Original Article

Comparative Evaluation of Simplified and Modified Histologic Criteria in the Diagnosis of Chronic Autoimmune Hepatitis

Mohammad H. Sanei[1], Babak Tamizifar[2], Elahe Mardani[3], Amir Ghaderi[2], Elnaz Tarigholeslami[3], Maryam Sanei[4]

[1]Department of Pathology, Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of General Physician, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The present study aimed at comparing simplified and modified histologic criteria alone and along with other indicators in the diagnosis of chronic autoimmune hepatitis (AIH).

Materials and Methods: In this cross-sectional study, 48 cases were selected from slides and paraffin blocks of patients suspected of chronic AIH according to clinical and laboratory data, including serology and autoantibody findings and viral hepatitis test results. Then, scores equal to 1 (compatible hepatitis), 2 (typical hepatitis), ≤6 (probable hepatitis), and ≥7 (definite hepatitis) were calculated based on the simplified histologic criteria, modified histologic criteria, and these two criteria, along with other indicators including antinuclear antibodies (Ab), smooth muscle Ab or liver-kidney microsomal Ab or soluble liver antigen (Ag) and serum immunoglobulin G (IgG) and absence of viral hepatitis.

Results: The results of this study revealed that based on the simplified histologic criteria, 43.8% and 56.3% of these cases were assigned a score of 1 and 2 points, respectively. However, calculating the total score using the simplified criteria along with other indicators showed that 60.4% and 39.6% of cases were assigned a score ≤6 and ≥7 points, respectively. Moreover, the modified histologic criteria indicated that 25% and 75% of cases were assigned a score of 1 and 2 points, respectively.

Conclusion: According to the findings of the present study, the modified histologic criteria compared to the simplified histologic criteria identified a higher percentage of patients assigned a score of 2 points. Moreover, modified histologic criteria, along with other indicators, were more accurate in detecting definite AIH (score ≥7 points).

Keywords: Autoimmune hepatitis, diagnosis, histology

Address for correspondence: Dr. Elahe Mardani, Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: ellahe.mardani94@gmail.com
Submitted: 13-Aug-2023; **Revised:** 19-Nov-2023; **Accepted:** 27-Nov-2023; **Published:** 28-Mar-2025

Introduction

Autoimmune hepatitis (AIH) is an autoimmune disease with an unknown cause and is diagnosed by determining hypergammaglobulinemia, increasing relevant autoantibodies in serum, periportal hepatitis in histology, and ruling out other diseases. The prevalence of this disease is estimated at 1.9 cases per hundred thousand people per year.[1-3]

It is challenging to distinguish this disease from other chronic liver diseases and can only performed by excluding other chronic liver diseases. Therefore, acquaintance with the clinical, laboratory, and histologic symptoms of AIH is of great importance.[4]

AIH diagnosis is based on a combination of clinical symptoms, liver biochemical tests, serological findings, viral hepatitis test results, and histologic findings in liver biopsy.[1,2] In 1992, the International AIH Group (IAIHG) determined criteria including 12 parameters to diagnose this disease;

Access this article online

Quick Response Code:

Website: https://journals.lww.com/ADBM

DOI: 10.4103/abr.abr_294_23

How to cite this article: Sanei MH, Tamizifar B, Mardani E, Ghaderi A, Tarigholeslami E, Sanei M. Comparative evaluation of simplified and modified histologic criteria in the diagnosis of chronic autoimmune hepatitis. Adv Biomed Res 2025;14:21.

however, examining all of them as routine check-ups was difficult, far from the reach of all areas, time-consuming, and expensive.[2-5] Therefore, in 2008, IAIHG proposed simpler criteria that included four parameters of autoantibodies, serum immunoglobulin G (IgG), viral hepatitis results, and histologic findings in liver biopsy (rosettes, emperipolesis, and interface hepatitis). Based on the score of the mentioned criteria, patients are divided into two categories of probable and definite AIH.[3]

