Prognosis of Probable Autoimmune Hepatitis Patients in a Retrospective Cohort Study

Koji Fujita (✉ 92m7v9@med.kagawa-u.ac.jp)  
Kagawa Daigaku  https://orcid.org/0000-0001-9390-7565

Kyoko Oura  
Kagawa Daigaku

Tomoko Tadokoro  
Kagawa Daigaku

Asahiro Morishita  
Kagawa Daigaku

Hideki Kobara  
Kagawa Daigaku

Kunihiro Tsutsui  
Kagawa Daigaku

Takashi Himoto  
Kagawa Kenritsu Hoken Iryo Daigaku

Tsutomu Masaki  
Kagawa Daigaku

Research article

Keywords: autoimmune hepatitis patients, International Autoimmune Hepatitis Group (IAIHG), disease

DOI: https://doi.org/10.21203/rs.3.rs-61802/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background: Autoimmune hepatitis (AIH) is an idiopathic inflammatory liver disease with genetic susceptibility and unknown environmental triggers, which results in failures of physiologic immunotolerance and destruction of the liver tissues. The gold standard for diagnosis is the International Autoimmune Hepatitis Group (IAIHG) scoring system: the disease is classified as definite or probable according to the scores. However, conventional research on probable AIH has focused on the Caucasian population and there is little data pertaining to the Asian population. Therefore, this study aimed to assess and compare the prognosis of Japanese patients with probable and definite AIH.

Methods: Patients with probable and definite AIH diagnosed based on IAIHG scores between 1987 and 2018 were enrolled in this retrospective study.

Results: Seventy-two patients with definite AIH and 49 patients with probable AIH were evaluated in the study. Univariate analysis revealed age, fibrosis stage 4, and the fibrosis-4 index were prognostic factors for overall survival. Multivariate analysis indicated that age and liver cirrhosis significantly affected the overall survival. When the cut off albumin-bilirubin score was set appropriately, cirrhosis was differentially diagnosed using albumin-bilirubin score with 100% sensitivity and 70.5% specificity. Classification of probable or definite disease did not alter overall survival with statistical significance.

Conclusions: Our findings suggest that probable AIH should be managed as definite AIH is managed in Japanese population. The albumin-bilirubin score helps identify liver cirrhosis and is a prognostic biomarker for overall survival.

Background

Autoimmune hepatitis is an idiopathic inflammatory liver disease based on genetic susceptibility and unknown environmental triggers, which result in failures of physiologic immunotolerance and destruction of liver tissues [1-3]. The clinical presentation is characterized by a variety of aspects, including an increase in serum hepatobiliary enzyme, serum IgG, elevation of autoantibody titer, histopathological findings of liver biopsy specimens, and complications of other autoimmune diseases [4-6].

The gold standard for diagnosis is the International Autoimmune Hepatitis Group (IAIHG) scoring system, which classifies the disease as definite or probable according to diagnostic scores [7]. The epidemiology, baseline characteristics, and treatment response of definite autoimmune hepatitis (AIH) are already established [8]. The differences in epidemiology between Caucasian and Asian AIH have also been summarized in detail [9, 10]. However, conventional research on probable AIH has focused on the Caucasian population and there is far less available evidence on the Asian population. The aim of this study was to clarify the prognosis of probable AIH patients in a Japanese population compared to the definite disease.

Methods
This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Kagawa University, Faculty of Medicine (Heisei-30-151) [11]. Informed consent was obtained from patients for analysis of clinical data. For patients who had died and had no relatives listed in their clinical records, we provided opt-out methods for the relatives of the dead participants by publishing a summary of this study on our university website [12, 13].

Study design

Patients were retrospectively assigned to definite AIH or probable AIH based on IAIHG scoring system. Survival rates of two groups were compared by Kaplan-Meier curves. Cox proportional hazard model was performed to identify independent risk factors for survival.

Patients

Among 1957 patients who underwent percutaneous liver biopsy examinations between November 1, 1987 and December 31, 2018, those who were suspected of having AIH, primary biliary cholangitis (PBC), or nonalcoholic steatohepatitis (NASH) were enrolled in this retrospective cohort study. Clinical data of the patients were reviewed and scored by the IAIHG criteria as described below. Definite and probable AIH patients were analyzed further.

