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＜Meeting Report＞

自己免疫性肝炎の診断指針・治療指針（2013年）

厚生労働省「難治性の肝・胆道疾患に関する調査研究」班　自己免疫性肝炎分科会
自己免疫性肝炎分科会長　恩地森一[1)2)*]
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Ⅰ．概念

自己免疫性肝炎（Autoimmune hepatitis：AIH）は中年以降の女性に好発する原因不明の肝疾患で，その発症進展には遺伝的素因[1]，自己免疫機序が関与することが想定されている．

臨床的には①抗核抗体，抗平滑筋抗体などの自己抗体陽性[2]，②血清IgG高値を高率に伴う．発症には急性，慢性のいずれも存在するが，無症候性で何らかの機会の血液検査でAST，ALTの上昇により発見されることがある．急性発症の場合には，①，②の特徴を示さず急激に進展，肝不全へと進行する場合がある．

多くの症例では，副腎皮質ステロイド投与が極めて良く奏効し，多くは投与によりAST，ALTは速やかに基準値内へと改善するが，治療開始が遅れた場合，有効性は低下する．また少数例では副腎皮質ステロイド抵抗性を示す．

組織学的には，典型例では慢性肝炎像を呈し，門脈域の線維性拡大，同部への単核球浸潤を認め，浸潤細胞には形質細胞が多いことが特徴である．肝細胞の，多数の巣状壊死，帯状，架橋形成性肝壊死もしばしばみられ，また肝細胞ロゼット形成も少なからずみられる．門脈域の炎症が高度の場合には胆管病変も伴うことがあるが，胆管消失は稀である．初診時既に肝硬変へ進展している症例もある．また，肝細胞癌を伴うこともある．

診断には上記の諸特徴に加え，肝炎ウイルスを含むウイルス感染，薬物性肝障害，非アルコール性脂肪肝炎など既知の肝障害の原因を除外することが重要である．診断には国際自己免疫性肝炎グループ（International Autoimmune Hepatitis Group：IAIHG）の改訂版国際診断スコアが有用で，副腎皮質ステロイド投与の可否については簡易型スコアが参考になる．

註

1. 本邦ではHLA-DR4陽性症例が高頻度である
2. 核抗抗体，抗平滑筋抗体が共に陰性の場合には肝腎ミクロソーム抗体1型の測定が必要である．なお，抗核抗体は培養HEp-2細胞を用いた免疫蛍光抗体法により判定する．

Ⅱ．診断

1. 他の原因による肝障害が否定される
2. 抗核抗体陽性あるいは抗平滑筋抗体陽性
3. IgG高値（＞基準上限値1.1倍）
4. 組織学的にinterface hepatitisや形質細胞浸潤がみられる
5. 副腎皮質ステロイドが著効する

典型例

上記項目で1を満たし，2～5のうち3項目以上を認める．

非典型例

上記項目で1を満たし，2～5の所見の1～2項目を認める．

註

1. 副腎皮質ステロイド著効所見は治療的診断となるので，典型例・非典型例ともに，治療開始前に肝生検を行い，その組織所見を含めて診断することが原則である．ただし，治療前に肝生検が施行できないときは診断後速やかに副腎皮質ステロイド治療を開始する．
2. 国際診断スコアが計算できる場合にはその値を参考とし，疑診以上は自己免疫性肝炎と診断する．
3. 診断時，既に肝硬変に進展している場合があることに留意する．
4. 急性発症例では，上記項目2，3を認めない場合がある．また，組織学的に門脈域の炎症細胞を伴わず，中心静脈域の壊死，炎症反応と形質細胞を含む単核球の浸潤を認める症例が存在する．
5. 診断が確定したら，必ず重症度評価を行い，重症の場合には遅滞なく，中等症では病態に応じ専門機関へ紹介する．なお，1のみを満たす症例で，重症度より急性肝不全が疑われる場合も同様の対応をとる．
6. 簡易型スコアが疑診以上の場合は副腎皮質ステロイド治療を考慮する．
7. 抗ミトコンドリア抗体が陽性であっても，簡易型スコアが疑診以上の場合には副腎皮質ステロイド治療を考慮する．自己免疫性肝炎での抗ミトコンドリア抗体陽性率は約10%である．
8. 薬物性肝障害（Drug-induced liver injury：DILI）の鑑別にはDDW-J 2004薬物性肝障害診断スコアおよびマニュアルを参考にする．
9. 既知の肝障害を認め，この診断指針に該当しない自己免疫性肝炎も存在する．