Evaluating the diagnostic accuracy of the mentioned criteria in several studies has shown that simplified criteria have a high specificity of about 95% for the diagnosis of AIH (for scores 6 and 7 points).[3,5] In contrast, the sensitivity of the simplified criteria has been low, especially for diagnosing definite cases of this disease.[3,4,6]

IAIHG has not provided specific criteria for diagnosing AIH in certain cases, including the presence of concurrent diseases such as non-alcoholic fatty liver and acute cases of the disease.[7,8] AIH in acute cases leads to clinical symptoms of acute hepatitis; therefore, in such cases, the disease cannot be diagnosed using the simplified criteria as used for chronic cases.[5,9-11]

Furthermore, histologic features play an important role in the diagnosis of AIH, and identifying the pattern of liver damage is considered as a prerequisite for using simplified criteria such that it can divide hepatitis into two categories: typical and atypical.[3] However, the validity of histologic features in simplified criteria has not been thoroughly investigated. Moreover, examining the features of the two parameters of rosettes and emperipolesis has been rarely conducted in specialized centers.[12,13]

In this regard, considering the problems that exist in the histologic criteria for AIH diagnosis, modified histologic criteria, including interface activity, confluent necrosis lobular activity, portal inflammation, the number of plasma cells, and cytokeratin 7 (CK7) and orcein (copper) staining to rule out biliary diseases, have been introduced.[14] Just a few studies have been conducted on using the histologic criteria of a simple system for the definite diagnosis of AIH and proposed new criteria.[14-16]

Therefore, this study aimed at investigating and comparing simplified and modified histologic criteria alone and along with other indicators in the diagnosis of AIH and the possibility of using the modified criteria to improve the diagnosis of this disease.

Materials and Methods

The present study was a retrospective cross-sectional study. The studied population comprised the slide and paraffin blocks of patients suspected of chronic AIH according to clinical and laboratory data, including serology and autoantibody findings and viral hepatitis test results. These slides and paraffin blocks were archived in the pathology department of Al-Zahra Hospital and Dr. Sanei's laboratory in Isfahan during 2015–2016.

From the mentioned population, 48 samples were included in the study at a confidence level of 95%, a test power of 80%, the prevalence of AIH in patients with hepatitis symptoms greater than 0.5 ($P = 0.5$), and an error level of 0.1.

Inclusion criteria consisted of the availability of medical information, including laboratory findings (serology and autoantibodies findings and viral hepatitis test results) from archived slides and paraffin blocks of suspected AIH patients. If the block was damaged and it was not possible to prepare a suitable slide for staining, the sample was excluded from the study.

After obtaining the code of ethics from the ethics committee of Isfahan University of Medical Sciences, the archived slide and paraffin blocks of patients suspected of AIH (according to serology and autoantibodies findings and viral hepatitis test results) that underwent liver biopsy in 2015–2016 to diagnose the type of hepatitis in the pathology department of Al-Zahra Hospital and Dr. Saneyi's laboratory in Isfahan were extracted and included in the present study. First, the patients' general characteristics, including age, gender, as well as serum autoantibody, IgG tests, and viral hepatitis results, were recorded in the data collection form. Then, the liver biopsy of the patients was examined.

The IAIHG has proposed a scoring system for diagnosing AIH, which consists of four parameters that embrace histologic findings, viral hepatitis test results, serum IgG, and serological tests such as autoantibodies.

Table 1: Criteria proposed by the International Autoimmune Hepatitis Group (IAIHG)

Variable	Cutoff	Points
Antinuclear antibody or smooth muscle antibody	Equal to or greater than 1:40	1
Antinuclear antibody or smooth muscle antibody	Equal to or greater than 1:80	2[a]
Or liver–kidney-microsomal antibody	Equal to or greater than 1:40	
Or soluble liver antigen	Positive	
Serum immunoglobulin G	More than upper normal limit	1
	More than 1.10 times the upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with autoimmune hepatitis	1
	Typical for autoimmune hepatitis	2
Absence of viral hepatitis	Yes	2

Each of these parameters is assigned a score of 1 or 2 based on the results [Table 1]; finally, if the sum of the total score is ≤6 points, the diagnosis of probable AIH is made, and if it is ≥7 points, definite AIH is suggested.

