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Original Article

Extrahepatic Autoimmune Diseases in Autoimmune Hepatitis: Their Prevalence, Predictors, and Influence on Early Treatment Outcomes

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Abstract

Background and Aims: Autoimmune hepatitis (AIH) frequently coexists with extrahepatic autoimmune diseases (EADs), but their prevalence, characteristics, progression, and treatment effect in the Han Chinese population remain unclear. This study aimed to evaluate the prevalence and spectrum of EADs and to assess their clinical features, disease course, and treatment outcomes in Han Chinese patients with AIH. ***Methods:*** Medical records of 371 Han Chinese patients with AIH (diagnosed from March 2016 to October 2023) were retrospectively analyzed. ***Results:*** Among the 371 AIH patients, 304 (81.94%) were female, with a median age of 52.5 years (interquartile range, 46.0–61.0). A total of 23.98% (89/371) had at least one EAD, including 27.06% (82/303) in type 1 AIH, 11.11% (7/63) in antibody-negative AIH, and none in type 2. A single EAD was the most common (20.21%, 75/371). The most frequent EADs were Sjogren's syndrome (8.63%) and autoimmune thyroid disease (8.36%). Compared with patients without EADs, those with EADs had lower alanine aminotransferase, red blood cell, and hemoglobin levels, but higher aspartate aminotransferase/alanine aminotransferase ratio and antinuclear antibody (ANA) positivity (all $P < 0.05$). ANA positivity was independently associated with EADs (odds ratio = 2.209, 95% confidence interval = 1.242–3.927, $P = 0.007$). After three months of treatment, the complete biochemical response rate was lower in the EADs group than in the non-EADs group (40.0% vs. 55.3%, $P = 0.024$), whereas no significant differences were observed at 6, 12, 24, or 36 months (all $P > 0.05$). ***Conclusions:*** In the Han Chinese population, 23.98% of AIH patients had EADs, with Sjogren's syndrome and autoimmune thyroid disease being the most common. ANA positivity was a significant risk factor for EADs. EAD patients had a poorer initial treatment response at three months, but comparable long-term biochemical response from six months.

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Introduction

Autoimmune hepatitis (AIH) is a combination of immune, genetic, and environmental factors that result in an abnormal attack on the immune system on hepatocytes.[1,2] The condition can present as acute or chronic, which, if left untreated, can progress to cirrhosis, liver failure, and even hepatocellular carcinoma. The condition is characterized by elevated aminotransferase and immunoglobulin G (IgG) levels, serum autoantibody positivity, as well as typical histological features, such as lymphoid and plasma cell infiltration and moderate-to-severe interface hepatitis.[3] It is evident that a considerable number of extrahepatic autoimmune diseases (EADs) exhibit genetic (HLA class I B8 and HLA class II DR3, DR4, and DR52a) and immune susceptibility characteristics analogous to those of AIH.[4] Consequently, these diseases are regarded as being associated with AIH and have been incorporated into the original and revised diagnostic criteria established by the International Autoimmune Hepatitis Group (hereinafter referred to as IAIHG).[5] A number of studies have demonstrated that treatment strategies for coexisting autoimmune diseases exhibit both similarities and differences, necessitating a comprehensive approach to address both conditions. The lack of timely treatment may lead to progressive liver injury and, in some cases, necessitate liver transplantation. This highlights the importance of early diagnosis and management of AIH and associated rheumatic autoimmune diseases to prevent disease progression.

Keywords: Autoimmune hepatitis; Extrahepatic autoimmune diseases; Sjogren's syndrome; Autoimmune thyroiditis; Immunosuppression; Treatment outcome; Drug-induced autoimmune hepatitis.

