

## Clinical Presentation, Treatment Outcome and Predictors of Severity in Autoimmune Hepatitis: A Retrospective, Multicenter Experience

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### ABSTRACT

**AIM:** Autoimmune Hepatitis (AIH) is a chronic hepatitis of unknown etiology. It affects adults and children and can progress to cirrhosis. We aim to investigate the mode of presentation, predictors of severity

and treatment outcome of AIH in Saudi patients.

**METHODS:** This is a multicenter retrospective study that involved patients diagnosed with AIH from 3 tertiary hospitals. Clinical, biochemical, radiological and histopathological data were collected and treatment outcomes were reported.

**RESULTS:** A total of 212 patients were included. Female: male ratio was 3:2 and the mean age was  $36.2 \pm 16.8$  years while 50 patients (23.6%) were above age of 50. Abnormal liver function tests (LFTs) were found in (45%). Presentation was chronic in 37.7%, acute in 30.7%, with evidence of liver cirrhosis in 28.8% and with a fulminant disease in 2.8%. Antinuclear antibody (ANA) and Anti-smooth muscle antibody (ASMA) were negative in 65 (30.6%) and 74 (35%) patients respectively. Pre-treatment liver biopsies in 166 patients showed advanced fibrosis (stage 3 and 4) in 63.3%. On multivariate analysis, platelets, alanine transaminase (ALT) level and immunoglobulin G (IgG) level were predictors of fibrosis. Complete response was achieved in 74.5% while 9% had partial response and 16.5% had no response to treatment.

**CONCLUSION:** The majority of AIH patients had advanced fibrosis at the time of diagnosis and liver cirrhosis was found in nearly one-third of cases. IgG, ALT, and platelet were predictors of advanced fibrosis. Complete response to treatment was achieved in two-third of patients. Relying on autoimmune markers for diagnosis can be misleading.

**Key words:** AIH; Auto-antibodies; Azathioprine; Liver Cirrhosis; Steroids

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## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of unknown etiology affecting primarily the liver. It is a common cause of chronic hepatitis, liver cirrhosis and end stage liver disease worldwide. AIH can occur at any age but often diagnosed at age of 40-60 and it affects women more than men with female to male ratio of 3-4:1<sup>[1]</sup>. The prevalence is estimated to range between 50 and 200 cases per 1 million in Western Europe and North America among the white population<sup>[2,3]</sup>, while the international prevalence among patients with liver disease is between 11-20%<sup>[4,5]</sup>. In Asian and African countries, where viral hepatitis are endemic, the incidence of AIH is not precisely known, probably due to under reporting, but expected to be lower than in Caucasians. In one study from India, AIH accounted only for 1.7% of all causes of liver diseases in a cohort of 2401 patients<sup>[6]</sup>. In Saudi Arabia, although the prevalence of AIH among patients with liver disease is not known, it may be much less as compared to North America and European countries. In one study of 112 liver transplant patients, 14.3% of liver transplant indications were due to AIH<sup>[7]</sup>. The clinical presentation of AIH is variable as well as the response to immunosuppressive treatment based on studies from western world<sup>[8]</sup>. Limited number of studies has reported AIH among Saudi patients. In one series by Abdo *et al.*, in which they included 39 patients, 26% of them were diagnosed incidentally through finding abnormal liver function tests (LFTs) and 38% had advanced fibrosis at the time of diagnosis. Seventy five percent had either complete or partial response while one-fourth considered non-responder<sup>[9]</sup>. In another study by Fallatah *et al.*, 41 patients were included; decompensated cirrhosis was found in 45% and response to treatment was either complete or partial in 54.8% of the patients<sup>[10]</sup>. We aim to study the clinical presentation, response to therapy, predictors of fibrosis and outcomes in patients with AIH in a multicenter setting from Riyadh, the capital of Saudi Arabia. The participating centers are tertiary care centers, with availability of large pool of patients, vast experience in the field and access to advanced investigative and therapeutic facilities including liver transplantation.