In this study, first, the histologic criteria proposed by IAIHG (simplified criteria) were checked, and its total score was calculated. Second, the modified histologic criteria of Linda Ferrell's group were checked, and its total score was also calculated.

So, in the simplified histologic criteria, if the biopsy findings included rosettes, emperipolesis, and interface hepatitis lymphoplasma cells, the case was assigned a score of 2 points and diagnosed as the typical AIH condition. If the biopsy findings comprised only interface hepatitis (without the presence of rosettes and emperipolesis), the case was assigned a score of 1 point and diagnosed as an AIH-compatible condition. Moreover, in the absence of any of these features, the case was assigned a score of zero points. Then, the total score was also calculated, and definite and probable AIH classification was proposed based on these criteria.

In the next step, the modified histologic criteria were also examined, and a score of 0, 1, and 2 points was determined for each patient. Then, the total score was calculated using these histologic criteria, and the classification of definite and probable AIH was conducted [Tables 2 and 3].

In CK7 and orcein (copper) staining, the result of orcein (copper) staining was reported as positive or negative, and the result of CK7 staining was considered positive if at least three periportal hepatocytes were stained in at least two foci.[14] Plasma cell counts in four states of lack of plasma cells, low plasma cells (<2 in most portal/lobular areas), moderate plasma cells (2–4 in most portal/lobular areas), and high plasma cells (≥5 in most portal/lobular areas) was classified.

The severity of inflammation was determined based on interface activity: A0–A4, confluent necrosis: B1–B6, lobular activity: C0–C4, and portal inflammation: D0–D4 [Table 2].

Statistical analyses

The collected data were entered into the Statistical Package for the Social Sciences (SPSS) software (Version 26). Qualitative and quantitative data were presented as number (%) and standard deviation (SD) ± means, respectively. The Chi-squared test was used to compare the frequency distribution of qualitative data. In order to compare the diagnostic value of the simplified and modified histologic criteria alone and along with other indicators in the diagnosis of AIH, receiver operating characteristic (ROC) analysis was used, and the indicators of sensitivity, specificity, and the area under the curve (AUC) were reported. In all analyses, a significance level of less than 0.05 was considered.

Results

The present study was conducted on 48 samples of 13 (27.1%) men and 35 (72.9%) women with a mean age of 42.26 ± 8.35 years.

Table 2: Ishak grading scheme

Description	Score
A. Periportal or periseptal interface hepatitis (piecemeal necrosis)	
None	A0
Mild (focal, few portal areas)	A1
Mild/moderate (focal, most portal areas)	A2
Moderate (continuous around o50% of tracts or septa)	A3
Severe (continuous around 450% of tracts or septa)	A4
B. Confluent necrosis	
None	B0
Focal confluent necrosis	B1
Zone 3 necrosis in some areas	B2
Zone 3 necrosis in most areas	B3
Zone 3 necrosis + occasional portal–central bridging	B4
Zone 3 necrosis + multiple portal–central bridging	B5
Panacinar or multiacinar necrosis	B6
C. Focal (spotty) lytic necrosis, apoptosis and focal inflammation	
None	C0
One focus or less per ×10 objective	C1
Two to four foci per ×10 objective	C2
Five to ten foci per ×10 objective	C3
More than 10 foci per ×10 objective	C4
D. Portal inflammation	
None	D0
Mild, some or all portal areas	D1
Moderate, some or all portal areas	D2
Moderate/marked, all portal areas	D3
Marked, all portal areas	D4

