiovascular disease.[42] It has been proposed that the presence of positive Ab in patients with obesity may be related to the fact that the dysfunctional adipose tissue releases multiple systemic inflammatory mediators that contribute to a loss of tolerance to self-antigens and the generation of Ab.[43,44]

Similarly, in a population-based cohort from the Dallas Heart Study involving 3,488 participants, positive ANA was associated with inflammatory mediators and biomarkers of vascular activation, but not with traditional cardiovascular risk factors.[40] Although the underlying pathophysiology remains unclear, these findings suggest that cardiovascular risk associated with ANA may involve pathways distinct from traditional risk factors, including dysregulation of endothelial cells and the immune system, leading to subclinical atherosclerosis.[45,46] In our cohort, the predominant cause of death was extrahepatic, such as infectious, cardiovascular, and cerebrovascular events. The retrospective nature of the study and the lack of measurement of inflammatory markers (such as C-reactive protein and cytokines) limit the evaluation of this theory in our cohort. Therefore, longer prospective studies with better assessment of systemic inflammation and a larger number of events are necessary to address this issue and draw strong conclusions.

Nevertheless, the observed association of both ANA and ASMA with worse outcomes in our cohort suggests that they may serve as markers of subclinical inflammation and help identify a subgroup of patients at higher risk for disease progression and poorer prognosis. However, whether the presence of positive Ab in MASLD reflects peripheral B-cell activation and a subsequent cascade of adaptive immune responses cannot be determined from our study and should be explored in future studies. Interestingly, although evidence remains limited, both B- and T-cell-mediated autoimmunity and immune dysregulation have been proposed as key mechanisms in MASLD pathogenesis.[47] A recent study demonstrated that the absence of specific B-cell populations or impaired antibody secretion (IgMi mice) protects against hepatic steatosis, inflammation, and fibrosis in an MASLD mouse model.[48] Moreover, the finding that Ab-covering hepatocytes can trigger antibody-dependent cytotoxicity in other chronic liver diseases[41] makes it plausible that a similar mechanism could occur in MASLD. However, this hypothesis has yet to be demonstrated.

Our study has some limitations that should be mentioned. First, it was a retrospective study based on tertiary centers, which could favor an overrepresentation of patients with available antibodies. Of those, only 460 (70%) patients in the original MASLD cohort with at least 1-year follow-up had Ab measurements and could therefore be included for the analysis. This is certainly a selection bias, and it could be speculated that patients with Ab determination had worse liver inflammation at baseline. We compared transaminase levels in individuals with available Ab with those without and found that transaminases were not significantly different, suggesting that the excluded group likely does not experience more severe inflammation. However, this inclusion bias can only be overcome by prospective evaluation of Ab in all patients with MASLD, which we are currently performing. Second, there was no longitudinal assessment of Ab and only a one-time evaluation at inclusion. Whether changes in Ab, either neutralization or new-onset antibody positivity, may have a meaningful impact on MASLD progression could not be analyzed and should be evaluated in the future. Third, although our study represents one of the largest histological cohorts of patients with MASLD, it is limited by the relatively low number of liver-related events and a median follow-up of only 4 years. Nonetheless, our cohort included a higher proportion of patients with advanced liver disease (45%) than those in previously published studies. Despite the limited number of events, the presence of positive Ab was significantly associated with worse clinical outcomes, underscoring the potential prognostic value of Ab in this population. Finally, it is worth mentioning that although this was a retrospective study, HEPAmet is a well-designed multicenter, prospectively monitored registry with homogeneous and clearly recorded data, which minimizes the unavailability of relevant clinical information.

In conclusion, our study demonstrates that the presence of positive Ab in patients with MASLD is independently associated with an increased risk of liver-related outcomes and poorer survival, irrespective of histological autoimmune features. Although the underlying pathophysiological mechanisms driving this association remain uncertain, these findings suggest that Ab could serve as a potential inflammatory biomarker for predicting disease severity and progression. To confirm this hypothesis, prospective studies should be designed to assess whether autoimmune features lead to more aggressive liver disease and to focus on the implied immune mechanisms. Our findings suggest that the presence of serological autoimmune features in patients with MASLD should provide a warning for close monitoring.

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Abbreviations

Ab, autoantibodies; AEEH, Association for the Study of the Liver; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ALP, alkaline phosphatase; APRI, AST-to-platelet ratio index; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; ERN RARE-LIVER, European Reference Network on Hepatological Diseases; Gg, gamma globulins; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HEp2, human epithelioma-2; HR, hazard ratio; IgG, immunoglobulin G; INR, international normalized ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MVA, multivariate analysis; NAS, non-alcoholic fatty liver disease score; OR, odds ratio; PNPLA, mammalian patatin-like phospholipase domain–containing proteins; T2DM, type 2 diabetes; ULN, upper limit of normal.

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Conflicts of interest

JMP reports having received consulting fees from Boehringer Ingelheim, MSD, and Novo Nordisk; speaking fees from Madrigal, Gilead, Intercept, and Novo Nordisk; and travel expenses from Gilead, Rubió, Pfizer, Astellas, MSD, CUBICIN, and Novo Nordisk. He also received educational and research support from Madrigal, Boehringer Ingelheim, Gilead, Pfizer, Astellas, Accelerate, Novartis, Abbvie, ViiV, and MSD. MCL reports received advisory fees from Advanz, Gilead, GSK, Ipsen, and Falk; lecture fees from Advanz, Gilead, Ipsen, and Cymabay; travel grants from Advanz and Ipsen; and a research grant from Mirum. IG reports receiving consulting fees and speeking feed from Boehringer Ingelheim and a research grant from Pfizer (PFIZER NASH-ASPIRE). The rest of the authors declare no conflicts of interest with respect to this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceived the idea for the study, designed the study, accessed and verified the data, undertook statistical analyses, interpreted the data, drafted and revised the manuscript, and were responsible for the decision to submit the manuscript: AS, MCL, IG. Acquired and interpreted the clinical data: PI, RMM, AJM, CEM, CJG, MP, CS, HHE, NJ. Reviewed and interpreted the liver biopsies: AD, MTA, CFA, CP, CP, AFG, ZC. Interpreted the data: JMP, SMM, JC, AA, MC, IO, PA, JGG, AJ, EP, MC, RN, MPG, PG, NF. Contributed to manuscript revision: AD, MTA, CFA, CP, AFG, ZC, PI, RMM, AJM, CEM, CJG, MP, CS, HHE, NJ, JMP, SMM, JC, AA, MC, IO, PA, JGG, AJ, EP, MC, RN, MPG, PG, NF.

Data availability statement

The data that support the findings of this study are available from the corresponding author (IG) upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101470.

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Author names in bold designate shared co-first authorship

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