Ⅲ．自己免疫性肝炎の重症度判定

<table>
<tr><th>臨床徴候</th><th>臨床検査所見</th><th>画像検査所見</th></tr>
<tr><td>①肝性脳症あり</td><td>① AST，ALT＞200 IU/l</td><td>①肝サイズ縮小</td></tr>
<tr><td rowspan="2">② 肝濁音界縮小または消失</td><td>②ビリルビン＞5 mg/dl</td><td>②肝実質の不均質化</td></tr>
<tr><td>③プロトロンビン時間＜60%</td><td></td></tr>
<tr><td colspan="3">重　症：次の1，2，3のいずれかが見られる．1．臨床徴候：①または②．2．臨床検査所見：①＋③または②＋③，3．画像検査所見：①または②</td></tr>
<tr><td colspan="3">中等症：臨床徴候：①，②，臨床検査所見：③，画像検査所見：①，②が見られず，臨床検査所見：①または②が見られる．</td></tr>
<tr><td colspan="3">軽　症：臨床徴候：①，②，臨床検査所見：①，②，③，画像検査所見：①，②のいずれも見られない．</td></tr>
</table>

註

1. 重症と判断された場合，遅滞なく肝臓専門医のいる医療機関への紹介を考慮する．
2. 重症の場合，劇症肝炎分科会の予後予測モデル，MELDも参考にする．
3. 中等症の症例で，プロトロンビン時間が60%以下，あるいは黄疸高度の場合も専門機関への紹介を考慮する．

Ⅳ．治療

1. 診断が確定した例では原則としてプレドニゾロンによる治療を行う．
2. プレドニゾロン初期投与量は充分量（0.6 mg/kg/日以上）とし，血清トランスアミナーゼ値と血清IgG値の改善を効果の指標に漸減する．維持量は血清トランスアミナーゼ値の正常化をみて決定する．
3. ウルソデオキシコール酸（600 mg/日）は，プレドニゾロンの減量時に併用あるいは軽症例に単独投与することがある．
4. 再燃を繰り返す例や副作用のためプレドニゾロンを使用しにくい例では，アザチオプリン（保険未収載，50-100 mg/日）の使用を考慮する．

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Diagnosis and treatment guide for autoimmune hepatitis in Japan, 2013

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Original Article

Prognosis of autoimmune hepatitis showing acute presentation

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Aim: The number of patients with autoimmune hepatitis (AIH) showing acute presentation has increased. This study aimed to assess their prognosis.

Methods: A survey of AIH patients by sending questionnaires was performed, and 96 patients showing acute presentation were investigated.

Results: The median age was 58 years and 78 patients (81%) were female. Eighty-four patients (88%) were positive for antinuclear antibody and/or anti-smooth muscle antibody. The median serum immunoglobulin G level was 2252 mg/dL. Twenty-five patients (26%) showed histological acute hepatitis. As initial treatment, 88 patients (92%) were treated with corticosteroid, and 28 of them received pulse steroid treatment. Overall, 11 patients (11%) reached fatal outcomes (nine death and two liver transplantation). Patients with histological acute hepatitis showed higher serum bilirubin levels, lower prothrombin activities and higher prothrombin time–international normalized ratios (PT-INR) and reached fatal outcomes more frequently. With a multivariate logistic regression analysis, prothrombin activity and PT-INR at presentation was associated with fatal outcomes. Nine of 13 patients (69%) showing prothrombin activity of 40% or lower at presentation and nine of 19 patients (47%) showing PT-INR of 1.5 or higher reached fatal outcomes. Furthermore, of 13 patients showing prothrombin activity of 40% or lower and/or PT-INR of 1.5 or higher at presentation who were treated with pulse steroid treatment, four (31%) died from infectious disease.[α]

Conclusion: Prothrombin activity and PT-INR are prognostic factors for AIH showing acute presentation. Physicians should pay attention to the development of infectious disease when pulse steroid treatment is performed.[α]

Key word: acute presentation, autoimmune hepatitis, prothrombin activity, prothrombin time–international normalized ratio, pulse steroid treatment[α]

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[α]Changes made on 30 November 2012, after first online publication: This version replaces the one previously published. The key difference between the two versions is that the revised version includes the variable of prothrombin time-international normalized ratios (PT-INR) in the study.