Table 3: Modified histologic criteria for diagnosing autoimmune hepatitis

Histologic score	Item
Histologic score 0	Features not observed in autoimmune hepatitis: florid duct lesion (primary biliary cholangitis), bile duct loss, or copper/CK7 positivity (latter applicable only in cases without any bridging fibrosis)
Histologic score 1[a]	(1) Hepatitis with mild or moderate necroinflammatory activity with any of the following: (a) Ishak A2 (mild/moderate interface activity) (b) Ishak B1 (focal confluent necrosis) (c) Ishak C2 (2–4 foci of lobular activity per ×10) (2) CK7 and copper stains negative (applicable only for cases with Ishak fibrosis score of 3, this feature is not applicable to acute cases)
Histologic score 2	Hepatitis picture with any of the following: (1) Plasma cells: numerous or in clusters (2) High necroinflammatory activity featuring at least one of the following: (a) Ishak score A3 or higher (at least moderate interface activity) (b) Ishak B2 or higher (confluent necrosis in zone 3 or beyond) (c) Ishak C3 or higher (5 or more foci of lobular activity per ×10)

CK7=cytokeratin 7

According to the report of the simplified histologic criteria, 21 (43.8%) cases of these samples were assigned a score of 1

point, and 27 (56.3%) cases were assigned a score of 2 points, which were known as compatible hepatitis and typical hepatitis, respectively. Moreover, calculating the total score using the mentioned criteria along with other indicators (including antinuclear Ab, smooth muscle antibodies (Ab) or liver-kidney microsomal Ab or soluble liver antigen (Ag) and serum IgG, and absence of viral hepatitis) was reported to be ≤6 points (probable hepatitis) in 29 (60.4%) cases and ≥7 points (definite hepatitis) in 19 (39.6%) cases.

Moreover, examining the modified histologic criteria revealed that 12 (25%) and 36 (75%) cases were assigned a score of 1 and 2 points, respectively. Regarding the modified histologic criteria along with other indicators, 8 (16.7%) cases had a score ≤6 points (probable hepatitis), and 40 (83.3%) cases had a score ≥7 points (definite hepatitis) [Table 4].

Comparative evaluation of the simplified and modified histologic criteria figured out that 12 (57.1%) cases of the 21 patients that were assigned a score of 1 point by the simplified histologic criteria were assigned a score of 2 points by the modified histologic criteria. In other words, a higher percentage of patients was assigned a score of 2 points using the modified histologic criteria (*P* value = 0.018). Compared to the simplified histologic criteria, the modified histologic criteria had a sensitivity and specificity of 66.67% and 75%, respectively (*P* value = 0.006) [Table 5, Figure 1].

Evaluating the total score obtained from the sum of the points of the simplified and modified histologic criteria along with other indicators was performed. The results revealed that 21 (72.4%) cases of the 29 patients were assigned a total simplified score of ≤ 6 points; consequently, probable hepatitis was proposed for them. Moreover, all patients were assigned a total modified score ≥7, as a result of which definite AIH was proposed for them (*P* value = 0.015). Compared to the total simplified score, the total modified score had a sensitivity and specificity of 57.5% and 100%, respectively (*P* value < 0.001) [Table 6, Figure 2].

Table 4: Frequency distribution of simplified and modified histologic findings among the studied cases

Histologic Findings	Histologic score	*n*	Percentage
Simplified criteria*	1	21	43.8%
	2	27	56.2%
Simplified criteria with other indicators**	≤6	29	60.4%
	≥7	19	39.6%
Modified criteria*	1	12	25%
	2	36	75%
Modified criteria with other indicators**	≤6	8	16.7%
	≥7	40	83.3%

*Score 1: Compatible hepatitis; Score 2: Typical hepatitis. **Score ≤6: Possible hepatitis; Score ≥7: Definite hepatitis

Table 5: Comparative evaluation of the score obtained from simplified and modified histologic criteria