Clinical data

The following clinical data were extracted from the patients’ medical records: age, sex, history of alcohol consumption and internal medicines, patient complications, and family history of autoimmune diseases. For laboratory data, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T-Bil), serum albumin (Alb), and immunoglobulin G (IgG) levels were recorded. T-Bil (mg/dl) was converted to T-Bil (µmol/l) according to the following equation: T-Bil (mg/dl) × 17.2. Serological evaluation was based on anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-type-1 liver-kidney microsomaal (LKM-1) antibody, anti-mitochondrial antibody (AMA), and anti-mitochondrial M2 antibody [14]. Other autoantibodies and human leukocyte antigen (HLA) typing were also referred to when the data were relevant. Albumin-bilirubin (ALBI) score was calculated based on a calculation from a previous report: (Log 10 T-Bil (µmol/l) × 0.66 + Alb (g/l) × (-0.085) [15]. Fibrosis-4 index (Fib-4 index), a conventional liver fibrosis index, was calculated using the following equation: age × AST (U/l) / (Plt (109/l) × √ALT (U/l)) [16].

Histopathological analysis

Pathological findings of liver biopsy specimens were evaluated according to IAIHG criteria [7]. In the current analysis, hepatic steatosis equal to or more than 5% accompanied by hepatocyte ballooning was designated as the prominent feature of NASH [17]. Pathological evaluation was performed by an experienced pathologist who specialized in liver pathology.
**Diagnosis of autoimmune hepatitis**

According to IAIHG criteria revised in 1999, diagnosis of pre-treatment definite AIH was determined based on a score above 15 [7]. Pre-treatment probable AIH was diagnosed in patients with scores ranging between 10 and 15. Post-treatment definite or probable AIH was diagnosed as described in the IAIHG criteria.\(^7\) To calculate diagnostic scores, 35 U/l was applied as the upper limit of the normal (ULN) AST values, and 40 U/l for ALT and 17.0 g/l for IgG. Three points were reduced in the IAIHG scoring system based on histological findings typical of NASH as described above.

Simplified AIH criteria were also applied in the current cohort [18]. The Paris criteria for diagnosis of overlap syndrome was not adopted in the current study [19].

Biochemical remission was defined as normal ALT levels at least 1 year after steroidal agents were first prescribed [1]. Moderate to severe AIH was defined using AST > × 5 ULN, or IgG > 2 ULN or confluent necrosis in liver pathology referring to a past study [20].

**Statistical analyses**

Continuous variables were presented as median and interquartile range and were analyzed using the Mann-Whitney *U* test or Spearman's rank correlation coefficient. Categorical variables were analyzed using Fisher's exact test or Chi-squared test depending on patient number in each category. Statistical analyses mentioned above were performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA). Cox proportional hazard model was analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) [21, 22]. *P* < 0.05 was considered statistically significant.

**Results**

**Characteristics of the patients**

The clinical data of 121 patients, including liver histopathology, were reviewed in the current study (Table 1). The cohort consisted of 72 patients with definite AIH (the definite cohort) and 49 patients with probable AIH (the probable cohort). Compared to definite AIH patients, probable patients included a higher proportion of males. They were more likely to be negative for ANA and positive for AMA or anti-mitochondrial M2 antibody and they had higher albumin levels, lower IgG levels, and lower ALBI scores. No patients were positive for LKM-1 in either cohort. Two patients of definite AIH presented positive for anti-smooth muscle antibody, but it did not contribute to diagnostic points because the patients were also positive for ANA. More patients in the probable cohort were positive for human leukocyte antigen death receptor 4 (HLA-DR4) compared to the definite cohort.

In the probable cohort, chronic nonsuppurative destructive cholangitis was detected in three patients and granuloma was detected in one patient according to histopathological examinations, which show typical
PBC features. One patient presented with hepatocyte ballooning with background steatosis equal to or more than 5%, which is the prominent histopathological feature of NASH. Positive hepatitis B antigens were detected in two patients, HCV-RNA was detected in five patients, and one patient had a history of taking pregabalin [23, 24]. Two patients showed remarkable alcohol consumption.