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INTRODUCTION

AUTOIMMUNE HEPATITIS (AIH) was first reported as a chronic and progressive disease in young women showing jaundice, hypergammaglobulinemia and amenorrhea by Waldenström in 1950.[1] Thereafter, AIH had been considered to be chronic liver disease characterized by histological interface hepatitis, hypergammaglobulinemia and circulating autoantibodies, and most patients successfully respond to corticosteroid treatment.[2] However, there has been no disease-specific marker for a diagnosis of AIH, and the diagnosis has been made based on various diagnostic criteria.[3-6]

After the proposal of the criteria for diagnosis of AIH in 1993 by the International Autoimmune Hepatitis Group (IAIHG),[3] the number of patients showing atypical features has increased.[7] AIH showing acute presentation corresponds to them. Up to now, several studies based on small cohorts were reported concerning clinical features of AIH showing acute presentation.[8-10] Generally, AIH showing acute presentation has been reported to be characterized by histological zone 3 necrosis.[8-10] On the other hand, clinical and laboratory features of AIH showing acute presentation have been controversial. Nikias *et al.*[8] reported that AIH showing acute presentation was undistinguished by clinical and laboratory features from the disease showing chronic presentation and probably acute exacerbation of pre-existing disease. However, Abe *et al.*[9] described that acute AIH showed higher serum transaminase levels and lower serum gammaglobulin levels compared with chronic AIH. Furthermore, the response to corticosteroid has been uncertain. Nikias *et al.*[8] showed that AIH showing acute presentation responded to corticosteroid as well as the disease showing chronic presentation. However, Abe *et al.*[9] reported that 60% of acute AIH showing serum bilirubin levels more than 10 mg/dL at presentation did not respond to corticosteroid. Ichai *et al.*[11] also described that corticosteroid was useless for severe AIH.

Recently, the classification of AIH showing acute presentation into two types was proposed.[12] One is the acute exacerbation phase in which patients show clinical features of acute hepatitis with histological evidence of chronic hepatitis, and another is the acute hepatitis phase in which patients exhibit histological features of acute hepatitis. However, clinical features of AIH showing acute presentation have yet to be fully implemented. This study aimed to mainly assess the prognosis of AIH showing acute presentation.

METHODS

Patients

THE INTRACTABLE LIVER and Biliary Diseases Study Group of Japan, sponsored by the Ministry of Health, Welfare and Labor of Japan, carried out a survey of AIH patients by sending questionnaires to the hospitals with active members of this group. Two hundred and fifty-four patients diagnosed as having type 1 AIH from January 2007 to December 2008 were registered. All patients were seronegative for hepatitis B surface antigen. Two-hundred and fifty-three patients were seronegative for anti-hepatitis C virus antibody, and one was seropositive for anti-hepatitis C virus antibody but seronegative for serum hepatitis C virus RNA. In patients without bleeding tendency, evaluation of liver histology was performed before or just after commencing the initial treatment; however, in patients showing bleeding tendency, liver specimens were obtained after the recovery of bleeding tendency or at autopsy or liver transplantation. [Correction made on 30 November 2012, after first online publication: 'All patients underwent liver biopsy' was corrected to reflect a distinction between patients with and without bleeding tendency.]

We tentatively defined AIH patients showing acute presentation as those with acute onset of symptoms in conjunction with serum bilirubin levels of more than 5 mg/dL and/or serum alanine aminotransferase (ALT) levels of more than 10-fold the upper normal limit and having no history of any prior liver disease. Ninety-eight

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of the 254 patients fulfilled the criteria and were investigated in this study.

Diagnosis of AIH

Autoimmune hepatitis was diagnosed based on the revised scoring system proposed by the IAIHG.[4] A definite diagnosis of AIH based on this revised scoring system required a pretreatment score exceeding 15, while a probable diagnosis required a score between 10 and 15. Patients with an overlapping syndrome or a coexistent liver disease (e.g. primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease and alcohol-induced liver injury) were excluded from this analysis.