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Research has demonstrated that 20–50% of patients diagnosed with AIH also exhibit comorbidity with other autoimmune diseases affecting diverse organ systems, including autoimmune thyroid disease (AITD), autoimmune connective tissue diseases, inflammatory bowel disease (IBD), glomerulonephritis, immune thrombocytopenic purpura, and a wide range of pulmonary, neurological, and endocrine system abnormalities.[6–8] The most commonly reported associations between primary biliary cirrhosis (PBC) and EADs include AITD, systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and IBD. EADs may precede or coexist with AIH and can also emerge years after the initial diagnosis of AIH. Studies have shown that the coexistence of EADs is more common among AIH patients who are smooth muscle antibody-negative, female, or have a positive family history of autoimmune diseases. The presence of EADs has been reported to influence the clinical phenotype of AIH; however, the extent to which it modifies disease progression or affects long-term clinical outcomes remains uncertain. A study from the Netherlands demonstrated that the combination of other autoimmune diseases was an independent risk factor for early relapse in patients with AIH following the discontinuation of immunosuppressive drugs.[9] Nevertheless, the extant literature on this subject is limited, with the majority of studies being case reports or conducted in other races. The present state of knowledge regarding the incidence of combined EADs and their biochemical, immunological, and pathological characteristics, as well as the response to treatment, remains incomplete. Furthermore, the limited number of studies conducted in the Han Chinese population is of particular concern. This study aimed to investigate the incidence of concomitant EADs among AIH patients in the Han population and to characterize their clinical, pathological, and therapeutic features, with the goal of providing clinical insights and improving the prognosis of patients with AIH.

Methods

Study population

This retrospective study was conducted to analyze the clinical data of patients diagnosed with AIH who were hospitalized at The Second Affiliated Hospital of Nanjing University of Chinese Medicine from March 2016 to October 2023. The study was approved by the Medical Ethics Committee of the Second Hospital of Nanjing (2024-LS-Ky-069; August 13, 2024).

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed according to the 1999 revised IAIHG criteria.[5,10] Patients with characteristics of drug-induced autoimmune hepatitis (DIAIH) were evaluated using both the simplified AIH score proposed by Hennes (score ≥ 7) and the Roussel Uclaf Causality Assessment Method (RUCAM) (score < 6).[11,12] EADs were defined as autoimmune disorders occurring concurrently with AIH and included one or more of the following: AITD, hyperthyroidism, rheumatoid arthritis, vitiligo, psoriasis, SLE, systemic sclerosis, antiphospholipid syndrome, autoimmune thrombocytopenia, autoimmune hemolytic anemia, interstitial pneumonia, type 1 diabetes, SS, and IBD. All of these diseases were diagnosed on the basis of internationally recognized criteria,[13–18] when available.

Exclusion criteria: (1) Patients with positive markers for any of the hepatitis viruses; (2) Pregnancy and lactation; (3) Overlap syndrome, primary biliary cholangitis, primary sclerosing cholangitis; (4) Incomplete hospitalization data; (5) Long history of heavy alcohol consumption; (6) Patients with suspected drug-induced liver injury were defined as those with a RUCAM score ≥ 6.

Laboratory indicators and liver biopsy pathology

Blood routine was performed using a blood cell analyzer (Model BC-3000; Maiduan Biomedical Electronics Co., Ltd., Shenzhen, China), while biochemical indicators were detected using an automatic biochemical analyzer (Model AU2700; Olympus Corporation, Tokyo, Japan). All patients selected for liver puncture biopsy were biopsied using an automatic adjustable biopsy gun (Bard Peripheral Vascular, Inc., Tempe, Arizona, USA), and liver puncture biopsy was performed using 16G puncture needles under ultrasonography guidance. The liver tissue obtained had to be over 2.0 cm in length, and a minimum of 11 portal tracts was required. Following fixation, the embedding of the liver tissue was conducted, after which serial sections were subjected to HE, Masson, and reticulin staining, or special stains according to the specific conditions. Two pathologists independently reviewed the sections under a light microscope for diagnosis, as well as grading of inflammatory activity and fibrosis staging. The Scheuer scoring system was utilized for grading inflammation (G) and staging fibrosis (S) in liver tissue.[19]

Treatment and biochemical response

All patients received standard non-specific immunosuppressive therapy according to the guidelines,[1] including predniso(lo)ne combined with azathioprine, predniso(lo)ne combined with mycophenolate mofetil, or predniso(lo)ne monotherapy. Adjustments to the dose were made according to the results of follow-up observations, in accordance with the principle of individualization. Meanwhile, patients with EADs received appropriate EAD treatment according to their guidelines.[13–18] Throughout the treatment period, patients were meticulously monitored for the occurrence of adverse reactions, including but not limited to osteoporosis, infection, hypertension, and cataracts. Furthermore, complete blood count, liver and renal function tests, and electrolyte levels were closely monitored. In addition, abdominal ultrasonography of the liver, gallbladder, and spleen was performed to identify any potential abnormalities.

The follow-up period began at the time of AIH diagnosis and initiation of treatment, with the final follow-up conducted in October 2024. The primary objective of follow-up was to evaluate treatment outcomes and disease progression, including the occurrence of newly developed cirrhosis, ascites, esophageal and gastric varices, variceal bleeding, hepatocellular carcinoma, and other related complications.