Emperipolesis was pointed out in the pathological work up in two patients of definite disease. Compared to the probable AIH patients, no patients in the definite AIH cohort showed the prominent features of NASH, HBV, or HCV infection, or history of alcohol or drug use.

In the total cohort, IAIHG scores were correlated with the simplified IAIHG scores with an $r$ value of 0.6252 (95% confidence interval, 0.4988 - 0.7255; $p$ value < 0.0001). Seventy-nine (65.3 %) of total 121 patients were credited with the simplified score equal to or above 6 points.

**Follow up of the patients**

Patients were followed up for a median of 4 years with the longest follow up period of 30 years (Table 1). Steroidal agents were administered to 41.2% of patients in the definite cohort. The number of patients in the probable cohort who underwent steroidal therapy was significantly smaller compared to the definite cohort. Two patients in the definite cohort were diagnosed with HCC during the follow up period but survived through the observation. In this study, 12.2% of probable AIH patients and 5.6% of definite patients died, and this difference was not significant. The cause of death was identified in seven patients—three due to liver failure, one due to rupture of abdominal aortic aneurysm, one due to bacterial peritonitis, one due to interstitial pneumonia, and one due to cryptococcus meningitis.

**Overall survival**

Univariate analysis was performed to determine the predictive prognostic factors for overall survival in the total cohort. As shown in Table 2, age, fibrosis stage 4, and the fibrosis-4 index were prognostic factors for survival. The hazard ratio of 1.885 for probable disease over definite one resulted in no statistical significance.

Multivariate analysis was performed to determine independent risk factors for overall survival employing five parameters: definite or probable disease, age, moderate to severe disease, Fibrosis stage 4, and nonremission under steroidal therapy (Table 2). Sex was not included in the analysis because sex was incorporated in IAIHG scoring system. The result indicated that age and fibrosis stage 4 significantly contributed to the overall survival. The hazard ratio for age was 1.099 per year in the multivariate analysis while the hazard ratio for fibrosis stage 4 was 8.943. Although the hazard ratio for probable disease increased up to 2.446, it remained statistically non-significant.

**Surrogate marker for fibrosis stage 4**

Fibrosis stage 4 was identified as a prognostic factor for overall survival in the current cohort. As surrogate biomarkers for fibrosis stage 4, fibrosis-4 index and ALBI score were evaluated. As shown in
Figure 1a, the median fibrosis-4 index values did not differ between patients with fibrosis stage 1 to 3 and patients with stage 4 ($p = 0.2225$), but ALBI scores were different in patients with fibrosis stage 4 compared to those with stage 1 to 3 ($p = 0.0001$), as indicated in Figure 1b. Receiver operating characteristic (ROC) analysis revealed that the area under curve for ALBI score was 0.8586. When the cut off ALBI score value was set at -1.994, fibrosis stage 4 was differentially diagnosed using ALBI score with 100% of sensitivity and 70.5% of specificity ($p = 0.0004$, Figure 1c).

**Discussion**

The current study aimed to clarify prognosis of probable AIH patients in the Japanese population. The data revealed that 1) prognosis of probable AIH does not differ from that of definite disease, 2) greater age and fibrosis stage 4 at baseline are independent risk factors for overall survival, and 3) the ALBI score serves as a surrogate marker for fibrosis stage 4 in the Japanese population.

A couple of studies have reported prognosis of probable autoimmune hepatitis. In an English population, 78 probable AIH patients were compared to 167 definite patients, and no significant difference in liver-related death or transplant-free survival [25]. Summing up probable and definite disease patients, cirrhosis at diagnosis and biochemical remission were indicated as prognostic factors in that study. Czaja et al. also performed a retrospective study of 17 probable AIH patients defined using the IAIHG scoring system [26]. They concluded that the classification of definite and probable was based mainly on sex and the alteration of laboratory data, which do not reflect disease severity or treatment response. The British Society of Gastroenterology stated in a public announcement that probable and definite AIH appeared to be the same disease in terms of outlook and response to immunosuppression [1]. A large-sized cross-sectional study reported in the United Kingdoms in 2018 omitted comparative analyses between the probable and definite AIH patients [27]. Another study prospectively evaluated prognostic factors of AIH using a cohort of 325 patients including both probable and definite diseases [28]. The study identified age at diagnosis as a risk factor for liver-related death or transplant-free survival.