Modified criteria*	Simplified criteria*		*P*
	1 (*n*=21)	2 (*n*=27)	
1 (*n*=12)	9 (42.9%)	3 (11.1%)	0.018
2 (*n*=36)	12 (57.1%)	24 (88.9%)	
Sensitivity (95% CI)		66.67 [49.0–81.4]	
Specificity (95% CI)		75.00 [42.8–94.5]	
Positive Predictive Value		88.9 [70.8–97.6]	
Negative Predictive Value		42.9 [21.8–66.0]	
AUC (95% CI)		0.708 [0.56–0.86]	
P		0.006	

CI=Confidence interval. *Score 1: Compatible hepatitis; Score 2: Typical hepatitis

Table 6: Comparative examination of the score obtained from the simplified and modified histologic criteria along with other indicators

Modified criteria with other indicators*	Simplified criteria with other indicators*		*P*
	≤6 (*n*=29)	≥7 (*n*=19)	
≤6 (*n*=8)	8 (27.6%)	0 (0%)	0.015
≥7 (*n*=40)	21 (72.4%)	19 (100%)	
Sensitivity (95% CI)		57.5 [40.9–73.0]	
Specificity (95% CI)		100 [63.1–100.0]	
Positive Predictive Value		100.0 [85.2–100.0]	
Negative Predictive Value		32.0 [14.9–53.5]	
AUC (95% CI)		0.787 [0.71–0.86]	
P		<0.001	

CI=Confidence interval, AUC=Area under curve. *Score ≤6: Possible hepatitis; Score ≥7: Definite hepatitis

Discussion

The results of this study showed that 43.8% and 25% of cases were assigned a score of 1 point (compatible hepatitis), and 56.3% and 75% of cases were assigned a score of 2 points (typical) based on the report of simplified and modified histologic criteria, respectively. Moreover, 60.4% and 16.7% of cases were assigned a score ≤6 points (probable hepatitis), and 39.6% and 83.3% of cases were assigned a score ≥7 points (definite hepatitis) based on the reports of the sum of the scores obtained from these histologic simplified and modified criteria along with other indicators (such as antinuclear Ab, smooth muscle Ab or liver-kidney microsomal Ab or soluble liver Ag and serum IgG and absence of viral hepatitis), respectively.

In this regard, it should be noted that according to the simplified criteria proposed by IAIHG, the presence of three histologic features in the patient's biopsy, including rosettes, emperipolesis, and interface hepatitis, is mandatory in the diagnosis of typical AIH, although many previous studies have questioned the use of rosettes and emperipolesis as essential features to determine typical AIH and have expressed the problems of histologic interpretation, the limitation of the use of an optical microscope, and the medium sensitivity.[17-19] Hence, some attempts have been made to standardize diagnosis and have sought to find criteria with the least complexity and

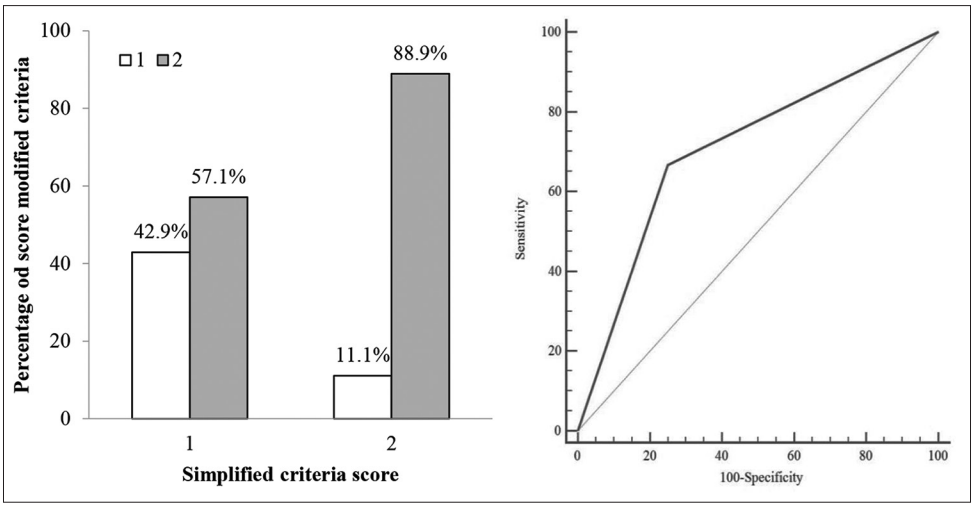

Figure 1: Frequency percentage and diagnostic value of the score obtained from the modified histologic criteria compared to the simplified histologic criteria