## MATERIAL AND METHODS

Retrospective charts review of all patients who had definite or probable diagnosis of AIH between January 1996 and December 2013 from three tertiary care centers (King Abdulaziz Medical City, Prince Sultan Military Medical City and King Faisal Specialist Hospital and Research Center), all located in Riyadh, Saudi Arabia. Diagnosis was based on the detailed criteria of the International Group of Autoimmune Hepatitis<sup>[11,12]</sup>. All adult patients (14 years and above) diagnosed as AIH, regardless of acute or chronic presentation and whether cirrhotic or not were included in the review. Patients were excluded if they have indeterminate AIH and if they had organ transplantation before the diagnosis of AIH. Demographic data, medical history on first presentation, laboratory diagnostic tests, histopathological findings, radiological findings and medications prescribed together with LFTs and other laboratory tests on follow up visits were collected. Grade of inflammation and stage of fibrosis on liver biopsy were reported according to METAVIR scoring system<sup>[13,14]</sup>. The main outcomes in this study were the mode of presentation, the stage of fibrosis at time of diagnosis and the response to treatment. Disappearance of symptoms, normalization of LFTs [particularly alanine transaminase (ALT), aspartate transaminase (AST)] and serum total bilirubin 2-3 years after starting treatment was classified as complete response. Improvement of LFTs by more than 50% from pretreat-

ment level without returning to baseline and without clinical deterioration after 2-3 years of adherence to treatment was labeled as partial response, while worsening clinical features and lack of improvement and/or worsening of LFTs that leads to mortality or require liver transplantation despite adherence to treatment was considered as treatment failure. Most of our patients did not have liver biopsy after treatment and therefore histological score was not considered as a parameter for response. Acute AIH was considered if there was abrupt onset of symptoms with elevated ALT or AST more than 10 times the upper normal level. Diagnosis of liver cirrhosis was based on clinical decompensation, liver histology showing advanced fibrosis or nodules formation and radiological findings of contour nodularity, coarse and heterogeneous texture and wide fissures or on fibrosis score by fibroscan.

### Ethical approval

This study was approved by local ethics and research committees from each contributing center.

### Statistical Analysis

Data were analyzed descriptively and inferentially using SPSS version 17. Categorical variables were analyzed with chi-square ( $\chi^2$ ) and numerical variables with student's t-test if they are normally distributed while Mann-Whitney test was used for non-parametric variables. Binary logistic regression was used to identify predictors of the major outcome.

## RESULTS

A total of 212 patients were included in the study with a median follow up of 64 months (2-317 months). One Hundred twenty nine were females with female:male ratio of 3:2. The mean age was  $36.2 \pm 16.8$  years and 50 patients (23.6%) were above 50 years of age at the time of diagnosis. Other baseline characteristics are shown in Table 1. Yellow discoloration of sclera, fatigue and abdominal pain were the most common symptoms occurring in 56.4, 36.3 and 22.2% respectively; while the most frequent findings on examination were jaundice (66.6%), ascites (23.5%) and splenomegaly (16%). Symptoms and signs were absent in almost one fifth of patients and the only clue to diagnosis was abnormal LFTs. Similarly, biochemical parameters were normal in a significant proportion of patients; total bilirubin was normal in 25.6%, alkaline phosphatase (ALP) in 28%, Albumin in 44.3% and international normalized ratio (INR) in 58.3%. On the other hand, about 95%, 91%, and 92% of patients had abnormal AST, ALT and gamma-glutamyl transferase (GGT) respectively. The trigger for further investigation in patients with normal ALT was high total

**Table 1** Baseline characteristics of patients.

Characteristics	Mean $\pm$ SD	Frequency	Percentage
Age	36.2 $\pm$ 16.8 years		
<b>Gender</b>			
Male		83	39.2%
Female		129	60.8%
<b>Mode of Presentation</b>			
Chronic hepatitis without cirrhosis		80	37.7%
Acute hepatitis		65	30.7%
Cirrhosis		61	28.8%
Fulminant Hepatic Failure		6	2.8%
<b>Autoimmune Diseases</b>			
Diabetes Mellitus		32	15.1%
Thyroid Diseases		23	10.8%
<b>BMI</b>	27.5 $\pm$ 6.1		

SD: standard deviation; BMI: body mass index.