In the current study, classification of probable or definite disease did not stratify patients according to biochemical response rate and overall survival, similar to past reports. Fibrosis stage 4 and age were also extracted as prognostic factors negatively correlated with overall survival in the total cohort. Our data showed that prognosis of probable AIH was not different to that of definite AIH in the Japanese population, orchestrating the results in Caucasian cohorts. Correlation of IAIHG and the simplified criteria was also comparable with that of a past study [27], as 2/3 of AIH patients diagnosed using IAIHG met the simplified criteria in the current data.

However, one apparent difference should be noted. Immunosuppression therapy was applied to 224 of 245 patients (91.4%) in the past report [25], while steroidal agents were prescribed for 41 of 121 patients (33.9%) alone in the current cohort. Application of immunosuppression therapy is generally considered in patients with an AST > × 5 ULN, or γ-globulin > 2 ULN or confluent necrosis in liver pathology at diagnosis [1, 20]. A Japanese nationwide survey using questionnaires reported that AIH patients presented with a
median AST of 177 U/l based on a total of 1668 AIH patients [29]. Contrary to this, a past study in England reported a median AST 489 U/l for definite AIH and 235 U/l for probable AIH at baseline [25]. It can be said that AIH disease severity is milder in the Japanese population than in English populations. In the current study, Japanese AIH patients presented with further milder inflammatory activity on liver biopsy examination.

In the Asian AIH population, ANA and HLA-DR4 results are more frequently positive compared to the Caucasian population. In the current study, 95.8% of definite AIH patients were positive for ANA and 90.0% of patients were positive in the total cohort, orchestrating the results of the Japanese nationwide survey [29]. However, HLA-DR4 was positive in a little 19.0% of the total cohort in the current study. Furthermore, probable AIH patients were positive for HLA-DR4 with larger a proportion than definite AIH ones. This discrepancy may be due to two reasons. Firstly, if a patient is positive for ANA, HLA-DR4 does not contribute to diagnosis of AIH in the IAIHG scoring system [7] and about 90% of Japanese AIH patients are positive for ANA [29] and secondly, HLA typing is not covered by insurance in Japan. Thus, clinicians should omit to determine HLA typing in clinical practice.

Anti-soluble liver antigen (SLA) antibody has not been covered by public insurance in Japan, either. Anti-SLA antibody is frequently detected in patients negative for conventional autoantibodies [30, 31]. The antibody is reported to correlate higher relapse rate of the disease with poorer prognosis [32]. However, no data were available for anti-SLA antibody in our study.

The IAIHG scoring system does not specifically mention how to exclude NASH from the diagnosis of AIH, or how to incorporate the typical features of NASH into the scoring system [7]. The cross-sectional study performed in the UK adopted a criterion for the issue as more than mild steatosis regardless of hepatocyte ballooning [27]. A past report presented evidence that baseline liver status was more frequently cirrhotic, and that patient survival was worse in AIH with NASH than pure AIH [33]. In the current study, hepatic steatosis equal to or more than 5% accompanied by hepatocyte ballooning was defined as NASH [17]. The complications of NASH with AIH was not subject to statistical analysis in our cohort because only a single patient fitted the above criteria.

Fibrosis stage 4 contributed to overall survival in the current study. In the management of AIH after initial diagnosis, surrogate markers for fibrosis stage should be useful as an alternative to liver biopsy examination. Liver biopsy maneuvers sometimes complicate liver hemorrhage. Our data clarified that the ALBI score had better diagnostic potential for distinguishing fibrosis stage 4 from stage 1 to 3 compared to the conventional biomarker of liver fibrosis, the fibrosis-4 index. This may be partially explained given that the value of fibrosis-4 index does not reflect the actual fibrosis stage because of the fluctuation of AST and ALT values depending on the inflammatory activity of the disease.

