Digestive and Liver Disease 42 (2010) 210–215

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Clinical features of autoimmune hepatitis diagnosed based on simplified criteria of the International Autoimmune Hepatitis Group

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ARTICLE INFO

Article history:
Received 27 January 2009
Accepted 17 June 2009
Available online 25 July 2009

Keywords:
Acute hepatitis
Antinuclear antibody
Diagnosis
Immunoglobulin G
Smooth muscle antibody

ABSTRACT

Background: Recently, simplified diagnostic criteria for autoimmune hepatitis have been proposed.
Aim: We aimed to evaluate usefulness of the simplified criteria.
Methods: We applied the simplified criteria to 176 autoimmune hepatitis patients diagnosed according to the revised scoring system proposed in 1999 (original criteria). Furthermore, in order to compare predictabilities between these two diagnostic criteria, we included 168 patients with other liver disease than autoimmune hepatitis.
Results: Of 176 autoimmune hepatitis patients, 85% were diagnosed with autoimmune hepatitis according to the simplified criteria, and patients diagnosed according to the simplified criteria showed a higher frequency of antinuclear antibodies and/or smooth muscle antibodies of 1:80 or greater and slightly higher serum levels of immunoglobulin G than those diagnosed according to the original criteria. However, 30% of male patients, 23% of patients with acute presentation, 50% of patients showing histological acute hepatitis and 46% of patients negative for antinuclear antibodies at presentation were not diagnosed with autoimmune hepatitis according to the simplified criteria. The simplified criteria showed lower sensitivity (85% vs. 100%) and higher specificity (99% vs. 93%) for autoimmune hepatitis than the original criteria.
Conclusions: The simplified criteria may be useless for the diagnosis of patients with atypical features, especially patients with histological acute hepatitis.

1. Introduction

The clinical characteristics of autoimmune hepatitis (AIH) are circulating autoantibodies, hypergammaglobulinemia, and histological interface hepatitis with lymphocytic and plasma cell infiltration into portal tracts [1,2]. The disease predominantly affects women and has generally good prognosis with immunosuppressive treatment.

In 1993, the International Autoimmune Hepatitis Group (IAIHG) proposed a scoring system to establish diagnostic criteria for AIH [3]. The specificity of this scoring system was insufficient, although the sensitivity was more than 90% [4]. Thus, in 1999, a revised scoring system (hereafter referred to as the original criteria) with sufficient specificity was proposed [4,5]. Even though the criteria were improved in this revision, the original criteria are complex and include a variety of parameters of questionable value. Several drugs (infliximab, minocycline, atorvastatin, hepatitis A vaccine) have been reported as possible triggers for AIH; however, "history of recent or current use of known or suspected hepatotoxic drugs" has been scored as −4 points [4,6–9]. Furthermore, 7.5% of AIH patients have circulating antimitochondrial antibodies (AMA); however, "positivity of AMA" has been scored as −4 points [10].

In 2008, the IAIHG proposed a simplified set of diagnostic criteria (hereafter referred to as the simplified criteria) that included autoantibodies such as antinuclear antibodies (ANA), smooth muscle antibodies (SMA), liver–kidney microsomal antibodies and antibodies to soluble liver antigen, immunoglobulin G (IgG), histology, and exclusion of viral hepatitis [11]. These criteria have 88% sensitivity and 99% specificity. The variables included in the simplified criteria are typical characteristics of AIH, so it is not clear whether AIH patients with atypical features (male, acute presentation, histological acute hepatitis, negativity for ANA) can be appropriately diagnosed. To determine the usefulness of the simplified criteria, we applied them to 176 AIH patients diagnosed according to the original criteria and 168 patients with other liver disease than AIH.

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1590-8658/$36.00
doi:10.1016/j.dld.2009.06.013

2. Methods

We included 176 patients who were admitted to the Okayama University Hospital or 6 affiliated hospitals between March 1989 and April 2008 and were diagnosed with definite or probable AIH based on the original criteria [4]. A definite diagnosis required a pretreatment score greater than 15, while a probable diagnosis required a score between 10 and 15. All patients were seronegative for hepatitis B surface antigen, anti-hepatitis C virus antibody, hepatitis C virus-RNA (as determined via polymerase chain reaction after reverse transcription), and anti-mitochondrial antibody, and all underwent liver biopsy. Patients with an overlapping syndrome or a coexistent liver disease (for example, primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic fatty liver disease, or alcohol-induced liver injury) were excluded from AIH patients.