Detection of antinuclear antibody (ANA) in most patients was carried out using an indirect immunofluorescence technique with HEp-2 cells. Anti-smooth muscle antibody (ASMA) was assayed using an indirect immunofluorescence technique with rodent kidney and stomach cells.

Statistics

The SPSS statistical program ver. 11.0.1 J (SPSS, Chicago, IL, USA) was used for the statistical analysis.

Continuous variables were expressed as median and range. Dichotomous variables were compared by the χ^2-test. The Mann–Whitney *U*-test was used to evaluate the significance of differences in the continuous variables. Univariate and multivariate logistic regression analyses were performed using parameters at presentation and histological features in order to identify prognostic factors. [Correction made on 30 November 2012, after first online publication: treatment method was removed as a variable on which logistic regression analyses was performed.] The variables, which showed $P < 0.2$ by univariate analysis, were included into the multivariate analysis. A receiver–operator curve (ROC) was plotted to evaluate how accurately prognostic factors elicited by logistic regression analyses performed in predicting poor outcomes.[13] The validity of the model was measured by the area under the ROC (AUROC). $P < 0.05$ was considered significant.

RESULTS

Clinical features

OF 98 PATIENTS, two were excluded for lack of clinical data. Thus, 96 patients were included into this analysis.

Clinical, laboratory and histological features are shown in Table 1. Twenty-two patients had extrahepatic concurrent autoimmune diseases: 13 had autoimmune thyroiditis; three had systemic lupus erythematosus; two had Graves' disease; one each had progressive systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, and both autoimmune thyroiditis and Sjögren's syndrome.

Table 1 Clinical features of study population

Patients, *n*	96
Age (years)	58 (13–80)
Sex, female	78 (81%)
Extrahepatic concurrent autoimmune disease	22 (23%)
Diagnosis based on the revised criteria	
Definite diagnosis	41 (43%)
Laboratory data	
Bilirubin (mg/dL)	6.1 (0.5–32.6)
AST (IU/L)	533 (48–2631)
ALT (IU/L)	606 (34–3175)
Prothrombin activity (%)	75 (16–120)
PT-INR	1.2 (0.9–4.4)
IgG (mg/dL)	2252 (1067–7650)
ANA or ASMA, *n*	
≥1:40	84 (88%)
≥1:160	49 (51%)
Human leukocyte antigen DR4, *n*	28/46 (61%)
Histology, *n*	
Acute hepatitis	25 (26%)
Cirrhosis	3 (3%)

ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; PT-INR, prothrombin time–international normalized ratio.[α]

Histologically, 25 patients (26%) were classified as being in the acute hepatitis phase, and the remaining 71 (74%) the acute exacerbation phase.

Human leukocyte antigen (HLA) DR status was measured in 46 patients. DR4 was found in 28 patients (61%). None had DR3. Extrahepatic concurrent autoimmune diseases were developed more frequently in patients with DR4 compared with those without DR4 (46% vs 17%; $P = 0.04$). Especially, frequency of autoimmune thyroiditis was higher in patients with DR4 (32% vs 0%; $P = 0.007$).

As initial treatment, 28 patients (29%) received pulse steroid treatment of methylprednisolone (500–1000 mg/day for 2–3 days) and 60 (63%) received conventional prednisolone (PSL) treatment with a median dose of 40 mg/day. The other eight patients were mainly treated with ursodeoxycholic acid (300–600 mg/day) or glycyrrhizin.

As adverse effects of corticosteroid, of the 88 patients treated with corticosteroid, nine (10%) developed

diabetes, five each hyperlipidemia and infectious disease (two fungal infection, two pneumocystosis, one bacterial infection), three osteoporosis, and one each osteonecrosis of femoral head and hypertension.

Overall, nine patients (9%) died without liver transplantation: five from liver failure; two from fungal infection; one from bacterial infection; and one due to pneumocystosis. Two patients (2%) received liver transplantation. Thus, 11 patients (11%) reached fatal outcomes.