The ALBI score was originally established to classify cirrhosis patients according to their prognosis [15]. An ALBI score less than -2.600 means better prognosis and is classified grade 1, an ALBI score between -2.600 and less than -1.390 is means moderate prognosis and is classified grade 2, an ALBI score more than -1.390 means a worse prognosis and is classified as grade 3. Currently, application of ALBI score is
limited in cirrhosis patients, similar to the Child Pugh score. However, our previous studies have clarified that the ALBI score has the potential to differentially diagnose fibrosis stage 4 from stage 1 to 3 in HCV infection, HBV infection, and PBC [34-36]. In AIH, ALBI score was able to diagnose fibrosis stage 4 regardless of the inflammatory severity of the hepatitis at any stage of the disease.

**Conclusions**

In the Japanese cohort, we have shown that: 1) the classification of AIH, probable or definite, does not alter overall survival, 2) greater age and fibrosis stage 4 at baseline independently stratified overall survival, similar to the results for the Caucasian population, and 3) fibrosis stage 4 was diagnosed more accurately using ALBI scores compared to the conventional biomarker, fibrosis-4 index. Definite and probable AIH patients in Japan can be monitored their liver fibrosis progression using ALBI score.

**Abbreviations**

Anti-mitochondrial antibody, AMA; anti-nuclear antibody, ANA; autoimmune hepatitis, AIH; International autoimmune hepatitis group, IAIHG; Nonalcoholic steatohepatitis, NASH; Primary biliary cholangitis, PBC; Receiver operating characteristic, ROC; smooth muscle antibody, SMA; type-1 liver-kidney microsomal antibody, LKM-1, 95% confidence interval, 95% CI

**Declarations**

*Ethics approval and consent to participate*

Participants in the study provided informed consent, and the study design was approved by the appropriate ethics review board.

*Consent for publication*

Not applicable.

*Availability of data and materials*

Our data will be available from the corresponding author on reasonable request.

*Competing interests*

No authors have any conflict of interest.

*Funding*

This study received no financial support.

*Authors’ contributions*
The author’s contributions are as follows. The study concept and design were configured by KF, data were acquired by KO, TK, and JT, data were analyzed and interpreted by AM, critical revision was performed by HK, KT and TH, and the study was supervised by TM.

Acknowledgements

Not applicable.

References

1. Gleeson D, Heneghan MA, Gastroenterology BSo: British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011, 60(12):1611-1629.

2. Liwinski T, Schramm C: Autoimmune hepatitis - update on clinical management in 2017. Clin Res Hepatol Gastroenterol 2017, 41(6):617-625.

3. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ: Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the study of liver diseases. Hepatology 2019.

4. Onji M, Zeniya M, Yamamoto K, Tsubouchi H: Autoimmune hepatitis: Diagnosis and treatment guide in Japan, 2013. Hepatol Res 2014, 44(4):368-370.

5. Manns MP, Lohse AW, Vergani D: Autoimmune hepatitis–Update 2015. J Hepatol 2015, 62(1 Suppl):S100-111.

6. Doycheva I, Watt KD, Gulamhusein AF: Autoimmune hepatitis: Current and future therapeutic options. Liver Int 2019, 39(6):1002-1013.

7. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ et al: International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999, 31(5):929-938.

8. Czaja AJ: Autoimmune hepatitis in diverse ethnic populations and geographical regions. Expert Rev Gastroenterol Hepatol 2013, 7(4):365-385.

9. Yang F, Wang Q, Bian Z, Ren LL, Jia J, Ma X: Autoimmune hepatitis: East meets west. J Gastroenterol Hepatol 2015, 30(8):1230-1236.

10. Enomoto H, Nishiguchi S: Similarities and Differences in Autoimmune Hepatitis Epidemiology between East and West: Autoimmune Hepatitis in East Asia, Southeast Asia, and South Asia. Inflamm Intest Dis 2017, 1(4):150-158.