Forty-two patients (26%) had concurrent autoimmune diseases: 18 had autoimmune thyroiditis, 4 had Sjögren's syndrome, 3 each had systemic lupus erythematosus, Graves' disease, or ulcerative colitis, 2 each had autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, progressive systemic sclerosis, or rheumatoid arthritis, one each had both autoimmune thyroiditis and autoimmune haemolytic anaemia, both systemic lupus erythematosus and Sjögren's syndrome, and both autoimmune thyroiditis and Sjögren's syndrome.

The titres of ANA were measured using an indirect immunofluorescence (IIF) technique with HEp-2 cells. SMA was assayed by the IIF technique using rat kidney and stomach cells. A serum titre of 1:40 or greater was positive for ANA or SMA. Antibodies to liver/kidney microsome type 1 (anti-LKM-1) were measured using an enzyme-linked immunosorbent assay using recombinant cytochrome P4502D6 as the antigen, and a serum value of 50.0 index or greater was positive. Twenty-four patients (13%) were negative for ANA (<1:40). Fifteen patients (9%) were positive for ANA titres of 1:40. Forty-five of 122 patients (37%) who were screened for SMA were negative for SMA (<1:40), and 24 were positive for SMA titres of 1:40. One hundred and fifty patients (85%) were positive for ANA and/or SMA titres of ≥1:80. None had anti-LKM-1. Sixty of 87 patients (69%) screened for human leukocyte antigen (HLA) DR status by the polymerase chain reaction sequence specific oligonucleotide hybridization method had DR4. None had DR3.

An acute presentation was defined by the presence of acute onset of symptoms (for example, jaundice and/or fatigue and/or anorexia) in conjunction with serum bilirubin levels ≥5 mg/dL and/or serum alanine aminotransferase (ALT) levels higher than 10-fold the upper normal limit.

Liver biopsy was performed with a Vim-Silverman needle (14-G) under laparoscopy, or with a 17-G needle under ultrasonography guidance, before or just after the introduction of initial treatment. Liver biopsy specimens were evaluated by two pathologists and diagnosed as acute or chronic hepatitis. A diagnosis of acute hepatitis was made on the basis of the presence of histologically predominant zone 3 necrosis with minimal lymphocytic and plasma cell infiltration into portal tracts, in the absence of interface hepatitis or portal fibrosis. Liver biopsy specimens diagnosed as showing chronic hepatitis underwent histological staging based on the classification of Desmet et al. [12].

All patients were re-scored according to the simplified criteria [11]. A definite diagnosis of AIH based on these simplified criteria required a pretreatment score greater than 6, while a probable diagnosis required a score of 6. Histologically, the required typical features were interface hepatitis, lymphocytic/lymphoplasmocytic infiltration into portal tracts, and rosetting of liver cells, while the compatible feature was chronic hepatitis with lymphocytic infiltration without all the other features considered typical.

To compare the clinical features of patients diagnosed with definite or probable AIH based on the original criteria to those of patients diagnosed with definite or probable AIH based on the simplified criteria, we analysed gender, age, frequency of acute presentation, concurrent autoimmune disease, laboratory data [albumin, bilirubin, aspartate aminotransferase (AST), ALT, IgG, ANA and/or SMA titre, HLA DR4], and histological features (staging of fibrosis, rosetting of liver cells, zone 3 necrosis).

Furthermore, in order to compare the predictability between the simplified criteria and the original criteria, we included 168 patients with other liver disease than AIH, who were admitted to the Okayama University Hospital between April 2005 and March 2008 and underwent liver biopsy (23 patients with chronic hepatitis B, 87 patients with chronic hepatitis C, 10 patients with drug-induced liver injury, 18 patients with primary biliary cirrhosis, 4 patients with primary sclerosing cholangitis, 17 patients with nonalcoholic steatohepatitis, 6 patients with simple steatosis, 3 patients with alcoholic liver disease).

