Autoimmune Hepatitis in the Asia-Pacific Area

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Abstract

Autoimmune hepatitis (AIH) has been considered as a relatively rare immunological liver disease, especially in the Asia-Pacific area. Although the diagnosis criteria and immunosuppressive treatment regimens have been established, there are still some challenges. According to the different presentations, the personalized management of patients who suffer from this disease, including those with chronic or acute severe onset, the autoantibody-negative phenotype and cirrhosis are necessarily descriptive. Each subgroup of patients should receive an individualized therapy. Here, we review the recent studies in autoimmune hepatitis, mainly focusing on the epidemiology and genetics, personalized diagnostics, individualized treatment strategies, special subgroups and outcomes. Most of the research in the literature is based on Japanese and Chinese populations.

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Introduction

Autoimmune hepatitis (AIH) was first reported in the early 1950s by the Swedish physician Jan Waldenström, who described a cohort of young women with chronic fluctuating hepatitis accompanied by hypergammaglobulinemia and extra-hepatic manifestations.1 In the 1990s, the comprehensive diagnostic criteria and revised criteria for research purposes were put forward by the International Autoimmune Hepatitis Group (IAIHG).2,3 The simplified scoring system, which is easier to use in routine clinical practice, was proposed in 2008, and subsequently validated in variant ethnic groups, including Chinese and Japanese populations.4–9 Although most of the previous AIH studies were performed in Europe and Northern America, more and more investigations from eastern countries have been reported in the past 10 years.10 In this review, we will focus on the present status of AIH in the Asia-Pacific area.

Epidemiology, natural history and genetics of AIH

In the Asia-Pacific area, AIH incidence ranges from 0.67 (southern Israel) to 2.0 (Canterbury, New Zealand) per 100000 people, and its prevalence ranges from 4.0 (Singapore) to 24.5 (Canterbury, New Zealand) per 100000 people (Table 1).11–16 Survival rates reported from these studies are listed in Table 1. The development of hepatocellular carcinoma (HCC) is strictly associated with long-standing cirrhotic AIH patients.17 Several studies from Japan, China, Iran, Israel and New Zealand have shown that the long-term survival in AIH is satisfactory and have identified the occurrence rate of HCC in AIH population as ranging from 3.3% to 5.1% (Tables 1 and 2).18–23

In 2012, the Japanese National Hospital Organization observed a large AIH cohort, which showed the 15-year survival rate to be 89.3% and 3.6% (7/193) of patients who developed HCC during follow-up. Cirrhosis was a particular risk factor for HCC (hazard ratio: 11.47, p = 0.005). Male sex was also related to the risk for HCC in this population (p = 0.033).18 Similarly, Hino-Arinaga et al.19 revealed that cirrhosis at diagnosis (odds ratio: 4.08, p = 0.0138) and abnormal alanine aminotransferase (ALT) (odds ratio: 3.66, p = 0.0236) at final follow-up were related to HCC. Cirrhotic patients are recommended to be closely monitored by abdominal ultrasonography as well as by detection of serum tumor markers for HCC.

AIH is a polygenic disease, and human leukocyte antigens (HLAs) are the most important genetic risk factors correlated to AIH. The genetic susceptibility maps to the DRB1 region on chromosome 6p21.3. Among European and North American patients with type I AIH, the dominant susceptible gene is HLA-DR3 (DRB1*0301) and -DR4 (DRB1*0401).1,2 HLA-DR3 patients have a higher risk for liver exhaustion and are younger than HLA-DR4 patients.24 HLA-DR4 (DRB1*0405) is more common in Chinese and Japanese case series, with the frequency ranging from 35.1% to 71.6%.22,25–27 It is related to concurrent immune diseases, treatment response and a beneficial outcome.28,29 HLA-DR14 was also related to excellent biochemical response in a Japanese population.27 However, Furumoto et al.28 thoroughly examined the implications of HLA-DR4 and did not find that the treatment efficacy depended on HLA-DR antigens in Japanese AIH patients. A study from Taiwan showed that the frequency of DR4 in AIH patients was only 36%.30 In Thailand, HLA-DRB1*0301 (odds ratio: 48–56
3.92, $p = 0.021$) and HLA-DQA1*0101 (odds ratio: 2.31, $p = 0.019$) were significantly associated with AIH when compared to controls.\textsuperscript{33}

HLA-DRB1*1501 (40%), HLA-DRB1*14 (30%), HLA-DRB1*0301 (20%) and HLA-DRB1*1301 (15%) were increased in type I AIH patients from western India.\textsuperscript{34} Recently, another study indicated that HLA-DRB1*04 (odds ratio: 3.292, $p = 0.008$) and DRB1*08 (odds ratio: 10.5, $p = 0.027$) were significantly associated with type I AIH in the north Indian population. In the same cohort, patients with type II AIH were found to be significantly associated with HLA-B1*14 (odds ratio: 3.5, $p = 0.047$).\textsuperscript{35}

Hassan et al.\textsuperscript{36} reported a genetic association of HLA DR6, along with its subtypes HLA-DRB1*14 and HLA-DRB1*13, in Pakistan patients with AIH. Moreover, 84.4% of the patients in that study presented with cirrhosis, and a single patient developed HCC.