11. Association WM: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013, 310(20):2191-2194.

12. Vellinga A, Cormican M, Hanahoe B, Bennett K, Murphy AW: Opt-out as an acceptable method of obtaining consent in medical research: a short report. BMC Med Res Methodol 2011, 11:40.
13. Montoy JC, Dow WH, Kaplan BC: Patient choice in opt-in, active choice, and opt-out HIV screening: randomized clinical trial. *BMJ* 2016, 532:h6895.

14. Gershwin ME, Rowley M, Davis PA, Leung P, Coppel R, Mackay IR: Molecular biology of the 2-oxo-acid dehydrogenase complexes and anti-mitochondrial antibodies. *Prog Liver Dis* 1992, 10:47-61.

15. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O’Beirne J, Fox R, Skowronska A, Palmer D et al: Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 2015, 33(6):550-558.

16. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL et al: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006, 43(6):1317-1325.

17. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ: The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018, 67(1):328-357.

18. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H et al: Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008, 48(1):169-176.

19. Chazouillères O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R: Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatology* 1998, 28(2):296-301.

20. Trivedi PJ, Hubscher SG, Heneghan M, Gleeson D, Hirschfield GM: Grand round: Autoimmune hepatitis. *J Hepatol* 2019, 70(4):773-784.

21. Hens N, Aerts M, Molenberghs G: Model selection for incomplete and design-based samples. *Stat Med* 2006, 25(14):2502-2520.

22. Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013, 48(3):452-458.

23. Einarsdóttir S, Björnsson E: Pregabalin as a probable cause of acute liver injury. *Eur J Gastroenterol Hepatol* 2008, 20(10):1049.

24. Doğan S, Ozberk S, Yurci A: Pregabalin-induced hepatotoxicity. *Eur J Gastroenterol Hepatol* 2011, 23(7):628.

25. Hoeroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, Gleeson D: Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. *Gastroenterology* 2011, 140(7):1980-1989.

26. Czaja AJ: Comparability of probable and definite autoimmune hepatitis by international diagnostic scoring criteria. *Gastroenterology* 2011, 140(5):1472-1480.

27. Gordon V, Adhikary R, Appleby V, Das D, Day J, Delahooke T, Dixon S, Elphick D, Hardie C, Hoeroldt B et al: Diagnosis, presentation and initial severity of Autoimmune Hepatitis (AIH) in patients attending 28 hospitals in the UK. *Liver Int* 2018, 38(9):1686-1695.
28. Baven-Pronk MAMC, Biewenga M, van Silfhout JJ, van den Berg AP, van Buuren HR, Verwer BJ, van Nieuwkerk CMJ, Bouma G, van Hoek B: *Role of age in presentation, response to therapy and outcome of autoimmune hepatitis*. *Clin Transl Gastroenterol* 2018, 9(6):165.

29. Takahashi A, Arinaga-Hino T, Ohira H, Torimura T, Zeniya M, Abe M, Yoshizawa K, Takaki A, Suzuki Y, Kang JH *et al.*: *Autoimmune hepatitis in Japan: trends in a nationwide survey*. *J Gastroenterol* 2017, 52(5):631-640.

30. Baeres M, Herkel J, Czaia AJ, Wies I, Kanzler S, Cancado EL, Porta G, Nishioka M, Simon T, Daehnrich C *et al.*: *Establishment of standardised SLA/LP immunoassays: specificity for autoimmune hepatitis, worldwide occurrence, and clinical characteristics*. *Gut* 2002, 51(2):259-264.

31. Eyraud V, Chazouilleres O, Ballot E, Corpechot C, Poupon R, Johanet C: *Significance of antibodies to soluble liver antigen/liver pancreas: a large French study*. *Liver Int* 2009, 29(6):857-864.

32. Kirstein MM, Metzler F, Geiger E, Heinrich E, Hallensleben M, Manns MP, Vogel A: *Prediction of short- and long-term outcome in patients with autoimmune hepatitis*. *Hepatology* 2015, 62(5):1524-1535.

33. Dyson JK, De Martin E, Dalekos GN, Drenth JPH, Herkel J, Hubscher SG, Kelly D, Lenzi M, Milkiewicz P, Oo YH *et al.*: *Review article: unanswered clinical and research questions in autoimmune hepatitis-conclusions of the International Autoimmune Hepatitis Group Research Workshop*. *Aliment Pharmacol Ther* 2019, 49(5):528-536.