Chronic hepatitis B and C were diagnosed by positive serology tests for serum hepatitis B surface antigen and anti-hepatitis C virus antibodies, respectively. Primary biliary cirrhosis was diagnosed with the presence of detectable antimitochondrial antibodies in serum and histologic findings [13]. Primary sclerosing cholangitis was diagnosed with cholangiographic findings and the presence of histological onion skin lesion [14]. The diagnosis of drug-induced liver injury was made based on the temporal relationship between drug ingestion and adverse reaction, exclusion of other diseases, some findings on liver biopsy [15]. Nonalcoholic steatohepatitis and simple steatosis were diagnosed by ultrasonography and histology after exclusion of other possible etiologies of fatty liver [16].

2.1. Statistics

Statistical analysis was performed using the SPSS statistical program (release 11.0.1J, SPSS Inc., Chicago, Illinois).

Continuous variables were expressed as medians and ranges. The Mann–Whitney *U*-test was used to evaluate differences in the continuous variables between two groups, and the Kruskal–Wallis *U*-test was performed among three groups. Dichotomous variables were compared by the χ^2-test. *P* values of less than 0.05 were considered significant.

3. Results

3.1. Diagnosis according to the simplified criteria in 176 AIH patients

Of 176 patients diagnosed with AIH according to the original criteria, 150 (85%) were also diagnosed with AIH according to the simplified criteria. Of 136 patients with definite AIH according to the original criteria, 107 (79%) scored ≥7 points (definite AIH), 20 (15%) scored 6 points (probable AIH), and 9 (6%) scored ≤5 points based on the simplified criteria. On the other hand, of 40 patients with probable AIH according to the original criteria, 12 (30%) scored ≥7 points, 11 (28%) scored 6 points, and 17 (42%) scored ≤5 points based on the simplified criteria. Thus, 26 patients (15%) who consisted of 9 patients with definite AIH and 17 with probable AIH according to the original criteria were not diagnosed as having AIH based on the simplified criteria (Fig. 1).

3.2. Comparison of clinical features between patients diagnosed according to the original criteria and those diagnosed according to the simplified criteria

Patients diagnosed according to the original criteria and those diagnosed according to the simplified criteria were indistinguishable by clinical and histological features. However, patients

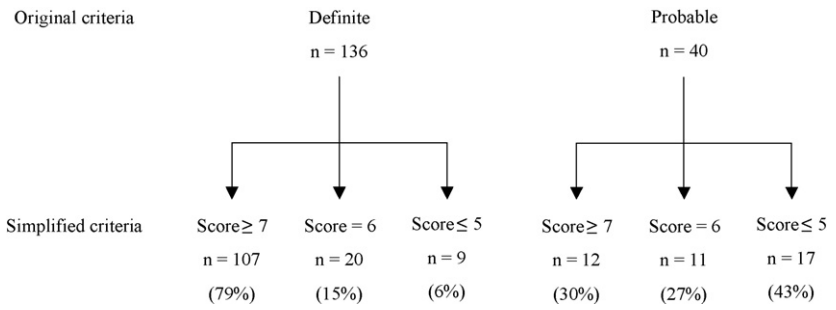

Fig. 1. Relation between the original criteria and the simplified criteria.

diagnosed according to the simplified criteria showed a higher frequency of ANA and/or SMA titres of 1:80 or greater and a slightly higher serum IgG levels ($P = 0.07$) than those diagnosed according to the original criteria (Table 1).

In AIH patients diagnosed according to the simplified criteria, patients with definite AIH had lower frequencies of acute presentation and histological acute hepatitis, a higher frequency of ANA and/or SMA titres of 1:80 or greater, and higher serum IgG levels than those with probable AIH. The same findings were shown in AIH patients diagnosed according to the original criteria, too. In particular, no patient with definite AIH according to the simplified criteria showed histological acute hepatitis. In patients diagnosed according to the original criteria, patients with definite AIH consisted of a higher proportion of females than those with probable AIH, while, in patients diagnosed according to the simplified criteria, no difference in the proportion of females was found between patients with definite AIH and those with probable AIH. Patients with probable AIH according to the simplified criteria showed a higher frequency of ANA and/or SMA titres of 1:80 or greater than those with probable AIH according to the original criteria (Table 2).

3.3. Simplified criteria in 136 patients with definite AIH based on the original criteria

According to the simplified criteria, patients with definite AIH showed higher serum IgG levels, a higher frequency of ANA and/or

Table 1
Clinical features of AIH patients diagnosed according to the original criteria and those diagnosed according to the simplified criteria.