AIH in acute hepatitis phase

Patients in the acute hepatitis phase showed higher serum bilirubin levels, lower prothrombin activities, and higher prothrombin time-international normalized ratios (PT-INR).[α] There were no differences in age, serum transaminase levels, serum immunoglobulin (Ig)G levels, positive rates of ANA or ASMA, and the frequencies of HLA DR4 between patients in the acute hepatitis phase and those in the acute exacerbation phase (Table 2).

Overall, eight of 25 patients (32%) in the acute hepatitis phase and three of 71 patients (4%) in the acute exacerbation phase reached fatal outcomes ($P = 0.0002$).

Pulse steroid treatment

Patients treated with pulse steroid treatment showed higher serum bilirubin levels, lower prothrombin activities, higher PT-INR and a higher frequency of patients in the acute hepatitis phase.[α] There were no differences in serum transaminase levels, serum IgG levels and the positive rate of ANA or ASMA between patients treated with pulse steroid treatment and those with conventional PSL treatment (Table 3).

Seven of 28 patients (25%) treated with pulse steroid treatment and two of 60 (3%) treated with conventional PSL treatment reached fatal outcomes ($P = 0.004$).

Prognostic factors for AIH showing acute presentation

By univariate logistic regression analysis, bilirubin, transaminase, prothrombin activity, PT-INR and acute hepatitis phase were associated with fatal outcomes (Table 4). [Correction made on 30 November 2012, after first online publication: 'acute hepatitis phase and pulse steroid treatment were associated with fatal outcomes' was corrected to 'PT-INR and acute hepatitis phase were associated with fatal outcomes'.]

Multivariate logistic regression analysis revealed that only prothrombin activity was significantly associated with fatal outcomes (Table 5). Similarly, when, instead of prothrombin activity, PT-INR was included into a multivariate model, only PT-INR was significantly associated with fatal outcomes (per 1.0 increase: odds ratio, 40.0; 95% confidence interval, 2.36–1000; $P = 0.01$).[α]

Table 2 Clinical features of type 1 autoimmune hepatitis in acute hepatitis phase

Variables	Acute hepatitis phase	Acute exacerbation phase	*P*
Patients, *n*	25	71	
Age (years)	56 (26–79)	61 (13–80)	0.52
Sex, female	21 (84%)	57 (80%)	0.68
Extrahepatic concurrent autoimmune disease	4 (16%)	18 (25%)	0.34
Definite diagnosis based on the revised criteria	11 (44%)	30 (42%)	0.88
Laboratory data			
Bilirubin (mg/dL)	14.6 (1.0–32.6)	3.9 (0.5–26.1)	0.001
AST (IU/L)	532 (70–1619)	533 (48–2631)	0.47
ALT (IU/L)	607 (86–3175)	604 (34–2388)	0.78
Prothrombin activity (%)	53 (16–102)	77 (20–120)	0.01
PT-INR	1.6 (1.0–4.4)	1.2 (0.896–3.0)	0.005
IgG (mg/dL)	2123 (1110–4322)	2262 (1067–7650)	0.37
ANA or ASMA			
≥1:40	22 (88%)	62 (87%)	0.93
≥1:160	10 (48%)	39 (55%)	0.20
Human leukocyte antigen DR4, *n*	5/11 (45%)	23/35 (66%)	0.23

ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; PT-INR, prothrombin time-international normalized ratio.[α] [Correction made on 30 November 2012, after first online publication: Table was corrected to reflect 'lgG (mg/dL)' and 'ANA or ASMA' as 'Laboratory data'.]

Table 3 Clinical features of type 1 autoimmune hepatitis patients treated with pulse steroid treatment

