Evaluation of Validity and Efficiency of Diagnostic Criteria in Autoimmune Hepatitis in Children

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ABSTRACT

Background: *Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease with various clinical symptoms, but treatment and prevention of hepatic failure and cirrhosis is possible with early diagnosis. However, no specific test has been approved for the diagnosis of AIH. In 2008, the International Autoimmune Hepatitis Group (IAIHG) developed a simplified diagnostic scoring system that has been widely used in practice. Nevertheless, it cannot distinguish AIH from Primary Sclerosing Cholangitis (PSC) and consensus is lacking with respect to its validity, sensitivity, and applicability for children patients. The newer 2018 version also requires validation. The present study intends to evaluate the validity and efficiency of the IAIHG simplified scoring system and new scoring system in children with AIH.*

Methods: *The present study is a non-interventional case–control study covering 152 patients with hepatic diseases (83 patients with AIH and 69 patients with Wilson disease (WD)). Titers of autoantibodies, IgG levels, hepatic histology, and absence of viral hepatitis were scored and calculated according to IAIHG diagnostic criteria. Statistics software package (SPSS) and draft receiver operating characteristic (ROC) curves was used to analyze data and determine value of diagnostic criteria.*

Result: *In our study, both scoring systems' accuracy was good in AIH diagnosis, although new score displays higher sensitivity and specificity, suggestive of greater accuracy and predictive strength.*

Conclusion: *Our study is the first validation study of the new scoring system in diagnosing AIH, and further studies require verifying this scoring system.*

Keywords: *Autoimmune hepatitis (AIH), simplified scoring system, new scoring system, autoantibody, IgG level, children*

INTRODUCTION

Autoimmune hepatitis (AIH) is an immune liver disease that was first described in 1950 by Waldenstrom. The clinical presentation of AIH is highly variable. It can present acutely, chronically, or silently. The current pathogenetic theory for AIH refers to a complex interplay of immune deficiencies, environmental stimuli, and host genetic capabilities. This condition induces a cellular immune attack on hepatocytes, ultimately leading to a progressive, inflammatory disease accompanied by necrosis and fibrosis.[1] AIH can affect all ages, sexes, and races, while its clinical presentation could be more severe in children. Early diagnosis and early treatment by immunosuppressive drugs may be curative and prevent the development of cirrhosis and hepatic insufficiency,[2] even though diagnosis of AIH is sometimes difficult in terms of variability of disease presentations and absence of confirmed diagnostic criteria.[1]

The first standard diagnostic criteria for AIH diagnosis in adults was approved and developed by the International Autoimmune Hepatitis Group (IAIHG) in 1993,[3] and, in 1999, it was revised with improved specificity and simplicity to be applicable to children.[3, 4] However, its clinical application was challenging because it was too complex and could not differentiate AIH from Primary Sclerosing Cholangitis (PSC) and Overlap Syndromes.[5] In 2008, IAIHG proposed a simplified scoring system that consisted of 4 parameters indicating the presence of autoantibodies associated with AIH (anti-nuclear antibody (ANA) , Smooth Muscle Antibody(SMA), anti-LKM1 (liver kidney microsomal), anti-LC-1 (liver cytosol), and anti-SLA (soluble liver antigen)), IgG (immunoglobulin G) levels, hepatic histologic findings and absence of viral hepatitis.[1, 4] This scoring system was clinically used by the scientific community. Still, its validity, sensitivity, and specificity remain controversial.[5] Also, this scoring system

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cannot differentiate between AIH and PSC. Also, autoantibody titers are usually low in children or sometimes may be negative, especially in the first stages of the disease.[6] Although this scoring system is validated for AIH diagnosis of pediatric populations, various studies have produced contradictory results regarding its efficiency and accuracy in children. At the same time, the new scoring system presented in 2018[6] needs validation. So, we decided to use the IAIHG scoring system (2008) and the new scoring system (2018) in the diagnosis of AIH in children compared to other acute liver diseases (Wilson disease(WD) as the most common differential diagnostic factor and one of the items in the new diagnostic scoring system[7]) to confirm their use of those systems in children.