	Original criteria	Simplified criteria
Patients, *n*	176	150
Gender, female (%)	153 (87)	134 (89)
Age (yr)	55 (16–79)	55 (16–79)
Form of clinical onset, acute presentation (%)	53 (30)	41 (27)
Concurrent autoimmune disease, *n* (%)	42 (24)	37 (25)
Laboratory data		
Albumin (g/dL)	3.8 (2.1–5.1)	3.8 (2.1–5.1)
Bilirubin (mg/Dl)	1.1 (0.3–29.2)	1.0 (0.3–22.6)
AST (IU/L)	162 (28–2330)	153 (33–2330)
ALT (IU/L)	203 (23–2161)	179 (25–2132)
IgG (mg/dL)	2541 (724–6562)	2625 (1085–6562)
ANA or ASMA ≥ 1:80, *n* (%)	150 (85)[a]	141 (94)[a]
HLA DR4, *n* (%)	60/87 (69)	50/70 (71)
Fibrosis staging, *n* (%)		
Acute hepatitis	10 (6)	5 (3)
Chronic hepatitis		
F1	51 (29)	45 (30)
F2	53 (30)	47 (31)
F3	44 (25)	37 (25)
F4	18 (10)	16 (11)
Rosetting of liver cells, *n* (%)	49 (28)	44 (29)
Zone 3 necrosis, *n* (%)	52 (30)	42 (28)

Significant difference from each other at level of [a]$P < 0.05$.

Table 2
Comparison of clinical features between AIH patients diagnosed according to the original criteria and those according to the simplified criteria.

	Original criteria		Simplified criteria	
	Definite	Probable	Definite	Probable
Patients, *n*	136	40	119	31
Gender, female (%)	127 (93)[a]	26 (65)[a]	108 (91)	26 (84)
Age (yr)	55 (16–79)	57 (16–77)	56 (18–79)	54 (16–74)
Form of clinical onset, acute presentation (%)	34 (25)[b]	19 (48)[b]	28 (24)[c]	13 (42)[c]
Concurrent autoimmune disease, *n* (%)	36 (26)	6 (15)	31 (26)	6 (19)
Laboratory data				
Albumin (g/dL)	3.8 (2.1–5.1)	3.8 (2.3–4.8)	3.8 (2.1–5.1)	4.0 (3.2–4.8)
Bilirubin (mg/Dl)	1.0 (0.3–29.2)	1.4 (0.3–25.8)	1.0 (0.3–22.6)	1.1 (0.3–17.0)
AST (IU/L)	155 (33–1716)	251 (28–2330)	153 (33–1716)	142 (40–2330)
ALT (IU/L)	184 (33–2132)	336 (23–2161)	171 (25–2132)	337 (28–1820)
IgG (mg/dL)	2610 (1085–6562)[d]	2003 (724–3990)[d]	2684 (1779–6562)[e]	1885 (1086–5894)[e]
ANA or ASMA ≥ 1:80, *n* (%)	129 (95)[f]	21 (53)[f,g]	117 (98)[h]	24 (77)[g,h]
HLA DR4, *n* (%)	48/66 (73)	12/21 (57)	40/55 (73)	10/15 (67)
Fibrosis staging, *n* (%)				
Acute hepatitis	5 (4)[i,j]	5 (13)[i]	0 (0)[j,k]	5 (16)[k]
Chronic hepatitis				
F1	38 (28)	13 (33)	35 (29)	10 (33)
F2	39 (29)	14 (34)	36 (30)	11 (35)
F3	38 (28)	6 (15)	33 (28)	4 (13)
F4	16 (11)	2 (5)	15 (13)	1 (3)
Rosetting of liver cells, *n* (%)	41 (30)	8 (20)	32 (27)	12 (39)
Zone 3 necrosis, *n* (%)	39 (29)	13 (33)	31 (26)	11 (35)

Significant difference from each other at level of [a,b,c,d,e,f,g,h,i,j,k]$P < 0.05$.

Table 3
The simplified criteria in 136 patients diagnosed with definite AIH based on the original criteria.