Complete biochemical response was defined as the normalization of serum aminotransferases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and IgG levels. Insufficient response was defined as failure to achieve a complete biochemical response. Non-response was defined as a decrease in serum transaminases of less than 50% within four weeks after initiation of treatment.

Statistical analyses

The analysis was conducted using SPSS 26.0 software. Continuous variables that conformed to a normal distribution were expressed as the mean ± standard deviation. Continuous variables that exhibited a skewed distribution were expressed as the median (P25, P75). Categorical variables were expressed as actual numbers and percentages. The Mann–Whitney test was employed to assess continuous variables. Intergroup comparisons of categorical variables were performed using the χ^2 test or Fisher's exact probability test.

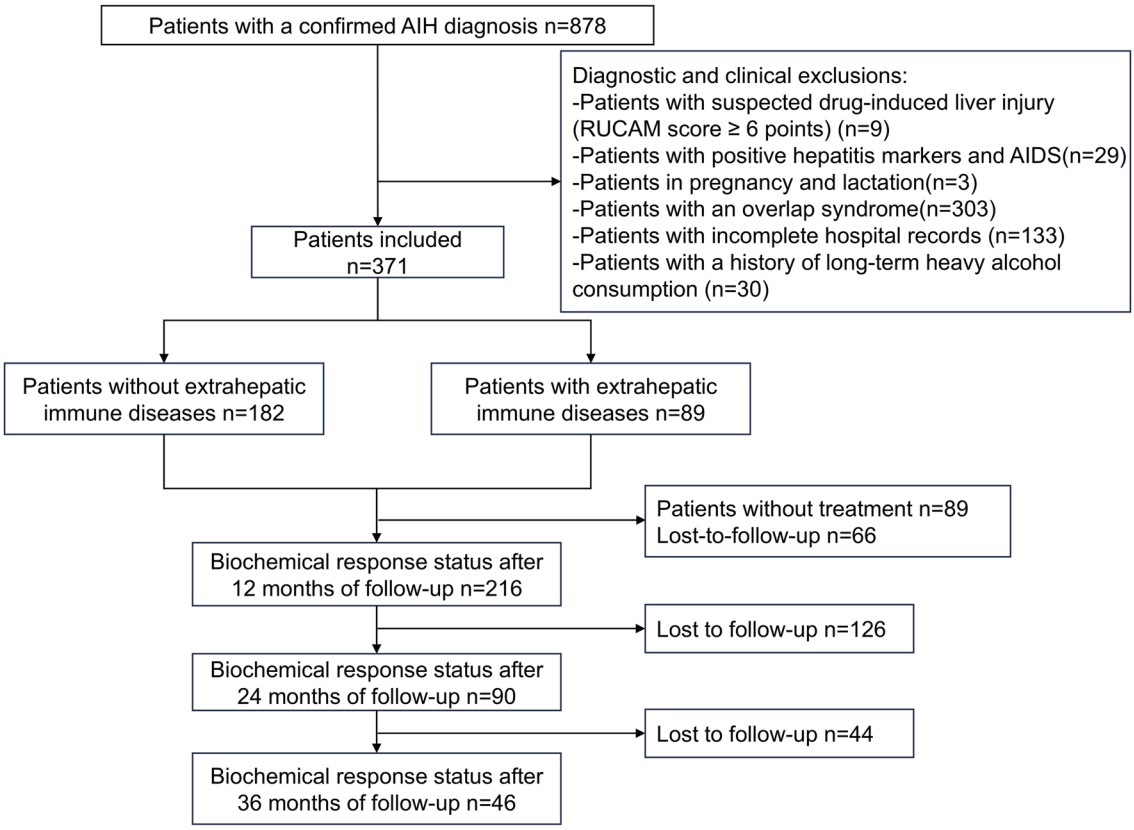

Fig. 1. Study design flowchart. AIH, autoimmune hepatitis; RUCAM, Roussel Uclaf Causality Assessment Method; AIDS, acquired immune deficiency syndrome.

Binary logistic regression analysis was used to determine the association between baseline clinical and biochemical variables and the occurrence of EADs. A *P*-value < 0.05 was considered statistically significant.