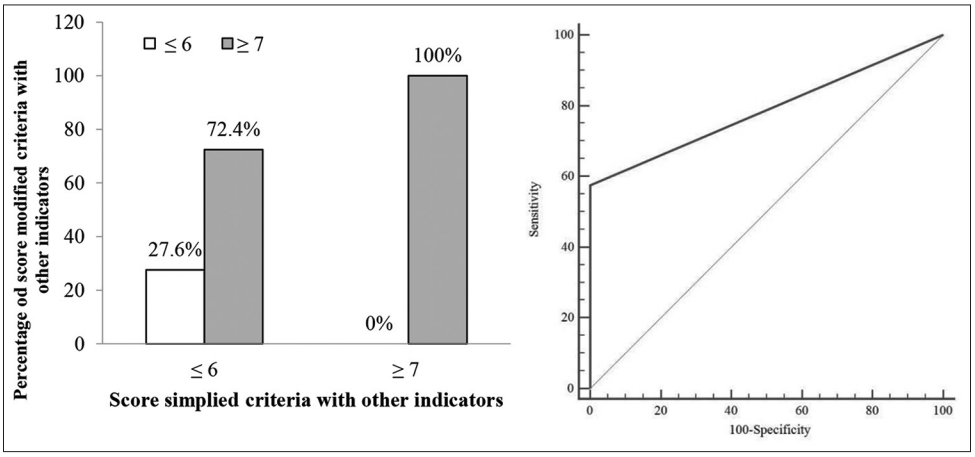

Figure 2: Frequency percentage and diagnostic value of the score obtained from the modified histologic criteria along with other indicators compared to the simplified histologic criteria along with other indicators

an easy clinical implementation.[20,21] For instance, modified histologic criteria with criteria such as interface activity, confluent necrosis, lobular activity, portal inflammation, the number of plasma cells, and CK7 and orcein (copper) staining have been proposed recently.[14-16] Therefore, in the modified histologic criteria, the histologic score of 1 or 2 points is specified based on the level of liver activity (interface and/or lobular and prominence of plasma cells).

Basically, a score of 1 point is assigned to mild hepatitis that has no evidence of biliary features, while a score of 2 points is assigned to numerous plasma cells or severe hepatitis. The absence of cholestatic features is mandatory on CK7 and copper stains, as a pattern like chronic hepatitis can be shown by chronic biliary disease. Chronic cholestasis has some well-known features, such as CK7-positive staining and copper accumulation in periportal hepatocytes. These features can differentiate biliary disease from chronic hepatitis.[12,13,22]

In the case of the presence of advanced fibrosis, CK7 positivity, and nonspecific copper accumulation can be observed regardless of etiology. Therefore, the mentioned feature cannot be employed for those having cirrhosis or bridging fibrosis. CK7 and copper stains are not useful in this respect as biliary disease is not considered for patients having presentations like acute hepatitis. Six primary biliary cholangitis cases were correctly scored using CK7 and copper stains, while a score of 1 point might be assigned to these cases considering the interface or lobular inflammatory activity.

In this regard, the findings of the present study revealed that the modified histologic criteria determined a higher percentage of patients with a score of 2 points than the simplified histologic criteria, such that its sensitivity and specificity as compared to the sensitivity and specificity of the simplified histologic criteria were reported to be 66.67% and 75%, respectively. Hence, it can be stated that the modified criterion can predict AIH cases with a higher sensitivity and specificity than the simplified criteria.