**Characteristics of AIH**

AIH has different clinical phenotypes and changeable presentations.\textsuperscript{37} The spectrum of initial manifestations ranges from asymptomatic or mild nonspecific symptoms to acute hepatic failure.\textsuperscript{38,39} Some patients may not present until the stage of decompensated cirrhosis. In general, the elevated concentrations of serum ALT, aspartate aminotransferase (AST) and immunoglobulin G (IgG)/gamma-globulin, and presence of autoantibodies are meaningful laboratory features.\textsuperscript{40} In addition, the interpretation of ALT, AST and IgG within the normal levels could predict the risk of relapse.\textsuperscript{41}

A typical histological characteristic of AIH is moderate or severe interface hepatitis (at the portal-parenchymal interface).\textsuperscript{42,43} Lymphocytes/plasma cells infiltrating portal and perportal areas, hepatocellular rosette formation and emperipolesis are also typical hallmarks of AIH. A recent study from our group showed that emperipolesis in AIH is related to higher levels of ALT/AST and more severe histological changes of necroinflammation.\textsuperscript{44}

**Diagnostic criteria of AIH**

AIH diagnosis is based on detection of clinical and biochemical features, including increased serum IgG/gamma-globulin levels, presence of autoantibodies, and typical or compatible histology. Exclusion of other diseases (e.g., non-alcoholic steatohepatitis (NASH), alcoholic liver disease, chronic viral hepatitis, drug-induced liver injury, and Wilson’s disease) is also important for diagnosing.\textsuperscript{17} The overall diagnostic accuracy of the revised IAIGHG criteria (1999)\textsuperscript{3} was 89.8%, but it is difficult to use in routine clinical investigation. The simplified IAIGHG diagnostic criteria (2008)\textsuperscript{4} has been proved as relatively reliable in classical subgroups of AIH patients, but is less reliable in atypical and pediatric-age patients.\textsuperscript{5-9,45}

Miyake et al.\textsuperscript{5} reported that the simplified criteria had lower sensitivity (85% vs. 100%) and higher specificity (99% vs. 93%) than the revised criteria following their study of 176 Japanese patients with AIH. In this cohort, 23% of cases showing acute presentation and 50% of cases with histological acute hepatitis were not diagnosed as AIH using the simplified criteria. Later, another study from Japan evaluated the diagnostic value of this new criteria in acute-onset AIH (29 non-severe type, 14 severe type and 12 fulminant type). Among the 55 total patients, 33 (60%) were diagnosed as “non-diagnostic” based on the simplified scoring system. Whereas, the revised criteria performed better in this atypical subgroup, with only 5 (9%) of acute-onset cases being missed by the AIH diagnosis.\textsuperscript{46}