Results

Demographic characteristics of AIH patients and frequency of extrahepatic immunological diseases

Among the 371 patients with AIH (Fig. 1), 303 (81.67%) had type 1 AIH, 5 (1.35%) had type 2 AIH, and 63 (16.98%) were antibody-negative. Overall, 89 patients (23.98%) had at least one EAD, including 82 (27.06%) with type 1 AIH, 7 (11.11%) with antibody-negative AIH, and none with type 2 AIH. Based on the number of EADs, a single EAD was most common (20.21%, 75/371), followed by two EADs (3.23%, 12/371), while three or more EADs were rare (0.53%, 2/371) (Fig. 2). Regarding specific types of EADs, SS was the most prevalent (8.63%), followed by AITD (8.36%), rheumatoid arthritis (1.89%), hyperthyroidism (1.62%), and SLE, systemic sclerosis, and interstitial pneumonitis (each 1.08%). The prevalence of EADs did not differ significantly among patients aged <40 years (22.41%, 13/58), 40–60 years (25.35%, 55/217), and >60 years (21.88%, 21/96) (χ^2 = 0.53, *P* > 0.05). Similarly, the distribution of both AITD and SS showed no significant differences among age groups (<40 years, 40–60 years, and >60 years; *P* > 0.05) (Table 1).

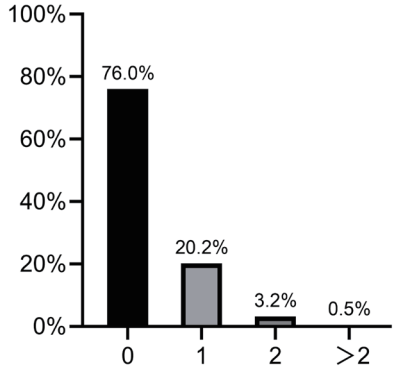

Fig. 2. Distribution of the number of extrahepatic autoimmune diseases among AIH patients. AIH, autoimmune hepatitis.

Comparison of demographics, laboratory tests, and pathology between AIH patients without and with EADs

There were no statistically significant differences in terms of age, gender, total bilirubin, AST, alkaline phosphatase, gamma-glutamyl transferase, albumin, globulin, creatinine, international normalized ratio, white blood cell, platelet, IgG, immunoglobulin M, smooth muscle antibody, anti-actin antibody, antimitochondrial antibody, anti-sp100, anti-gp210, anti-liver/cytosol antibody type 1, and soluble liver antigen/liver-pancreas antibodies between patients with and without EADs (all *P* > 0.05). In the EAD group, ALT, red blood cell (RBC) count, and hemoglobin (Hb) levels were significantly lower than those in the non-EAD group (*P* < 0.05). Conversely, the AST/ALT ratio and antinuclear antibody (ANA)

Table 1. Frequency of EADs among AIH patients as stratified by age (n = 371)

EADs, n (%)	Total (n = 371)	<40y (n = 58)	40–60y (n = 217)	>60y (n = 96)	*P*
Autoimmune thyroid diseases	37 (9.97)	1 (1.72)	27 (12.44)	9 (9.38)	–
Autoimmune thyroiditis	31 (8.36)	5 (8.62)	18 (8.30)	8 (8.33)	0.997
Hyperthyroidism	6 (1.62)	0 (0.00)	5 (2.30)	1 (1.04)	–
Autoimmune connective tissue disorder	56 (15.09)	6 (10.34)	34 (15.67)	16 (16.67)	–
Sjogren's syndrome	32 (8.63)	1 (1.72)	21 (9.68)	10 (10.42)	0.122
Rheumatoid arthritis	7 (1.89)	2 (3.45)	5 (2.30)	0 (0.00)	–
Systemic lupus erythematosus	4 (1.08)	1 (1.72)	2 (0.92)	1 (1.04)	–
Systemic sclerosis	4 (1.08)	0 (0.00)	2 (0.92)	2 (2.08)	–
Psoriasis	3 (0.81)	1 (1.72)	1 (0.46)	1 (1.04)	–
Vitiligo	2 (0.54)	1 (1.72)	0 (0.00)	1 (1.04)	–
Antiphospholipid syndrome	2 (0.54)	0 (0.00)	1 (0.46)	1 (1.04)	–
Autoimmune hematological disease	6 (1.62)	2 (3.45)	4 (1.84)	0 (0.00)	–
Immune thrombocytopenia	3 (0.81)	1 (1.72)	2 (0.92)	0 (0.00)	–
Autoimmune hemolytic anemia	3 (0.81)	1 (1.72)	2 (0.92)	0 (0.00)	–
Lung disorders	4 (1.08)	1 (1.72)	1 (0.46)	2 (2.08)	–
Interstitial pneumonia	4 (1.08)	0 (0.00)	2 (0.92)	2 (2.08)	–
Renal disease	1 (0.27)	1 (1.72)	0 (0.00)	0 (0.00)	–
Autoimmune gastrointestinal disease	2 (0.54)	0 (0.00)	2 (0.92)	0 (0.00)	–
Inflammatory bowel disease	2 (0.54)	0 (0.00)	2 (0.92)	0 (0.00)	–
Type 1 diabetes mellitus	1 (0.27)	0 (0.00)	1 (0.46)	0 (0.00)	–