Consistent with the findings of this study, the results of Balitzer *et al*.'s[14] study also showed that the use of the modified

histologic criteria led to an increase in the number of AIH cases (with a score of 2 points) from 8 to 77%.

However, among retrospective studies published to validate the simplified criteria, the overall sensitivity for probable AIH (≤6 points) was in the range of 65–95%, and the overall specificity was in the range of 90–98%. Furthermore, for definite AIH cases (≥7 points), overall sensitivity was in the range of 15–87%, and overall specificity was 100%.[23] However, it seems no specific test can be applied to all patients with AIH due to the heterogeneous clinical characteristics of AIH, and it may be difficult to diagnose it in some patients with unusual manifestations. Therefore, the four indicators of liver histology, autoantibody titers, IgG levels, and the exclusion of viral hepatitis were used in the simplified criteria to differentiate between patients with and without AIH. These indicators, along with the scores of simplified or modified histologic criteria, can play a significant role in increasing and improving the accuracy of diagnosis.

In our study, the sum of the scores of simplified and modified histologic criteria, along with other indicators, showed that the modified histologic criterion had a higher percentage in identifying definite cases than the simplified histologic criterion such that as compared to the total simplified score, the total modified score had a higher sensitivity (57.5%) and specificity (100%) and can identify a higher percentage of definite AIH cases.

Qiu *et al*.'s[19] study also indicated that the simplified criteria had a high sensitivity (90%) and specificity (95%) for diagnosing probable AIH and also had a satisfactory diagnostic accuracy for definite AIH with a sensitivity of 62% and a specificity of 99%. Among definite AIH patients diagnosed by the modified criteria, less frequent positivity for autoantibodies or lower titers and lower IgG levels were reported for patients with excluded or downgraded diagnoses using the simplified criteria. However, significantly higher histologic scores were obtained by these patients compared to those with accordant diagnosis. The mentioned finding indicated the centrality of liver histology in AIH diagnosis, particularly in the case of employing the simplified criteria.

The present study revealed that the percentage of definite or typical cases increased from 75% to 83.3% by adding other indicators to the modified histologic criteria. In another study, it was reported that using the proposed histologic features, the histologic score of 2 increased from 8 to 77%, while the total simplified score of > 6 increased from 69 to 86%.[14] However, some other studies reported it to be about 65–95%, which was in line with the findings of our study.[3,6,23]

According to the reports of previous studies, it seems that the modified histologic criteria seem to improve the diagnosis of acute AIH, which in turn leads to well-timed immunosuppressive therapy because the high necroinflammatory activity might probably result in fast fibrosis progression in case of being left untreated.[14]

Finally, it should be mentioned that the small sample size and the limitation in the classification of AIH, primary biliary cholangitis, and nonautoimmune acute hepatitis can be the weak points of this study. However, the comparison of the simplified and modified criteria with and without other indicators among the Iranian race as the first study in this context can be considered as one of its strengths. Therefore, it is suggested to conduct more studies to achieve more definitive results regarding the distinction between these two criteria and their validation in the Iranian race.