One validating study from Korea showed the sensitivity and positive predictive values of the simplified criteria were 69.9% and 86.4% respectively for the diagnosis of “probable AIH”.\textsuperscript{47} In 2011, our group validated these two IAIGHG diagnostic criteria.
| Country or region | Scale of the cohort | Period | Survival rate or mortality | Poor outcomes | Risk factors |
|-------------------|---------------------|--------|---------------------------|---------------|-------------|
| Japan18           | n = 193 (nationwide multicenter cohort) | 1995–2008 | 10-year survival rate: 94.2% |
|                   |                     |        | 15-year survival rate: 89.3% |               | HCC: 7/193 (3.6%) |
|                   |                     |        | Mean follow-up: 8.0±4.5 years | Male sex     |                   |
| Japan19           | n = 180 (multicenter cohort) | 1978–2008 | Mean follow-up: 80.2±66.5 months |
|                   |                     |        | 10-year survival rate: 94% |               | HCC: 6/180 (3.3%) |
|                   |                     |        | 15-year survival rate: 89.3% |               |                   |
|                   |                     |        | Mean follow-up: 80.2±66.5 months | Male sex     |                   |
| Japan20           | n = 4869 (multicenter cohort) | 1990–2012 | 1-year survival rate: 69.8% |
|                   |                     |        | 3-year survival rate: 65.8% |               | HCC: 250/4869 (5.1%) |
|                   |                     |        | 5-year survival rate: 56.4% |               |                   |
|                   |                     |        | 10-year survival rate: 39.4% |               |                   |
| Iran21            | n = 102 (single center cohort) | 1997–2008 | Mean follow-up: 60±38.4 months |
|                   |                     |        | 10-year survival rate: 94% |               | Decompensated cirrhosis: 13/102 (12.7%) |
|                   |                     |        | 15-year survival rate: 96% |               | LT: 6/102 (5.9%) |
|                   |                     |        | 20-year survival rate: 88.4% |               | Death: 3/102 (2.9%) |
| Japan22           | n = 203 (multicenter cohort) | 1974–2010 | The survival of patients was similar to the general Japanese population |
|                   |                     |        | Mean follow-up: 131 months |               | HCC or CCC: 203 (3.9%) |
|                   |                     |        | 10-year survival rate: 96% |               | Hepatic malignancy and liver-related death: 22 (10.8%) |
|                   |                     |        | 15-year survival rate: 90% |               |                   |
|                   |                     |        | 20-year survival rate: 80% |               |                   |
| Canterbury, New Zealand23 | n = 133 (population-based AIH cohort) | 1980–2011 | Mean follow-up: 9 years |
|                   |                     |        | 10-year adverse liver event-free survival rate: 80% |
|                   |                     |        | 20-year-old & >60-year-old: 80% |
|                   |                     |        | 10-year-old: 80% |
|                   |                     |        | 10-year-old: 60% |
|                   |                     |        | Median follow-up time: 9 years |

Abbreviations: ALT, alanine aminotransferase; CCC, cholangiocellular carcinoma; HCC, hepatocellular carcinoma; LT, liver transplantation; NM, not mentioned.
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scoring criteria in 127 type I AIH patients. The specificity and sensitivity of simplified criteria was 95% and 90%, respectively. Patients with negative autoantibodies, alkaline phosphatase/AST ratios of less than 1.5, and normal IgG concentrations but high gamma-globulin levels were more likely to miss the diagnosis of AIH according to the simplified criteria. In these patients, the revised criteria, along with histological examination, could help to conclude a correct diagnosis opportunely.

It is reported that the majority of AIH cases are detected at advanced stages and have higher mortality rates in South Asia compared to those in East Asia.48 Our group has shown that transient elastography can dependable evaluate liver fibrosis in AIH via liver stiffness measurement \( r = 0.752, p < 0.01 \).49 Transient elastography can be routinely used during AIH patient follow-up because of its noninvasive advantage. Since biochemical and histological features are nonspecific, it is essential to find some new and highly specific markers for accurate diagnosis of AIH.

**Treatment of AIH**

The targets of treatment in AIH are to lessen liver inflammation and fibrosis, and obtain complete biochemical and histological remission. Prednisolone monotherapy and prednisolone/azathioprine combination regimen are two widely used treatments to induce remission in AIH.50-52 A clinical study of AIH from India showed that timely initiation of immunosuppressive therapy was associated with a favorable prognosis.53 Our group evaluated the immunosuppressive treatment response of 115 consecutive Chinese AIH patients and found the complete biochemical remission rate was 87% within 36 months.54 Azathioprine is the produg of 6-mercaptopurine (6-MP). The most common side effect is cytopenia. Recently, a study from two large European liver centers showed that 75% (15/20) of AIH cases with prior azathioprine intolerance responded to 6-MP therapy. Moreover, 6-MP was well tolerated in these 15 patients.55 Budesonide is only recommended for non-cirrhotic AIH cases,56 because cirrhosis patients have an increased risk of portal vein thrombosis.57 Intravenous glycyrrhizin has been used in treating liver diseases for more than 30 years in the Asian countries, mainly in Japan. Fujiwara and colleagues57-59 established a model \( \text{Risk score} = 0.113 + 0.0006056 \times \text{IgA (mg/dL)} + 0.155 \times \text{ratio of aspartate aminotransferase to ALT} - 0.007079 \times \text{platelet} \times 10^4/\text{mm}^3 \) for determining cirrhosis in type I AIH patients. Risk score \( > 0.20 \) was estimated to be cirrhotic, with specificity and sensitivity of 83% and 90%, respectively. From 1975 to 2010, Abe et al.65 found that 20.4% of patients with type I AIH (n = 250) were cirrhotic in a Japanese population. During the follow-up period, the relapse rate was high in patients who developed cirrhosis. Therefore, lifespan maintenance therapy is encouraged in this population.66