AIH, autoimmune hepatitis; EADs, extrahepatic autoimmune diseases.

positivity rate were significantly higher in the EAD group ($P < 0.001$) (Table 2). No significant differences were observed in the degree of hepatic fibrosis or inflammation between the two groups ($P > 0.05$).

Risk factors associated with the development of EADs in AIH

Factors showing significant differences in baseline characteristics between AIH patients without and with EADs ($P < 0.05$) were included in multifactorial binary logistic regression analysis. ANA positivity at baseline (odds ratio = 2.209, 95% confidence interval = 1.242–3.927, $P = 0.007$) was significantly associated with the occurrence of EADs in AIH patients, whereas baseline ALT, AST/ALT, RBC, and Hb were not identified as independent risk factors for the occurrence of EADs (all $P > 0.05$) (Fig. 3).

Treatments and follow-ups

A total of 89 cases were not treated at our hospital, while 216 cases received treatment and were followed up. Following a three-month treatment period, the rate of complete biochemical response was higher in the AIH without EADs group than in the AIH with EADs group (55.3% vs. 40.0%, $P = 0.024$). However, there was no difference between the two groups at 6, 12, 24, or 36 months of treatment ($P > 0.05$) (Table 3).

The average duration of follow-up was 30.65 months (range, 3–60). No new cases of cirrhotic ascites, ruptured esophagogastric variceal bleeding, or hepatic encephalopathy were observed, but hepatocellular carcinoma developed in five cases (1.35%). Pretreatment complications were observed in 31 out of 371 patients (8.36%), including ascites (31/371, 8.36%), hepatic encephalopathy (7/371, 1.89%), bleeding from esophagogastric fundal varices (5/371, 1.35%), and spontaneous bacterial peritonitis (2/371, 0.54%) (Table 4).

The study observed a range of facial changes, including weight gain, acne, round face, purple lines, alopecia, buffalo hump, and facial hirsutism, in 85% of patients following six months of glucocorticoid treatment. The following severe adverse effects were observed: diabetes mellitus in 19.91% of cases, hypertension in 29.17%, fracture in 1.39%, and lung infection in 2.78%. No cases of psychosis, pancreatitis, or malignant tumors in other parts of the body were observed. Leukopenia was observed in 1.35% (n = 5) of cases following azathioprine treatment (Table 4).

Discussion

The liver, being the largest lymphoid organ involved in immune response and maintenance of immune tolerance, is also one of the target organs for autoimmune diseases.[20] The present study revealed that 64.15% of the subjects were above 50 years of age, and 81.94% were female. These demographics are consistent with those reported in other studies,[21–23] which have indicated that immune disorders are more prevalent in the female population. This phenomenon has been attributed to the influence of sex hormones, specifically estrogens and luteinizing hormone, as previously demonstrated in a separate study.[24] As demonstrated by several recent studies,[25,26] the presence of the X chromosome has been identified as a significant contributing factor to the risk

Table 2. Comparison of demographics, laboratory tests, and pathology between AIH patients with and without EADs