**Table 2** The association between autoimmune markers and presence of high ALT, high total bilirubin and advanced fibrosis at the time of diagnosis.

Test	Frequency of Positive Test	Odd Ratio for high ALT	P Value	Odd Ratio for high TB	P Value	Odd Ratio For advanced Fibrosis	P Value
ANA	62.4%	0.545	0.314	0.580	0.145	1.520	0.244
ASMA	63%	2.129	0.134	1.680	0.136	0.720	0.334
ANA and ASMA	38.7%	1.390	0.589	0.758	0.456	1.422	0.358
AMA	11.2 %	0.726	0.690	0.809	0.711	0.684	0.513
IgG (1-2 times ULN)	56.1%	1.758		2.581		3.482	
IgG (>2 times ULN)	27.2%	9.333	0.096	5.606	0.015	3.000	0.024

ALT: alanine transaminase; TB: Total bilirubin; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; AMA: Anti-mitochondrial antibody; IgG: immunoglobulin G; ULN: upper limit of normal.

**Table 3** Predictors of advanced fibrosis at the time of diagnosis by univariate analysis.

Variable	Odd Ratio	P value
Total Bilirubin	1.033	0.331
High ALT	0.243	0.001
High AST	2.156	0.022
ALP	1.064	0.836
GGT	1.571	0.920
INR	2.224	0.034
Low Albumin	1.786	0.007
High Creatinine	0.385	0.379
WBC	2.613	0.517
Low Hemoglobin	1.683	0.022
Low Platelet	4.932	0.001

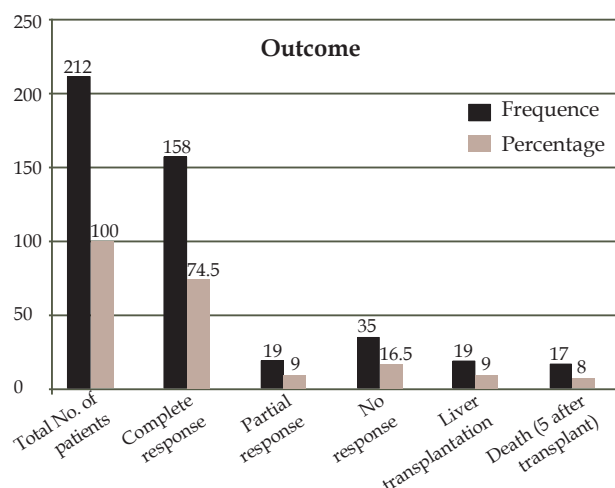
ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; WBC: white blood cells.

**Table 4** Predictors of advanced fibrosis at the time of diagnosis by multivariate analysis.

Variable	Odd Ratio	95% CI	P value
Age	1.005	0.978-1.033	0.696
Gender	0.555	0.200-1.542	0.259
High IgG	4.070	1.097-15.107	0.036
ALT	0.998	0.996-0.999	0.034
Platelet	0.994	0.990-0.999	0.009
Low Albumin	1.186	0.365-3.858	0.777
High INR	1.360	0.349-5.299	0.657

IgG: immunoglobulin G; ALT: alanine transaminase; INR: international normalized ratio.

bilirubin in 5 patients and radiological features of chronic liver disease in the rest of patients. The most common reason for initiating investigation for AIH was finding abnormal liver function tests on routine testing(45%). The presentation was of chronic hepatitis as evident by an insidious and indolent course in 37.7% of cases, acute as defined by abrupt onset of symptoms together with significant rise in LFTs in 30.7% of the patients while over one fourth of them (28.8%) had evidence of one or more of liver cirrhosis manifestations. Fulminant disease however was rare and seen in 2.8%. Antinuclear antibody (ANA) was positive in 132 patients (62.4%) and anti-smooth muscle antibody (ASMA) was positive in 133 patients (63%). ANA and ASMA together were positive in 38.7% while both were negative in 17.2% and liver/kidney microsomal antibody (Anti-LKM) was positive in 7.6% of cases. Positivity of auto-antibodies did not significantly affect the level of ALT, total bilirubin or the incidence of advanced fibrosis, while serum level of IgG was associated with high total bilirubin ( $P = 0.015$ ), advanced fibrosis ( $P = 0.024$ ) and high ALT level although the later did not reach statistical significance ( $P = 0.096$ ) (Table 2). Pre-treatment liver biopsy was reviewed in 166 patients; inflammation was moderate to severe in 88% and advanced fibrosis (stage 3 and 4) was found in 63.3% of them. The most common microscopic finding was portal and lobular plasma cell infiltration (85%) followed