**Cirrhosis**

About 25% of AIH patients are cirrhotic at presentation.50 Miyake et al.64 established a model [risk score = \( -0.113 + 0.0006056 \times \text{IgA (mg/dL)} + 0.155 \times \text{ratio of aspartate aminotransferase to ALT} - 0.007079 \times \text{platelet} \times 10^4/\text{mm}^3 \)] for determining cirrhosis in type I AIH patients. Risk score \( > 0.20 \) was estimated to be cirrhotic, with specificity and sensitivity of 83% and 90%, respectively. From 1975 to 2010, Abe et al.65 found that 20.4% of patients with type I AIH (n = 250) were cirrhotic in a Japanese population. During the follow-up period, the relapse rate was high in patients who developed cirrhosis. Therefore, lifespan maintenance therapy is encouraged in this population.66

Cirrhosis is related to a higher proportion (25% vs. 8%) of drug-related complications67,68 and fragmentary response to therapy. In the corticosteroid part of the regimen, prednisolone (lo)ne is appropriate for AIH patients at the advanced cirrhosis stage. With respect to the immunosuppressive regimen, the main side effect of azathioprine or 6-MP is cytopenia, which can be frequent in cirrhosis and cirrhosis-related
or platelet counts <50

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terizes type III AIH remains controversial.52
(primary biliary cholangitis (PBC): 6.7%, hepatitis B/C: 9.5%); second, the group of patients (58.1%) than those in their control groups
interferon-

recommended.

HCC development in AIH does exist and is associated with cirrhosis, although it is less common than other causes of liver diseases.92 For the cirrhosis subgroup, routine imaging examinations, like those by ultrasound, should be done at 6-month intervals to exclude HCC.93

**Autoantibodies**

The common diagnostic markers of type I AIH are ANA and/or anti-smooth muscle antibodies (ASMA). Type I AIH affects both children and adults. Anti-liver kidney microsome-1 and/or anti-liver cytosol-1 (LC-1) characterize type II AIH. Type II AIH usually occurs in children and/or adolescents.94

**Autoantibody-negative AIH**

Some serum autoantibody-negative patients with typical AIH histological characteristics are diagnosed with cryptogenic hepatitis.95 In 2009, a retrospective analysis from Miyake and colleagues96 showed that 13.6% (24/176) of patients with type I AIH were negative for ANA. Although ANA-negative cases had acute-onset more frequently, the corticosteroid response was not different between ANA-positive cases and ANA-negative cases.96

Serum antibody-negative AIH is not rare in the Chinese population. Our center has found 10.2% (17/167) of AIH cases with absence of ANA and ASMA at presentation, with 4 patients becoming autoantibody-positive (ANA) during the follow-up period.97 Compared with classical AIH, the antibody-negative group had lower IgG concentrations. The IAIHG criteria (1999) are confident for evaluating antibody-negative AIH. Moreover, the complete biochemical remission rates have shown no significant differences within 24 months between classical and autoantibody-negative AIH cases. In our routine practice, physicians should attach importance to this phenotype of AIH, making early diagnosis and starting corticosteroid treatment promptly to improve prognosis.

**Anti–soluble liver antigen/liver pancreas antigen (anti-SLA/LP)-positive AIH**

Anti-SLA/LP is useful to identify AIH cases without classical serum autoantibodies. It is related to severe disease course and relapse.98 Zhao et al.98 reported that SLA-specific interferon-γ responses were more continual in their AIH group of patients (58.1%) than those in their control groups (primary biliary cholangitis (PBC): 6.7%, hepatitis B/C: 4.3%, healthy subjects: 0%). Whether anti-SLA/LP characterizes type III AIH remains controversial.52

**Antimitochondrial antibodies-positive AIH**

Antimitochondrial antibodies, assay markers of PBC, may occur in AIH without any other evidence of PBC.17 Anticentromere antibodies (ACA) are commonly observed in PBC,99 while occasionally detected in AIH. Himoto et al.100 studied the clinical characteristics of ACA-seropositive AIH cases in their cohort and found that 17% (8/47) of the patients had ACA. Compared with the classical AIH group, the ACA-positive group had lower serum IgG concentrations and higher proportion of concurrent autoimmune diseases.100 About 50% of AIH patients have a clinical history of jaundice.101 Second-line immunosuppressive treatment (i.e. mycophenolate mofetil or tacrolimus) should be premeditated in icteric AIH patients who fail standard therapy.52,102,103

**AIH patients with characteristics of PBC**

Characteristics of PBC may occur in AIH, most habitually as AIH-PBC overlap syndromes.104 The Paris criteria (1998) include three AIH criteria and three PBC criteria.105 Since serum ASMA positivity are less common and IgG concentrations are rare above 2× the upper limit of normal (ULN) in the Asia-Pacific area,10 the diagnostic value of these AIH-PBC overlap syndrome criteria is probably not satisfactory. A study from China106 reported that the sensitivity rate of serum IgG concentration >1.3×ULN was 60%, while that of Paris criteria was only 10%.