	AIH without EADs (n = 282)	AIH with EADs (n = 89)	*P*
Age at diagnosis (years)	53.00 (47.00, 61.00)	54.00 (46.00, 59.00)	0.521
Gender, male	57 (20%)	10 (11%)	0.059
TBIL (μmol/L)	25.75 (14.53, 59.90)	25.40 (12.80, 64.60)	0.337
AST (U/L)	93.45 (42.20, 258.28)	78.30 (34.80, 190.00)	0.166
ALT (U/L)	104.70 (36.35, 320.43)	59.30 (26.00, 154.80)	**0.005**
AST/ALT	0.95 (0.62, 1.44)	1.25 (0.92, 1.74)	**0.000**
ALP (U/L)	118.95 (88.25, 168.00)	110.10 (75.30, 164.00)	0.198
GGT (U/L)	92.80 (47.55, 179.38)	78.20 (34.00, 165.00)	0.182
ALB (g/L)	37.85 (33.13, 42.00)	36.70 (31.80, 41.60)	0.173
GLB (g/L)	30.00 (25.90, 35.18)	30.10 (26.00, 36.00)	0.861
Cr (μmol/L)	48.90 (17.60, 59.88)	44.00 (8.80, 60.00)	0.330
INR	1.13 (1.03, 1.27)	1.13 (1.05, 1.28)	0.620
RBC (10^{12}/L)	3.99 (3.59, 4.37)	3.95 (3.41, 4.23)	**0.008**
WBC (10^9/L)	4.84 (3.87, 5.94)	4.24 (3.29, 5.56)	0.079
PLT(10^9/L)	147.00 (97.00, 193.00)	136.00 (82.00, 171.00)	0.097
Hb (g/L)	123.00 (111.00, 135.00)	121.00 (99.00, 132.00)	**0.040**
IgG (g/L)	15.95 (12.30, 19.60)	16.30 (11.70, 21.30)	0.640
IgM (g/L)	1.40 (0.97, 2.06)	1.51 (1.08, 2.18)	0.130
ANA	203 (72.5%)	76 (87.36%)	**0.005**
SMA	41 (14.64%)	6 (7.06%)	0.067
AAA	3 (1.1%)	0 (0%)	0.590
AMA	10 (3.55%)	14 (15.73%)	0.251
Sp100	1 (0.4%)	1 (1.2%)	0.406
gp210	17 (6.1%)	2 (2.4%)	0.265
LC-1	5 (1.8%)	0 (0%)	0.352
SLA/LP	7 (2.5%)	2 (2.4%)	1.000
G			0.214
G1	0/199 (0%)	0/55 (0%)	
G2	57/199 (28.64%)	22/55 (40%)	
G3	117/199 (58.79%)	29/55 (52.73%)	
G4	25/199 (12.56%)	4/55 (7.27%)	
S			0.682
S1	37/199 (18.59%)	8/55 (14.55%)	
S2	91/199 (45.73%)	30/55 (54.55%)	
S3	39/199 (19.60%)	10/55 (18.18%)	
S4	32/199 (16.08%)	7/55 (12.73%)	

Values in bold are significant ($P < 0.05$). AIH, autoimmune hepatitis; EADs, extrahepatic autoimmune diseases; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALB, albumin; GLB, globulin; Cr, creatinine; INR, international normalized ratio; RBC, red blood cell; WBC, white blood cell; PLT, platelet; Hb, hemoglobin; IgG, immunoglobulin G; IgM, immunoglobulin M; ANA, antinuclear antibody; SMA, smooth muscle antibody; AAA, anti-actin antibody; AMA, anti-mitochondrial antibody; LC-1, liver cytosol type 1; SLA/LP, anti-soluble liver antigen/liver-pancreas antigen; G, grade, histology (severity of inflammation); S, stage, histology (fibrosis score).

of developing autoimmune diseases. The most common was type I AIH (81.67%), followed by antibody-negative AIH (16.98%), and type 2 AIH was the least common (1.35%). Type 2 AIH is relatively more prevalent among children, whereas our study primarily focused on adult patients. Notably, DIAIH often mimics AIH in both clinical phenotypes and serological features, which may lead to misclassification and confound the analysis of EADs in AIH patients.[12] To minimize this bias, our study excluded patients with a RUCAM score ≥ 6, which has been validated as a reliable tool for distinguish-

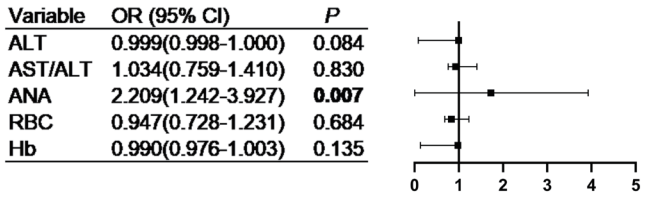

Fig. 3. Binary logistic regression analysis of risk factors for EADs. Values in bold are significant ($P < 0.05$). ALT, alanine aminotransferase; AST/ALT, aspartate aminotransferase to alanine aminotransferase ratio; ANA, antinuclear antibody; RBC, red blood cell; Hb, hemoglobin; OR, odds ratio; CI, confidence interval.

ing DIAIH from AIH.[27]