Variables	Pulse steroid treatment	Conventional PSL treatment	*P*
Patients, *n*	28	60	
Age (years)	56 (13–77)	60 (22–80)	0.61
Sex, female	22 (79%)	49 (82%)	0.73
Extrahepatic concurrent autoimmune disease	6 (21%)	14 (23%)	0.84
Definite diagnosis based on the revised criteria	11 (39%)	26 (43%)	0.72
Laboratory data			
Bilirubin (mg/dL)	13.9 (1.5–32.6)	3.5 (0.5–26.1)	0.0002
AST (IU/L)	598 (98–2297)	518 (48–2631)	0.21
ALT (IU/L)	718 (86–3175)	598 (34–2388)	0.52
Prothrombin activity (%)	53 (18–95)	81 (20–105)	<0.0001
PT-INR	1.5 (1.0–3.5)	1.1 (0.9–4.4)	<0.0001
IgG (mg/dL)	2177 (1249–6554)	2316 (1110–7650)	0.89
ANA or ASMA, *n*			
≥1:40	24 (86%)	53 (88%)	0.73
≥1:160	13 (46%)	31 (52%)	0.65
Human leukocyte antigen DR4, *n*	9/16 (56%)	18/29 (62%)	0.70
Acute hepatitis phase	13 (46%)	10 (17%)	0.003

ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; PSL, prednisolone; PT-INR, prothrombin time–international normalized ratio.[α] [Correction made on 30 November 2012, after first online publication: Table was corrected to reflect 'lgG (mg/dL)' and 'ANA or ASMA' as 'Laboratory data'.]

Receiver–operator curves of prothrombin activity and PT-INR for estimating fatal outcomes are shown in Figure 1.[α] The AUROC of prothrombin activity and PT-INR were 0.93 and 0.92, respectively.[α] When the prognosis of patients presenting prothrombin activity of 40% or lower at presentation was estimated to be fatal, the sensitivity and specificity were 95% and 82%, respectively. On the other hand, when the prognosis of patients presenting PT-INR of 1.5 or higher at presentation was estimated to be fatal, the sensitivity and specificity were 88% and 82%, respectively.[α]

The prognosis of patients showing prothrombin activity of more than 40% or PT-INR of less than 1.5 at presentation was sufficient (Table 6).[α] On the other hand, nine of 13 patients (69%) showing prothrombin activity of 40% or lower and nine of 19 patients (47%) showing PT-INR of 1.5 or higher reached fatal outcomes.[α] In 28 patients undergoing pulse steroid treat-

Table 4 Prognostic factors related to fatal outcomes by univariate logistic regression model

Variables	Odds ratio	95% CI	*P*
Age, per 1-year increase	0.99	0.95–1.03	0.73
Sex, female	0.57	0.14–2.41	0.45
Definite diagnosis based on the revised criteria	2.14	0.56–8.16	0.26
Bilirubin, per 1 mg/dL increase	1.20	1.09–1.32	0.0001
AST, per 1 IU/L increase	1.00	0.99–1.00	0.03
Prothrombin activity, per 1% increase	0.90	0.86–0.95	<0.0001
PT-INR, per 1.0 increase	27.8	5.49–143	<0.0001
IgG, per 1 mg/dL increase	1.00	1.00–1.00	0.96
ANA or ASMA, ≥1:160	2.06	0.56–7.58	0.27
Acute hepatitis phase	10.7	2.55–44.6	0.001

ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CI, confidence interval; IgG, immunoglobulin G; PT-INR, prothrombin time–international normalized ratio.[α] [Correction made on 30 November 2012, after first online publication: Data for Pulse steroid treatment was removed from Table 4.]

Table 5 Prognostic factors related to fatal outcomes by multivariate logistic regression model

Variables	Odds ratio	95% CI	*P*
Bilirubin, per 1 mg/dL increase	1.04	0.88–1.22	0.64
AST, per 1 IU/L increase	0.99	0.99–1.00	0.07
Prothrombin activity, per 1% increase	0.91	0.84–0.98	0.01
Acute hepatitis phase	1.92	0.22–17.1	0.56

AST, aspartate aminotransferase; CI, confidence interval.
[Correction made on 30 November 2012, after first online publication: Data for Pulse steroid treatment was removed from Table 5; Odds ratio for 'AST' was changed from '1.00' to '0.99', and for 'Acute hepatitis phase', from '1.87' to '1.92'; '95% CI' changed for 'Bilirubin' from '0.88–1.23' to '0.88–1.22', and for 'Acute hepatitis phase', from '0.15–22.6' to '0.22–17.1'; *P* changed for 'Prothrombin activity' from '0.02' to '0.01', and for 'Acute hepatitis phase', from '0.62' to '0.56'.]