**Figure 1** Treatment outcome at the end of follow up period.

by interface hepatitis (82%). On univariate analysis, high AST, low albumin, low Hemoglobin and platelet were associated with presence of advanced fibrosis while high ALT was inversely related to stage of fibrosis (Table 3). On multivariate analysis, high serum IgG and low platelet were significantly associated with advanced fibrosis; on the other hand, advanced fibrosis was less likely in patients with high ALT ( $P = 0.034$ ), (Table 4). Different doses of immunosuppressive agents (mainly steroids in the form of prednisone/prednisolone and azathioprine) were used with different timing of introducing azathioprine. Treatment was used according to discretion and experience of the treating hepatologist. Only 4.2% and 2% of patients required mycophenolate or tacrolimus respectively. The main reason for using the later two immunosuppressive therapy was either unresponsiveness to steroid and azathioprine or to intolerance of azathioprine. Complete response was achieved in 74.5% while 9% had partial response and 16.5% had no response to treatment (Figure 1). The response could not be assessed based on transaminases level in 9% since these patients had normal baseline ALT and AST. These patients however showed clinical improvement and did not develop liver related complication. Seventeen patients (8%) died and 19 patients (9%) had liver transplantation. Decompensated cirrhosis was the cause of death in 12 patients while the rest had fulminant hepatitis.

## DISCUSSION

This study has shown that AIH is a frequently encountered cause of chronic liver disease in Saudi Arabia. It has an insidious onset and no specific symptoms in large proportion of patients however acute and severe form of presentation can occur but less frequently. The prevalence of advanced fibrosis was very high in this cohort with almost one third of patients having cirrhosis on presentation. Our

patients had favorable response to treatment with complete or partial response in 83% of them.

Autoimmune hepatitis is a complex disease that represents a challenge in diagnosis and management due to the diversity of the clinical presentation, wide spectrum of the disease and variable response to treatment<sup>[15]</sup>. AIH can affect different age groups and although recognized by the presence of auto-antibodies and elevated immunoglobulins, these markers are absent in a significant proportion of patients that may reach 30%<sup>[16]</sup>. The quiescent course of the disease especially at early stage is another challenge since disease can progress slowly and evolve to cirrhosis without significant symptoms<sup>[17]</sup>. As shown in our cases, the only finding that provoked the investigation for AIH was asymptomatic elevation of liver enzymes in 45% of the patients. Relying on classical presentation of AIH for diagnosis will lead to missing a large number of patients and thus not considered as an appropriate approach. Instead a high index of suspicion coupled to thorough assessment of patients is necessary whenever AIH is entertained in the diagnosis. The female: male ratio in our study of 3:2 is similar to what was reported by Abdo *et al.* and Fallatah *et al.*<sup>[9,10]</sup> and showed that AIH was more prevalent amongst Saudi females, however the female: male ratio was less than that was reported in the western world which is estimated to be 3-4:1. The peak age of incidence in this cohort was less than that described in the literature (20-40 years) and both findings may indicate a different environmental exposure or genetic predisposition in this part of the world. Majority of our patients were presented with chronic and insidious onset who were either asymptomatic or may have nonspecific symptoms of chronic illness, which was similar to most of published studies. Acute presentation was reported previously in 25-70% and often can be confused with acute viral, ischemic and drug induced hepatitis<sup>[19]</sup>. We found similar figure in our cohort (30.7%) nevertheless, the acuteness of symptoms did not specify accurately the onset of disease since a large proportion of these patients had significant fibrosis at the time of presentation and thus they most likely had acute on top of chronic liver disease. We did not find difference in response to treatment between acutely presented patients and those who have presented with more insidious onset. Liver cirrhosis is very prevalent in AIH (28% in this cohort) and always a predictor of poor outcome<sup>[19]</sup>. Similar figures were reported from several studies. Kim and his colleagues reported that 22.7% of their patients had liver cirrhosis at presentation in a cohort of Korean AIH patients<sup>[20]</sup>. Cirrhosis was more prevalent in AIH patients who presented with jaundice, reaching 50% in one European study<sup>[21]</sup> and 43% in our series. In contrast to AIH patients with early fibrosis who have excellent survival after treatment, liver cirrhosis increases the probability of death and need for liver transplant in patients with AIH and increase their risk of developing hepatocellular carcinoma<sup>[22]</sup>. Reversibility of fibrosis however was reported in cirrhotic and non-cirrhotic patients<sup>[23]</sup>. Immunosuppressive therapy remains the mainstay in treatment of autoimmune hepatitis. Induction by corticosteroids with or without azathioprine results in rapid improvement of transaminases in majority of patients. We treated all patients with a combination of prednisolone and azathioprine initially. Small proportions of patients were shifted to mycophenolate (4.2%) and tacrolimus (2%) due to intolerance to azathioprine or to unresponsiveness to steroid and azathioprine. Majority of AIH patients respond favorably to immunosuppression, in our cases, the response to treatment was observed in the first few weeks after treatment in most of the patients, however complete normalization of LFTs took up to 24 months. Three-fourth of our patients achieved that endpoint and remained in remission after long duration of