Our study showed that 23.98% of patients had at least one EAD, with a single EAD being the most common (20.21%), two EADs being the second most common (3.23%), and more than two EADs being the least common (0.53%). This prevalence was approximately the same as the 26% observed in a retrospective study in the Netherlands,[28] but lower than the 43.6% reported by Efe *et al*.[29] In our study, the most common EAD was SS (8.63%), followed by AITD (8.36%), contrary to a recent nationwide study in Japan in which AITD was the most common and SS (7.2%) was second. Some patients in our study were antimitochondrial antibody positive; however, alkaline phosphatase, gamma-glutamyl transferase, and liver histopathology did not show any PBC-related changes. Thus, these patients were not diagnosed with overlap PBC, although it is possible that they were in a pre-PBC stage, which warrants further follow-up. The high prevalence of AITD can be explained by HLA-dependent genetic factors, cross-reactivity of anti-thyroid autoantibodies with other tissue antigens, and autoreactive T-cells or co-epithelial antigens as an underlying pathophysiological mechanism.[30] The incidence of autoimmune hypothyroidism has been reported to increase with age in elderly Italian AIH patients[31]; however, our study did not observe this phenomenon, possibly due to ethnic or cohort differences. Hypothyroidism is more prevalent than hyperthyroidism, a finding consistent with several previous cohort studies.[8,32] In pediatric patients with AIH,[6,33] ulcerative colitis was the most common.

Studies have shown the prevalence of SLE among AIH patients to be 0.7–2.8%, compared to 1.08% in our study. In a retrospective analysis of 805 hospitalized SLE patients in Taiwan from 2014 to 2023,[34] only 5 (0.6%) had overlapping AIH; all were ASMA positive, and interfacial hepatitis was observed in the liver histopathology of all patients with SLE-AIH overlap, whereas only nonspecific abnormalities were found in the liver biopsy specimens of patients with lupus hepatitis. It was also reported that SLE-AIH overlap patients who failed CS/AZA therapy progressed to end-stage liver disease and required liver transplantation. In our study, a 14-year-old child underwent liver and renal biopsy, which confirmed AIH cirrhosis combined with SLE, and renal histopathology suggested III+IV lupus nephritis. Treatment with mycophenolate mofetil and tacrolimus resulted in recovery of liver function and recompensation of cirrhosis; however, proteinuria persisted and only resolved after the addition of the biologic agent belimumab, suggesting that treatment regimens need to be individualized to control coexisting hepatic and rheumatic autoimmunity in order to provide better management of this complex clinical situation.

In our study, ALT, RBC, and Hb levels were lower in the group with EADs compared to the group without EADs. It has been hypothesized that patients with EADs may experience earlier detection of liver abnormalities and consequently receive more timely or targeted treatment due to medical visits related to EADs. AIH and rheumatic autoimmune diseases share similar immunological features, including ANA positivity and abnormal immunoglobulin levels.[35] The elevated AST/ALT ratio observed in the cohort with EADs may be attributable to the indirect impact of such diseases on hepatocyte mitochondrial function. This alteration in mitochondrial function can be caused by changes in hepatic energy metabolism or levels of oxidative stress, resulting in the release of substantial quantities of AST from the mitochondria and cytoplasm.

Table 4. Complications and corticosteroid-related adverse effects during follow-up

Follow-up outcomes	n,%
Complications	
Hepatocellular carcinoma	5 (1.35)
Ascites	31 (8.36)
Hepatic encephalopathy	7 (1.89)
Esophagogastric variceal bleeding	5 (1.35)
Spontaneous bacterial peritonitis	2 (0.54)
Corticosteroid-related adverse effects	
Fracture (lumbar spine)	3 (1.39)
Osteoporosis	27 (12.5)
Pulmonary infection	6 (2.78)
Cataract	1 (0.46)
Vitamin D deficiency	3 (1.39)
Leukopenia	5 (1.35)
Diabetes mellitus	43 (19.91)
Hypertension	63 (29.17)

Data are presented as n (%). The average follow-up time was 30.65 months (range, 3–60).

Table 3. Comparison of treatment outcomes between AIH patients with and without EADs

Follow-up duration	n	AIH without EADs (CBR/IR/NR)	AIH with EADs (CBR/IR/NR)	*P*
3 months	216	88/70/1	26/36/3	0.024
6 months	216	103/47/1	43/19/3	0.141
12 months	216	118/33/0	49/15/1	0.619
24 months	90	57/6/0	25/2/0	0.748
36 months	46	27/2/0	15/2/0	0.576

AIH, autoimmune hepatitis; EADs, extrahepatic autoimmune diseases; CBR, complete biochemical response; IR, insufficient response; NR, non-response.