34. Fujita K, Oura K, Yoneyama H, Ting Ting S, Takuma K, Nakahara M, Tadokoro T, Nomura T, Morishita A, Tsutsui K *et al.*: *Albumin-bilirubin score indicates liver fibrosis staging and prognosis in chronic hepatitis C patients*. *Hepatol Res* 2019.

35. Fujita K, Nomura T, Morishita A, Oura K, Yoneyama H, Kobara H, Tsutsui K, Himoto T, Masaki T: *Albumin-Bilirubin Score Differentiates Liver Fibrosis Stage and Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Virus Infection: A Retrospective Cohort Study*. *Am J Trop Med Hyg* 2019, 101(1):220-225.

36. Fujita K, Nomura T, Morishita A, Shi T, Oura K, Tani J, Kobara H, Tsutsui K, Himoto T, Masaki T: *Prediction of Transplant-Free Survival through Albumin-Bilirubin Score in Primary Biliary Cholangitis*. *J Clin Med* 2019, 8(8).

**Tables**
| Table 1.                                      | Total | Definite | Probable | P value |
|----------------------------------------------|-------|----------|----------|---------|
| Number of patients                            | 121   | 72       | 49       | -       |
| Age (years)                                   | 58 (49 - 71) | 58 (49 - 69) | 58 (50 - 73) | 0.3559 |
| Female/male                                   | 104/17 | 67/5     | 37/12    | 0.0082 |
| IAIHG                                         | 17 (13 - 19) | 18 (17 - 20) | 13 (12 - 14) | < 0.0001 |
| Simplified score                              | 6 (5 - 7) | 7 (6 - 7) | 5 (4 - 6) | < 0.0001 |
| T-Bil (µmol/l)                                | 13.8 (10.3 - 24.1) | 13.8 (10.3 - 27.5) | 13.8 (10.3 - 20.6) | 0.5066 |
| Total protein (g/l)                           | 75 (67 - 82) | 75 (66 - 82) | 75 (68 - 82) | 0.5169 |
| Albumin (g/l)                                 | 37 (32 - 41) | 35 (30 - 40) | 39 (33 - 42) | 0.0175 |
| AST (U/l)                                     | 72 (41 - 125) | 87 (39 - 141) | 56 (45 - 110) | 0.2601 |
| ALT (U/l)                                     | 70 (39 - 134) | 83 (38 - 142) | 63 (41 - 101) | 0.2808 |
| ALP (U/l)                                     | 301 (212 - 435) | 308 (213 - 436) | 299 (200 - 430) | 0.8571 |
| Platelet (x 10^9/l)                           | 195 (151 - 236) | 190 (151 - 234) | 198 (161 - 257) | 0.3407 |
| IgG (g/l)                                     | 23.1 (17.4 - 28.5) | 25.3 (18.8 - 30.2) | 19.5 (13.0 - 25.0) | 0.0053 |
| ANA ≥ x40                                     | 109 (90.0%) | 69 (95.8%) | 40 (81.6%) | 0.0138 |
| Positive for AMA or Anti M2 Ab                | 20 (16.5%) | 4 (5.6%) | 16 (32.7%) | 0.0001 |
| Positive for HLA-DR4                         | 23 (19.0%) | 9 (12.5%) | 14 (28.6%) | 0.0270 |
| Moderate to severe status                     | 41 (33.9%) | 28 (38.9%) | 13 (26.5%) | 0.1586 |
| Fibrosis stage 4                              | 9 (7.4%) | 6 (8.3%) | 3 (6.1%) | 0.7376 |
| ALBI score                                    | -2.347 (-2.729 - -1.828) | -2.273 (2.648 - -1.719) | -2.528 (-2.760 - -1.994) | 0.0470 |
| Fibrosis-4 index                              | 2.473 (1.585 - 3.999) | 2.651 (1.687 - 3.780) | 2.093 (1.334 - 5.388) | 0.6251 |
| Follow up period, years                       | 4 (1 - 10) | 4 (1 - 11) | 3 (1 - 8.5) | 0.4913 |
| Steroid therapy                               | 41 (33.9%) | 30 (41.2%) | 11 (22.4%) | 0.0284 |
| Nonremission                                  | 9 (7.4%) | 6 (8.3%) | 3 (6.1%) | 0.7376 |
|                | Count 1 | Count 2 | Count 3 | p-value |
|----------------|---------|---------|---------|---------|
| HCC            | 2 (1.7%)| 2 (2.8%)| 0 (0%)  | 0.5140  |
| Death          | 10 (5.8%)| 4 (5.6%)| 6 (12.2%)| 0.3130  |