follow up. Compliance however remains an important determinant for maintenance of remission. Our study has the advantage of being a multicenter, hence we avoided the possibility of selection bias, furthermore it has a reasonably large number of patient. However, as the nature of retrospective design, there are some limitations that include the lack of specified timing for performing the laboratory tests and the follow up between the 3 centers. This has led to exclusion of substantial number of patients from enrollment in this study. Further, It was possible that many patients were lost follow up and we were unable to document their outcome. Despite these limitations, our study highlighted the importance of AIH in this part of the world and the need for prospective studies to identify patients earlier with appropriate diagnosis, management and, therefore, better outcome.

## CONCLUSION

Autoimmune hepatitis is an important cause of chronic liver disease in Saudi Arabia. The majority of patients were found to have advanced fibrosis at the time of diagnosis and liver cirrhosis was found in nearly one-third of cases. High serum IgG, low (Normal) ALT and low platelet were predictors of advanced fibrosis. Liver transplantation was infrequent indication in our patients. Relying on autoimmune markers for diagnosis can be misleading in substantial number of patients with negative autoimmune markers. High index of suspicion and more comprehensive evaluation, that may include liver biopsy, is needed whenever this diagnosis is entertained. More than 90% patients were treated with standard therapy using steroid and azathioprine. Complete response to treatment was achieved in two-third of patients.

## CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

## REFERENCES

- 1 Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010; **51**: 2193-213.
- 2 Nishioka M, Morshed SA, Kono K, Himoto T, Parveen S, Arima K, Watanabe S, Manns MP. Frequency and significance of antibodies to P450IID6 protein in Japanese patients with chronic hepatitis C. *J Hepatol*. 1997; **26**: 992-1000.
- 3 Nishioka M, Morshed SA, McFarlane IG. Geographical Variation in the Frequency and Characteristics of Autoimmune Liver Diseases. In: Krawitt EL, Wiesner RH, Nishioka M, editors. Autoimmune liver diseases. 2nd ed. Amsterdam: Elsevier; 1998: 413-424
- 4 Czaja AJ. Diagnosis and therapy of autoimmune liver disease. *Med Clin North Am*. 1996; **80**: 973-94.
- 5 Cancado ELR, Porta G. Autoimmune Hepatitis in South America. In: Manns MP, Paumgartner G, Leuschner U, editors. Immunology and liver. Dordrecht, Boston, London: Kluwer Academic Publishers; 2000: 82-92.
- 6 Choudhuri G, Somani SK, Baba CS, Alexander G. Autoimmune hepatitis in India: profile of an uncommon disease. *BMC Gastroenterol*. 2005; **5**: 27.
- 7 Khalaf H, Mourad W, El-Sheikh Y, Abdo A, Helmy A, Medhat Y, Al-Sofayan M, Al-Sagheir M, Al-Sebayel M. Liver transplantation for autoimmune hepatitis: a single-center experience. *Transplant Proc*. 2007; **39**: 1166-70.
- 8 Czaja AJ. Challenges in the diagnosis and management of autoimmune hepatitis. *Can J Gastroenterol*. 2013; **27**: 531-9.