Research has indicated that patients with persistently high ratios are more prone to rapid progression of liver fibrosis during follow-up.[36]

There was no significant difference in the degree of inflammation and hepatic fibrosis between the two groups, indicating that patients with EADs did not have increased disease progression. Furthermore, patients with EADs exhibited milder grades of inflammation and fibrosis, which may be related to the fact that some of the patients were seen in other departments for their EADs and were given appropriate treatment (e.g., predniso(lo)ne), thereby controlling the inflammation in the liver. In the study conducted by Wong *et al*.,[20] it was observed that in half of the patients, the diagnosis of EADs was made subsequent to the clarification of the diagnosis of AIH. Furthermore, it was noted that AIH patients with EADs demonstrated a higher grade of liver fibrosis. The study hypothesizes that the degree of inflammation and fibrosis in the liver may be related to the timing of the diagnosis of EADs.

The study demonstrated that AIH patients with EADs exhibited a lower percentage of complete responses at the three-month treatment stage. This finding is consistent with the results of a Danish study,[19] which may be attributable to the impact of EADs on the immune status of AIH patients or interference of EADs with the effectiveness of treatment. However, no differences were observed between the two groups after six months of treatment, suggesting that immunosuppressive treatments are more effective in controlling hepatic inflammation. Nevertheless, patients with comorbidities of SLE and rheumatoid arthritis require additional treatments to manage other immune diseases.

The mean duration of follow-up was 30.65 months. No new complications such as cirrhosis, ascites, esophagogastric variceal rupture, bleeding, or hepatic encephalopathy were observed. However, hepatocellular carcinoma developed in five cases (1.35%). Pre-treatment complications such as ascites (8.36%), hepatic encephalopathy (1.89%), esophagogastric fundal variceal hemorrhage (1.35%), and spontaneous bacterial peritonitis (0.54%) still occurred. This finding suggests the necessity for ongoing treatment and monitoring of complications in the decompensated phase of cirrhosis. In our study, the incidence of leukopenia following azathioprine treatment was 1.35%, which was significantly lower than the reported incidence of hematocrit (46%) and severe hematological abnormalities (6%) in azathioprine treatment of AIH.[37] This discrepancy may be explained by the routine testing for *TPMT* and *NUDT15* gene variants before azathioprine initiation, which allowed for the identification and exclusion of patients at risk for leukopenia. The incidence of diabetes mellitus at follow-up was 19.91%, which was lower than the figures reported in other studies.[38] Furthermore, the fracture incidence of 1.39% was lower than the 5–15% recorded in long-term treatment cohorts (≥12 months), which may be attributable to monitoring of bone mineral density with earlier intervention.

Our study has several limitations. First, the data were obtained from a single center and retrospective research, which inherently introduces limitations in data completeness and potential selection bias. Second, although the number of EADs was relatively large, some individual diseases had very few cases, making it difficult to assess disease severity or perform meaningful comparisons between AIH and specific EADs. The paucity of type 2 AIH cases also hindered detailed subgroup analyses of its clinical features and associations with particular EADs, potentially obscuring unique characteristics of this subtype. Third, this study exclusively included patients of Han Chinese ethnicity, which helped minimize potential confounding from population stratification but limits the generalizability of our findings to other ethnic groups.

Conclusions

EADs are frequently seen in patients with AIH, with SS and AITD being the most prevalent. ANA positivity was identified as a risk factor for the occurrence of EADs. Patients with EADs demonstrated a poorer early treatment response but achieved comparable therapeutic outcomes after six months of therapy. These findings underscore the importance of routine EADs screening in AIH clinical evaluation, as well as tailored monitoring of early treatment efficacy to optimize patient management.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (QFX, YFY), acquisition of data (YYM, WHZ), analysis and interpretation of data (KYO, CSY, YYM), chart preparation and table construction (JNC, WHZ, YYM), drafting of the manuscript (YYM), critical revision of the manuscript for important intellectual content (QFX, YFY), administrative, technical, or material support (BL), and study supervision (QFX). All authors made substantial contributions to this study and approved the final version of the manuscript.

Ethical statement

The study protocol was approved by the Medical Ethics Committee of the Second Hospital of Nanjing (2024-LS-Ky-069; August 13, 2024) and was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained.

Data sharing statement

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

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