	Score ≥ 7	Score = 6	Score ≤ 5
Patients, *n*	107	20	9
Gender, female (%)	100 (93)	18 (90)	9 (100)
Age (yr)	55 (18–79)	55 (16–74)	58 (34–78)
Form of clinical onset, acute presentation (%)	25 (23)	7 (35)	2 (22)
Concurrent autoimmune disease, *n* (%)	29 (27)	4 (20)	3 (33)
Laboratory data			
Albumin (g/dL)	3.8 (2.1–5.1)	4.0 (3.3–4.5)	4.0 (3.0–4.2)
Bilirubin (mg/dL)	1.0 (0.3–22.6)	1.1 (0.4–17.0)	1.1 (0.6–29.2)
AST (IU/L)	167 (33–1716)	133 (53–1704)	97 (37–861)
ALT (IU/L)	183 (33–2132)	211 (56–1820)	132 (47–720)
IgG (mg/dL)	2747 (1779–6562)[a,b]	1821 (1085–5894)[a]	1554 (1370–1960)[b]
ANA or ASMA ≥ 1:80, *n* (%)	106 (99)[c,d]	16 (80)[c]	7 (78)[d]
HLA DR4, *n* (%)	38/52 (73)	7/10 (70)	3/4 (75)
Fibrosis staging, *n* (%)			
Acute hepatitis	0 (0)[e,f]	4 (20)[e]	1 (11)[f]
Chronic hepatitis			
F1	29 (27)	6 (30)	3 (33)
F2	33 (31)	5 (25)	1 (11)
F3	30 (28)	4 (20)	4 (45)
F4	15 (14)	1 (5)	0 (0)
Rosetting of liver cells, *n* (%)	30 (28)	10 (50)[g]	1 (11)[g]
Zone 3 necrosis, *n* (%)	28 (26)	8 (40)	3 (33)

Significant difference from each other at level of [a,b,c,d,e,f,g] $P < 0.05$.

SMA titres of 1:80 or greater, and a lower frequency of histological acute hepatitis than did those with probable AIH and those who scored ≤5 points. On the other hand, patients with probable AIH had a higher frequency of histological rosetting of liver cells than those who scored ≤5 points, and a slightly higher frequency of histological rosetting of liver cells compared to those with definite AIH ($P = 0.05$) (Table 3).

3.4. Simplified criteria in 40 patients with probable AIH based on the original criteria

According to the simplified criteria, patients with definite AIH or probable AIH showed higher serum IgG levels and a higher frequency of ANA and/or SMA titres of 1:80 or greater than those who scored ≤5 points. Patients with definite AIH had a slightly lower frequencies of acute presentation and histological acute hepatitis than those who scored ≤5 points (both $P = 0.07$). In particular, 4 of 5 patients with acute hepatitis scored ≤5 points according to the simplified criteria (Table 4).

3.5. Diagnosis according to the simplified criteria in male patients

Of the 23 male patients, 2 (9%) showed histological acute hepatitis, 18 (78%) did not showed histological rosetting of liver cells, 8 (35%) had serum IgG levels under the upper normal limit, and 6 (26%) had both ANA and SMA titres of 1:40 or less. Sixteen patients (70%) were diagnosed with AIH according to the simplified criteria (11 patients with definite diagnosis). The 16 patients were older [64 (31–76) years vs. 38 (19–61) years: $P = 0.004$] and had a lower frequency of histological zone 3 necrosis (13% vs.

Table 4
The simplified criteria in 40 patients diagnosed with probable AIH based on the original criteria.

	Score ≥ 7	Score = 6	Score ≤ 5
Patients, *n*	12	11	17
Gender, female (%)	8 (67)	8 (73)	10 (59)
Age (yr)	61 (20–74)	50 (16–71)	52 (19–77)
Form of clinical onset, acute presentation (%)	3 (25)	6 (55)	10 (59)
Concurrent autoimmune disease, *n* (%)	2 (17)	2 (18)	2 (12)
Laboratory data			
Albumin (g/dL)	3.8 (3.2–4.7)	3.9 (3.2–4.8)	3.7 (2.3–4.7)
Bilirubin (mg/dL)	0.9 (04–14.9)	0.8 (0.3–13.7)	1.8 (0.4–25.8)
AST (IU/L)	91 (35–1502)	430 (40–2330)	393 (28–1690)
ALT (IU/L)	121 (25–1467)	638 (28–1783)	526 (23–2161)
IgG (mg/dL)	2427 (2003–3990)[a]	2759 (1696–3820)[b]	1513 (724–2906)[a,b]
ANA or ASMA ≥ 1:80, *n* (%)	11 (92)[c]	8 (73)[d]	2 (12)[c,d]
HLA DR4, *n* (%)	2/3 (67)	3/5 (60)	7/13 (54)
Fibrosis staging, *n* (%)			
Acute hepatitis	0 (0)	1 (9)	4 (24)
Chronic hepatitis			
F1	6 (50)	4 (36)	3 (18)
F2	3 (25)	6 (55)	5 (28)
F3	3 (25)	0 (0)	3 (18)
F4	0 (0)	0 (0)	2 (12)
Rosetting of liver cells, *n* (%)	2 (17)	2 (18)	4 (24)
Zone 3 necrosis, *n* (%)	3 (25)	3 (27)	7 (41)

Significant difference from each other at level of [a,b,c,d] $P < 0.05$.