Data are presented as median (interquartile range) or number (%).

IAIHG, International Autoimmune Hepatitis Group; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; ANA, anti-nuclear antibody; AMA, anti-mitochondrial antibody; HLA-DR4, human leukocyte antigen death receptor 4; ALBI, albumin-bilirubin score; HCC, hepatocellular carcinoma
Table 2.
Predictive prognostic factors for overall survival

| Characteristic                  | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | Hazard ratio        | 95% CI                | P value | Hazard ratio | 95% CI        | P value |
| Probable AIH                   | 1.885               | 0.574 - 6.190         | 0.2963  | 2.446        | 0.660 - 9.075 | 0.1810  |
| Age (years)                    | 1.073               | 1.012 - 1.139         | 0.0193  | 1.099        | 1.029 - 1.173 | 0.0047  |
| Male sex                       | 1.478               | 0.313 - 6.981         | 0.6221  | -            | -              | -       |
| T-Bil (μmol/l)                 | 0.993               | 0.971 - 1.017         | 0.5784  | -            | -              | -       |
| Total protein (g/l)            | 0.698               | 0.357 - 1.363         | 0.2920  | -            | -              | -       |
| Albumin (g/l)                  | 0.944               | 0.854 - 1.043         | 0.2576  | -            | -              | -       |
| AST (U/l)                      | 0.998               | 0.993 - 1.004         | 0.5513  | -            | -              | -       |
| ALT (U/l)                      | 0.992               | 0.978 - 1.005         | 0.2260  | -            | -              | -       |
| ALP (U/l)                      | 1.000               | 0.998 - 1.002         | 0.8143  | -            | -              | -       |
| Plt (×10^9/l)                  | 0.990               | 0.978 - 1.002         | 0.0993  | -            | -              | -       |
| Negative for ANA               | 1.004               | 0.128 - 7.880         | 0.9968  | -            | -              | -       |
| IgG (mg/dl)                    | 1.000               | 0.999 - 1.001         | 0.5656  | -            | -              | -       |
| Moderate to severe status      | 1.023               | 0.268 - 3.910         | 0.9730  | 0.421        | 0.088 - 2.025 | 0.2803  |
| Fibrosis stage 4               | 4.004               | 1.058 - 15.15         | 0.0410  | 8.943        | 1.972 - 40.55 | 0.0045  |
| ALBI score                     | 1.98                | 0.826 - 4.747         | 0.1257  | -            | -              | -       |
| Fibrosis-4 index               | 1.279               | 1.054 - 1.552         | 0.0126  | -            | -              | -       |
| Nonremission                   | 1.977               | 0.426 - 9.176         | 0.3843  | 4.949        | 0.781 - 31.35 | 0.0895  |
IAIHG, International Autoimmune Hepatitis Group; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; Plt, platelet; ANA, anti-nuclear antibody; ALBI, albumin-bilirubin score; CI, confidence interval

Figures

Figure 1

Staging of liver fibrosis in autoimmune hepatitis a) using albumin bilirubin score and b) using the fibrosis-4 index. The albumin-bilirubin score differentiates stage 4 from stage 1-3 (p = 0.0001), but the fibrosis-4 index did not (p = 0.2225). c) Receiver operating characteristic analysis reveals that an albumin-
bilirubin score of -1.994 diagnoses stage 4 with area under the curve of 0.8586 (p = 0.0004). ALBI, albumin-bilirubin; CI, confidence interval