ment, three of nine patients (33%) with prothrombin activity of 40% or lower and seven of 13 patients (54%) with PT-INR of 1.5 or higher survived. Of 13 patients showing prothrombin activity of 40% or lower and/or PT-INR of 1.5 or higher treated with pulse steroid treatment, four (31%) died from infectious disease. [Correction made on 30 November 2012, after first online publication: 'Pulse steroid treatment did not improve their prognosis compared with conventional PSL treatment. Of nine patients showing prothrombin activity of 40% or lower and treated with pulse steroid treatment, four (44%) died from infectious disease.' was replaced with the data of prothrombin activity and PT-INR and survival outcomes for the 28 patients undergoing pulse steroid treatments.]

DISCUSSION

CURRENTLY, ACCEPTABLE CRITERIA for acute presentation or severe disease in AIH do not exist and have been under investigation by the Intractable Liver and Biliary Diseases Study Group of Japan. In this study, we tentatively defined AIH patients showing acute presentation as those with acute onset of symptoms in conjunction with serum bilirubin levels of more than 5 mg/dL and/or serum ALT levels of more than 10-fold the upper normal limit and having no history of any prior liver disease. Hereafter, the establishment of criteria for acute presentation or severe disease in AIH is desired.

Autoimmune hepatitis showing acute presentation has been reported to include not only histological acute

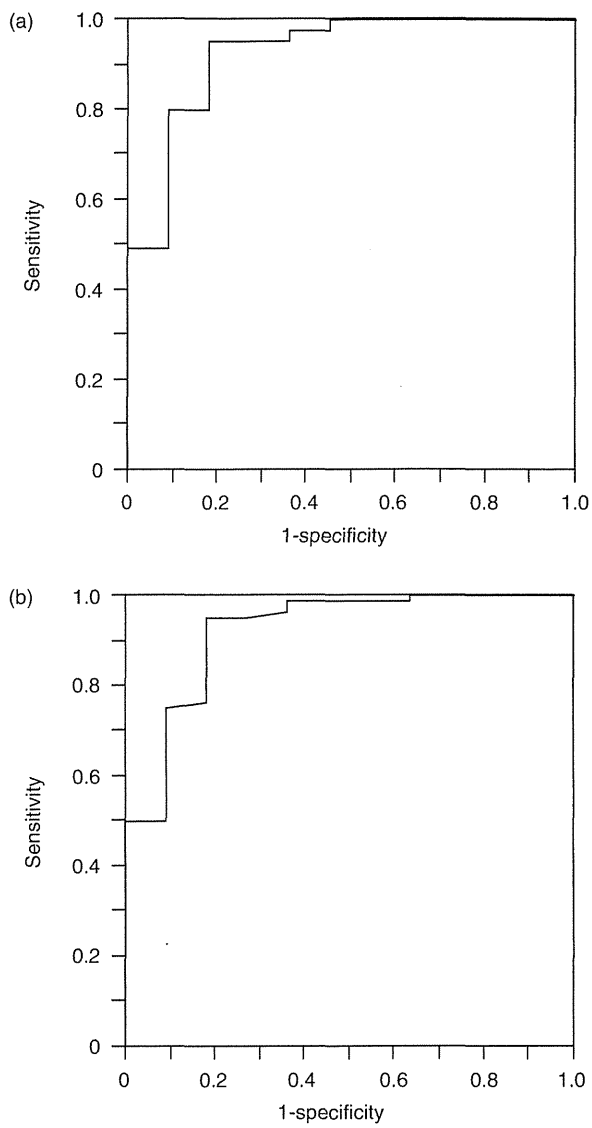

Figure 1 Receiver-operator curves (ROC) of (a) prothrombin activity and (b) prothrombin time-international normalized ratio (PT-INR) for estimating poor prognosis. The areas under the ROC were 0.93 and 0.92, respectively. When the prognosis of patients presenting prothrombin activity of 40% or lower at presentation was estimated to be fatal, the sensitivity and specificity were 95% and 82%, respectively. On the other hand, when the prognosis of patients presenting PT-INR of 1.5 or higher at presentation was estimated to be fatal, the sensitivity and specificity were 88% and 82%, respectively.[α] [Correction made on 30 November 2012, after first online publication: Figure 1 was replaced with the corrected figure.]