57%: $P = 0.02$), higher serum IgG levels [2314 (1085–3987) mg/dL vs.1525 (1170–1932) mg/dL: $P = 0.003$], and a higher frequency of ANA and/or SMA titres of 1:80 or greater (94% vs. 29%: $P = 0.001$) than the other 7 patients.

3.6. Diagnosis according to the simplified criteria in patients with acute presentation

Of 53 patients with acute presentation, 10 (19%) showed histological acute hepatitis, 34 (64%) did not showed histological rosetting of liver cells, 14 (26%) had serum IgG levels under the upper normal limit, and 14 (26%) had both ANA and SMA titres of 1:40 or less. Forty-one patients (77%) were diagnosed with AIH according to the simplified criteria (28 patients with definite diagnosis). The 41 patients showed a lower frequency of histological acute hepatitis (12% vs. 42%: $P = 0.02$), higher serum IgG levels [2630 (1662–4528) mg/dL vs. 1554 (724–2218) mg/dL: $P < 0.0001$], and a higher frequency of ANA and/or SMA titres of 1:80 or greater (90% vs. 17%: $P < 0.0001$) than the other 12 patients.

3.7. Diagnosis according to the simplified criteria in patients with histological acute hepatitis

Of 10 patients with histological acute hepatitis, 5 (50%) did not showed histological rosetting of liver cells, 4 (40%) had serum IgG levels under the upper normal limit, and 5 (%) had both ANA and SMA titres of 1:40 or less. All five patients (50%) who were diagnosed with AIH according to the simplified criteria were classified into probable diagnosis. The five patients had higher serum IgG levels [2986 (2630–3602) mg/dL vs. 1538 (1370–1724) mg/dL: $P = 0.01$] than the other five patients.

3.8. Diagnosis according to the simplified criteria in ANA-negative (<1:40) patients

Of 24 ANA-negative patients, 4 (17%) showed histological acute hepatitis, 18 (75%) did not showed histological rosetting of liver cells, 6 (25%) had serum IgG levels under the upper normal limit. Thirteen patients (54%) were diagnosed with AIH according to the simplified criteria (9 patients with definite diagnosis). The 13 patients had higher serum IgG levels [2722 (2047–3602) mg/dL vs. 1654 (724–2906) mg/dL: $P = 0.001$] and a higher frequency of SMA titres of 1:80 or greater (69% vs. 0%: $P = 0.002$) than the other 11 patients.

3.9. Predictability of the simplified criteria

Of 168 patients with other liver disease than AIH, according to the original criteria, one with primary biliary cirrhosis had a score of 16 points. Furthermore, 10 patients (1 patient with chronic hepatitis B, 2 patients with chronic hepatitis C, 2 patients with primary biliary cirrhosis, 1 with primary sclerosing cholangitis, and 4 patients with nonalcoholic steatohepatitis) scored between 10 and 15 points. The remaining 157 patients scored <10 points. On the other hand, according to the simplified criteria, one with drug-induced liver injury had a score of 6 points and the other 167 were scored $\leq$5 points.

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the diagnosis of AIH were 100%, 93%, 94%, 100% and 97%, respectively, according to the original criteria and 85%, 99%, 99%, 87% and 92%, respectively, according to the simplified criteria.