Recently, our group analyzed the clinical data of 323 patients with PBC, 46 (14.2%) of them with features of AIH. The 5-year survival rate of these 46 cases was 58%, which was less than 81% in other PBC cases without AIH features.107 Corticosteroids added to ursodeoxycholic acid is useful to increase the response rates in AIH-PBC overlap syndrome patients.108 A nationwide study from Japan showed that the simplified AIH scoring system was beneficial for selection of patients who require corticosteroids administration109 (Fig. 1).

**AIH patients within the context of NASH**

Like in western countries, with the increased frequency of overweight and obesity during the past two decades, NASH has become an emerging problem in the Asia-Pacific area. It has been noted that low titers of ANA and ASMA are present in up to one-third of NASH patients.110,111 Meanwhile, some NASH patients also present mild hypergammaglobulinaemia. The similarities in autoantibody and elevated IgG levels lead to diagnostic confusion. Under such circumstances, histological examination is critical.15

Due to the side effects of corticosteroids (e.g., obesity, hypertension and diabetes), using the lowest dose of corticosteroids combined with dietary and exercise approach should be recommended in this population.17 One case report from Japan described a patient with NASH-AIH overlap who successfully achieved histological remission with a combination of prednisolone therapy and weight loss112 (Fig. 1).

**AIH patients within the context of chronic hepatitis B**

Chronic hepatitis B is considered the dominant reason of HCC in Asia-Pacific regions. Sui et al.113 have reported that the hepatitis B surface antigen (HBsAg)-positivity rate of Chinese AIH patients is 0.83%, but sufferers with AIH still have high risk of hepatitis B virus (HBV) infection and/or reactivation due
to immunosuppressive treatment. By now, there is a worldwide consensus (at least among hepatologists) that HBsAg-positive patients should be protected against HBV reactivation when receiving immunosuppressive therapy. At present, the most reliable test used in clinical practice to diagnose HBV reactivation is the demonstration of a rise of one log in serum HBV DNA levels. Entecavir or tenofovir is recommended for such patients during immunosuppressive therapy and for 12 months after cessation of therapy. It is worth mentioning that the identification of anti-hepatitis B core positivity in the absence of HBsAg in candidate AIH patients for immunosuppressive therapy requires further investigation due to the risk of HBV reactivation.115 (Fig. 1).

**IgG4-related AIH**

IgG4-related AIH, which was first reported in 2007,116 shows more severe inflammatory activity compared with classical AIH. However, it is hard to determine whether a substance of AIH-like IgG4 disease exists or expresses a separate disease entity.17 Umemura et al.117 defined IgG4-related AIH as the infiltration of IgG4-positive plasma cells (>10 cells per high power field) and serum IgG4 level ≥135 mg/dL, and found only 3.3% (2/60) cases fulfill the criteria in Japanese patients with type 1 AIH. Prednisolone treatment is valid in IgG4-related AIH patients for induction and maintenance therapy.118 A case report from China described a patient who developed IgG4 de novo AIH after ribavirin + pegylated-interferon alpha-2a treatment119 (Fig. 1).

**Conclusions and perspectives**

The typical phenotype of AIH is well recognized, but the special subgroups like autoantibody seronegative AIH, acute severe AIH, presenting with concomitant features of PBC, and within the context of other liver diseases, make the diagnosis and therapy challenging. At present, the main misunderstandings are as follows: (1) Diagnosis is made only by serum autoantibodies, ignoring the diagnostic value of serum IgG; (2) Clinical and pathological diagnosis cannot be well combined to guide the treatment; (3) The indications for immunosuppressive therapy are not properly applied in clinical practice; (4) Insufficient immunosuppressive therapy (<3 years) or poor patient compliance; (5) Biochemical remission is not equivalent to histological remission.

Special phenotypes of AIH should be diagnosed and treated with flexible criteria and tailored management. Prompt immunosuppressive treatment is critical. For fulminant patients and those who have progressed to end-stage liver disease, liver transplantation could be conducted and the prognosis turns toward being quite optimistic. Nonetheless, further original studies that focus on the clinic and pathology of AIH in the Asia-Pacific area are needed.

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**Conflict of interest**

The authors have no conflict of interests related to this publication.

**Author contributions**

Wrote the review (QXW, LY), edited the review (XM).

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