Table 6 Survival rate without liver transplantation based on prothrombin activity and PT-INR at presentation and treatment

	Pulse steroid treatment	Conventional PSL treatment	Others
Prothrombin activity			
≤40%	3/9 (33%)	1/2 (50%)	0/2 (0%)
>40%	18/19 (95%)	57/58 (98%)	6/6 (100%)
PT-INR			
<1.5	14/15 (93%)	55/56 (98%)	6/6 (100%)
≥1.5	7/13 (54%)	3/4 (75%)	0/2 (0%)

PSL, prednisolone; PT-INR, prothrombin time-international normalized ratio.[α] [Correction made on 30 November 2012, after first online publication: This version of Table 6 replaced the one previously published.]

hepatitis (acute hepatitis phase) but also acute exacerbation of the pre-existing chronic disease (acute exacerbation phase).[10,12,14] In this study, a quarter of patients showing acute presentation were classified as being in the acute hepatitis phase. In the previous reports, the percentage of patients in the acute hepatitis phase in AIH patients showing acute presentation has been reported to be 18–55%.[8,9,14] A half or more of AIH patients showing acute presentation may be classified as being in the acute exacerbation phase. [Correction made on 30 November 2012, after first online publication: in the previous version of this article, this paragraph was included as part of the following paragraph. 'In the previous reports, the percentage of patients in the acute hepatitis phase in AIH patients showing acute presentation has been reported to be 18–55%.[8,9,14] A half or more of AIH patients showing acute presentation may be classified as being in the acute exacerbation phase.' was added to the text.]

We evaluated the clinical features of AIH patients showing acute presentation. In comparison with the previous national surveys in Japan reported in 1993 and 1997,[6,15] serum IgG levels of AIH patients showing acute presentation in this study seemed to be lower. The national survey in 1997 revealed that a mean serum IgG level of AIH patients was 3143 mg/dL.[6] [Correction made on 30 November 2012, after first online publication: 'The national survey in 1997 revealed that a mean serum lgG level of AIH patients was 3143 mg/dL.[6]' was added to the text.] On the other hand, in this study, there was no difference in serum IgG levels between AIH patients in the acute hepatitis phase and those in the acute exacerbation phase. Thus, lower serum IgG levels may be characteristic of AIH showing acute presentation.

Up to now, clinical characteristics of AIH in the acute hepatitis phase have not been fully clarified. In this study, the survival of AIH patients showing acute presentation was generally good; however, AIH in the acute hepatitis phase showed severer hepatic failure and reached fatal outcomes more frequently than those in the acute exacerbation phase. Thus, AIH patients in the acute hepatitis phase may require liver transplantation more frequently, although there are no differences in laboratory findings between these two groups. Liver biopsy in patients with severe hepatic failure may involve an increased risk of bleeding. A new marker to distinguish between these two groups has been desired for the prediction of prognosis and the decisions regarding treatment.

In this study, prothrombin activity and PT-INR were found to be associated with the prognosis of AIH patients showing acute presentation, and prothrombin activity of 40% or lower and PT-INR of 1.5 or higher seemed to have acceptable accuracy to predict their prognosis.[α] Prothrombin activity of 40% or lower and PT-INR of 1.5 or higher are used as diagnostic parameters for acute liver failure.[α,16,17] Thus, for clinical physicians, prothrombin activity of 40% or lower and PT-INR of 1.5 or higher may be reasonable and easy to accept as prognostic factors for AIH patients showing acute presentation although a prospective validation study is required.[α]

The efficacy of pulse steroid treatment for AIH, which is sometimes performed for the purpose of improving intrahepatic inflammation quickly in patients with severe disease, has been uncertain. In the present study, pulse steroid treatment showed favorable outcome in patients with prothrombin activity of more than 40% or PT-INR of less than 1.5, but the prognosis was not good enough in those with prothrombin activity of 40% or lower and/or PT-INR of 1.5 or higher. The efficacy of pulse steroid treatment for AIH with severe liver disease needs to be clarified in future. [Correction made on 30 November 2012, after first online publication: 'In this study, pulse steroid treatment did not improve the prognosis of AIH showing acute presentation' was replaced with 'In the present study, pulse steroid treatment