4. Discussion

The IAIHG proposed new simplified diagnostic criteria for AIH to facilitate the early diagnosis and the initiation of adequate immunosuppressive treatment in routine clinical practice [11]. In this study, 85% of patients diagnosed with AIH according to the original criteria were also diagnosed with AIH according to the simplified criteria. Thus, the simplified criteria are considered useful for the diagnosis of AIH. On the other hand, patients diagnosed according to the simplified criteria showed a higher frequency of ANA and/or SMA titres of 1:80 or greater and a slightly higher serum IgG levels than those diagnosed according to the original criteria. Approximately 20% of patients with atypical features, most of whom had serum IgG levels under the upper normal limit or both ANA and SMA titres of 1:40 or less, were not diagnosed with AIH according to the simplified criteria. Similarly to the report by Czaja [17], the simplified criteria showed greater specificity for a diagnosis of AIH than the original criteria in this study. AIH patients diagnosed according to the simplified criteria may have more typical features of the disease, and roles of autoantibodies and hypergammaglobulinemia for the diagnosis of AIH seem to be more important in the simplified criteria compared with in the original criteria.

Autoantibodies are still essential factors for a diagnosis of AIH; however ANA is negative in 20–30% of patients with type 1 AIH [18,19]. ANA-negative patients are not rare. Czaja [20] reported that 68% of ANA-positive patients lost their ANA during corticosteroid treatment, and that improvements in hypergammablobulinemia and histological necroinflammatory activity affected with the loss of ANA. They also reported that some patients who lost their ANA had recurrent positivity for ANA during relapse. ANA commonly disappear and reappear. On the other hand, in the IAIHG Report [4], the response to immunosuppressive treatment, especially relapse after an initial response, is a characteristic of AIH. Recently, we reported usefulness of the determination of ANA during the follow-up and the response to immunosuppressive treatment in the diagnosis of AIH with negativity for ANA at presentation [21]. The determination of ANA during the follow-up and the response to immunosuppressive treatment may be helpful and essential in order to confirm the diagnosis of AIH in patients negative for ANA at presentation.

In the original criteria, +2 points are assigned to female patients. In the diagnosis of AIH, the original criteria are advantageous to female patients compared with male patients. On the other hand, in the simplified criteria, gender is excluded from parameters associated with the diagnosis of AIH. However, in this study, 30% of the male patients diagnosed according to the original criteria were not diagnosed as AIH according to the simplified AIH. We considered that this was because 35% of male patients showed serum IgG levels under the upper normal limit and 26% had both ANA and SMA titres of 1:40 or less. Of the female patients diagnosed according to the original criteria, 15% showed serum IgG levels under the upper normal limit and 13% had ANA titres of 1:40 or less. Thus, 88% of the female patients were diagnosed as AIH according to the simplified AIH. A diagnosis of AIH for male patients may be distressful.

In this study, 5 of 10 AIH patients with histological acute hepatitis diagnosed according to the original criteria were not diagnosed with AIH according to the simplified criteria. Recently, the number of AIH patients with histological acute hepatitis has been increasing; however the diagnosis in these patients is not easy. They have lower serum IgG levels than those of AIH patients with chronic hepatitis [22,23]. Furthermore, the typical or compatible histological features of the simplified criteria do not include the features of acute hepatitis. In severe and fulminant forms of AIH, corticosteroid therapy is of little benefit, and many patients with these forms of AIH require liver transplantation [24]. In AIH patients with acute hepatitis, an accurate and prompt diagnosis is important. Thus, a new specific marker useful for the diagnosis of AIH with histological acute hepatitis is required.

In the simplified criteria, typical histology requires the presence of rosetting of liver cells. +2 points are assigned to patients

with typical histology; however +1 point is assigned to patients without rosetting of liver cells even if interface hepatitis and lymphocytic/lymphoplasmocytic infiltration into portal tracts exist. In this study, approximately 70% of patients did not show rosetting of liver cells although all liver biopsy specimens were 1.5 cm or more in length. Rosetting of liver cells is a form of liver cell regeneration developing in isolated surviving hepatocytes or small groups of hepatocytes within areas of collapse and is found in chronic active hepatitis due to various causes [25]. We consider that the necessity of rosetting of liver cells for the diagnostic criteria for AIH should be re-estimated.

In conclusion, the simplified criteria are generally useful for the diagnosis of AIH, and patients diagnosed with AIH according to the simplified criteria have more typical AIH features than those diagnosed according to the original criteria. However, approximately 20% of patients with atypical features diagnosed with AIH according to the original criteria are not diagnosed with AIH according to the simplified criteria. The simplified criteria may be useless for the diagnosis of patients with atypical features, especially patients with histological acute hepatitis who require a prompt introduction of immunosuppressive treatment. To improve the diagnostic ability of these criteria in patients with atypical features, a new specific marker for AIH may be required.

Conflict of interest statement

None.

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