Conclusion

According to the findings of the present study, a higher percentage of patients was assigned a score of 2 points based on the modified histologic criteria compared to the simplified histologic criteria. Moreover, the addition of other indicators (liver histology, autoantibody titers, IgG levels, and the exclusion of viral hepatitis) to these two histologic criteria resulted in an increase in definite AIH cases (a score ≥7 points). Therefore, in general, the diagnostic value of the modified histologic criteria alone or along with other indicators can have an acceptable diagnostic value in differentiating definite from probable AIH patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lohse AW, Sebode M, Jørgensen MH, Ytting H, Karlsen TH, Kelly D, *et al*. Second-line and third-line therapy for autoimmune hepatitis: A position statement from the European reference network on hepatological diseases and the International Autoimmune Hepatitis Group. J Hepatol 2020;73:1496-506.
2. Ducazu O, Degroote H, Geerts A, Schouten J, Van Vlierberghe H, Verhelst X. Diagnostic and prognostic scoring systems for autoimmune hepatitis: A review. Acta Gastro Enterol Belg 2021;84:487-95.
3. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-76.
4. Floreani A, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PS, Krawitt E, *et al*. Etiopathogenesis of autoimmune hepatitis. J Autoimmun 2018;95:133-43.
5. Yeoman AD, Westbrook RH, Al-Chalabi T, Carey I, Heaton ND, Portmann BC, *et al*. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group (IAIHG) criteria in acute and chronic liver disease. Hepatology 2009;50:538-45.
6. Domerecka W, Kowalska-Kępczyńska A, Michalak A, Homa-Mlak I, Mlak R, Cichoż-Lach H, *et al*. Etiopathogenesis and diagnostic strategies in autoimmune hepatitis. Diagnostics 2021;11:1418.
7. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E. Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54:374-85.
8. Wang CR, Tsai HW. Autoimmune liver diseases in systemic rheumatic diseases. World J Gastroenterol 2022;28:2527-45.
9. Pape S, Snijders RJ, Gevers TJ, Chazouilleres O, Dalekos GN, Hirschfield GM, *et al*. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76:841-9.

10. Muratori P, Granito A, Lenzi M, Muratori L. Limitation of the simplified scoring system for the diagnosis of autoimmune Hepatitis with acute onset. Liver Int 2021;41:529-34.
11. Tanaka A. Autoimmune hepatitis: 2019 update. Gut Liver 2020;14:430-8.
12. Mounajjed T, Oxentenko AS, Qureshi H, Smyrk TC. Revisiting the topic of histochemically detectable copper in various liver diseases with special focus on venous outflow impairment. Am J Clin Pathol 2013;139:79-86.
13. Lesna M, Hamlyn AN, Watson AJ. Intrahepatocytic copper and copper-binding protein in primary biliary cirrhosis. Digestion 1981;22:113-8.
14. Balitzer D, Shafizadeh N, Peters MG, Ferrell LD, Alshak N, Kakar S. Autoimmune hepatitis: Review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. Modern Pathology 2017;30:773-83.
15. Gurung A, Assis DN, McCarty TR, Mitchell KA, Boyer JL, Jain D. Histologic features of autoimmune hepatitis: A critical appraisal. Hum Pathol 2018;82:51-60.
16. Liwinski T, Schramm C. Autoimmune hepatitis—update on clinical management in 2017. Clin Res Hepatol Gastroenterol 2017;41:617-25.
17. Miyake Y, Iwasaki Y, Kobashi H, Yasunaka T, Ikeda F, Takaki A, *et al*. Clinical features of autoimmune hepatitis diagnosed based on simplified criteria of the International Autoimmune Hepatitis Group. Dig Liver Dis 2010;42:210-5.
18. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, *et al*. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54:931-9.
19. Qiu D, Wang Q, Wang H, Xie Q, Zang G, Jiang H, *et al*. Validation of the simplified criteria for diagnosis of autoimmune hepatitis in Chinese patients. J Hepatol 2011;54:340-7.
20. de Boer YS, van Nieuwkerk CM, Witte BI, Mulder CJ, Bouma G, Bloemena E. Assessment of the histopathological key features in autoimmune hepatitis. Histopathology 2015;66:351-62.
21. Kumari N, Kathuria R, Srivastav A, Krishnani N, Poddar U, Yachha SK. Significance of histopathological features in differentiating autoimmune liver disease from nonautoimmune chronic liver disease in children. Eur J Gastroenterol Hepatol 2018;25:333-7.
22. Goldstein NS, Soman A, Gordon SC. Portal tract eosinophils and hepatocyte cytokeratin 7 immunoreactivity helps distinguish early-stage, mildly active primary biliary cirrhosis and autoimmune hepatitis. Am J Clin Pathol 2001;116:846-53.
23. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, *et al*. 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 2020;72:671-722.