- 9 Abdo AA. Clinical presentation, response to therapy, and predictors of fibrosis in patients with autoimmune hepatitis in Saudi Arabia. *Saudi J Gastroenterol.* 2006; **12**: 73-6.
- 10 Fallatah H, Akbar HO, Qari YA. Autoimmune hepatitis: Single-center experience of clinical presentation, response to treatment and prognosis in Saudi Arabia. *Saudi J Gastroenterol.* 2010; **16**: 95-9.
- 11 Johnson PJ, McFarlane IG. Meeting Report: International Autoimmune Hepatitis Group. *Hepatology* 1993; **18**: 998-1005.
- 12 Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Büschenfelde KH, Mieli-Vergani G, Nakanuma Y, Nishioka M, Penner E, Porta G, Portmann B, Reed W, Rodes J, Schalm S, Scheuer P, Schrumpf E, Seki T, Toda G, Tsuji T, N. Tygstrup, Vergani D, Zeniya M. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol.* 1999; **31**: 929-38.
- 13 Beddosa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The Metavir cooperative study group. *Hepatology* 1996; **24**: 289-93.
- 14 Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; **20**: 15-20.
- 15 Fallatah HI, Akbar HO. Autoimmune liver disease - are there spectra that we do not know? *Comp Hepatol.* 2011; **10**: 9.
- 16 Czaja AJ. Autoantibody-negative autoimmune hepatitis. *Dig Dis Sci.* 2012; **57**: 610-24.
- 17 Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology.* 2005; **42**: 53-62.
- 18 Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. *Dig Dis Sci.* 2013; **58**: 897-914.
- 19 Verma S, Gunuwan B, Mendler M, Govindrajan S, Redeker A. Factors predicting relapse and poor outcome in type I autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission and plasma cell activity in the liver biopsy. *Am J Gastroenterol.* 2004; **99**: 1510-6.
- 20 Kim BH, Kim YJ, Jeong SH, Tak WY, Ahn SH, Lee YJ, Jung EU, Lee JI, Yeon JE, Hwang JS, Um SH, Seo YS, Kim YS, Song BC, Kim JH, Jung YK, Park CK, Kim KA, Min HJ, Cho EY, Lee ES, Kwon SY, Chae HB, Kim DJ, Shin SR. Clinical features of autoimmune hepatitis and comparison of two diagnostic criteria in Korea: a nationwide, multicenter study. *J Gastroenterol Hepatol.* 2013; **28**: 128-34.
- 21 Panayi V, Froud OJ, Vine L, Laurent P, Woolson KL, Hunter JG, Madden RG, Miller C, Palmer J, Harris N, Mathew J, Stableforth B, Murray IA, Dalton HR. The natural history of autoimmune hepatitis presenting with jaundice. *Eur J Gastroenterol Hepatol.* 2014; **26**: 640-5.
- 22 Migita K, Watanabe Y, Jiuchi Y, Nakamura Y, Saito A, Yagura M, Ohta H, Shimada M, Mita E, Hijioka T, Yamashita H, Takezaki E, Muro T, Sakai H, Nakamura M, Abiru S, Komori A, Ito M, Yatsushashi H, Nakamura M, Ishibashi H; Japanese NHO-Liver-network study group. Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization-autoimmune hepatitis prospective study). *Liver Int.* 2012; **32**: 837-44.
- 23 Czaja AJ. The prevention and reversal of hepatic fibrosis in autoimmune hepatitis. *Aliment Pharmacol Ther.* 2014; **39**: 385-406.