MATERIALS AND METHODS

The present study is a non-interventional case–control study in 152 patients with liver diseases (83 patients with AIH and 69 patients with WD) 1-18 years old patients, who were referred to hepatology clinic and Namazi hospital which are affiliated to Shiraz University of Medical Science from September 2012 to September 2018. Signed consent forms were existing in all the patient files in terms of using their data for clinical trials. Based on IAIHG criteria, the inclusion criteria included the presence of clinical symptoms, AIH confirmation based on serological tests, IgG levels, ANA, SMA, LKM, SLA, and P-ANCA autoantibodies, as well as unusual histological findings (compatible with AIH); such as acute hepatitis, portal lymphoplasmacytic infiltration, interface hepatitis, rosette formation, and emperipolesis.[8] Exclusion criteria included cases with a history of liver transplantation, patients who were treated with both AIH and WD diagnosis concomitantly, and those without appropriate response to standard AIH treatment. Once the demographics of patients were examined, the simplified diagnostic scoring criteria presented in 2008 by IAIHG[5] and the new scoring system of 2018[6] were compared. In the case of the simplified scoring system, a score of 6 means "probable" AIH while a score of 7 or higher is considered as "definitive" AIH, in the case of the new scoring system, a score of 7 means "probable" AIH while a score of 8 or higher is considered as "definitive" AIH. IgG was evaluated in respect to globin level by subsequently calculating serum globin in proportion to IgG.[5] Those cases with normal serum globin levels were received 0 score, while those with higher levels were scored 1 and cases 1.1 times larger than the normal level in the simplified scoring system received a score of 2 and cases 1.2 times larger than normal level than the upper normal level were scored 2 in the new scoring system. Data analysis and drawing of receiver operating characteristic (ROC) curves were performed by SPSS software to verify the specificity and sensitivity of the simplified and new scoring system and positive predictive value (PPV) and negative predictive value (NPV) values were calculated.

Main Points

- *Juvenile autoimmune hepatitis is a progressive liner disease, especially in childhood, with different presentations.*
- *Autoimmune hepatitis is curable by early diagnosis and proper treatment, but there is no specific diagnostic test.*
- *A simplified scoring system was developed for identifying AIH which is used widely in practice.*
- *A new scoring system was developed in 2018, but there is no study done to identify its accuracy and efficiency.*
- *Two scoring systems have good performance in the diagnosis of autoimmune hepatitis in childhood.*
- *A new scoring system has higher accuracy and predictive value.*

This article was found to be in accordance with the ethical principles and the national norms and standards with approval ID: IR.SUMS.MED.REC.1397.158.

The main limitation of our study is the small number of patients in 2 groups. In addition lack of other liver diseases except WD to compared with AIH

RESULTS

A group of 152 children under the age of 18 was studied (83 patients with AIH (case group, 46 girls, and 37 boys) and 69 patients with WD (control group, 25 girls, and 44 boys)). The average ages of patients with AIH and those with WD were 9.21% and 9.87%, respectively. Levene's test of homogeneity showed no significant age difference between AIH and WD groups (P = .298) while chi-square test showed a significant sex difference between AIH and WD groups (F > M, P = .007). The subjects were evaluated for autoantibody titer, frequency of IgG levels, and histologic information as factors involved in the scoring system and AIH diagnosis, as shown in Table 1.

The autoantibody titers of ANA, SMA, and LKM showed that the frequency of people with AIH in each group was higher in all 3 of antibodies, and the frequency of subjects in the low-titer autoantibodies was significantly higher. Hepatic histology also showed that typical AIH and compatible AIH had the maximum frequency (56.6% and 30.1%, respectively) compared to non-compatible AIH (13.2%) in the AIH group. In comparison,

Table 1. Frequency of Diagnostic Indicators Per Subjects

Diagnostic Indicator	AIH-WD (Total)	Total Percentage
ANA		
	124 (64-60)	81.6
	17 (10-12)	14.4
	16 (5-11)	7.2
SMA		
	134 (66-68)	88.2
	13 (3-10)	8.6
Anti-LKM		
	139 (67-72)	91.4
	13 (2-11)	8.6
Anti-SLA		
Negative	152 (69-83)	100
ANA (titers in New scoring system)		
	118 (64-54)	77.6
	23 (5-18)	15.1
	11 (0-11)	7.2
SMA (titers in New scoring system)		
	133 (66-67)	87.5
	13 (2-11)	8.6
	6 (1-5)	3.9
LKM (titers in New scoring system)		
	133 (67-66)	87.5
	14 (1-13)	9.2
	5 (1-4)	3.3
pANCA		
Negative	152 (69-83)	100
IgG		
Normal	70 (48-22)	46
Higher than normal	53 (13-39)	34.9
More than 1.1 times Larger than normal	29 (22-7)	19.1
IgG (titers in New scoring system)		
Normal	70 (48-22)	46
Higher than normal	55 (16-39)	36.2
More than 1.2 times Larger than normal	27 (5-22)	17.8
Liver biopsy (histology)		
Non-compatible AIH	75 (64-11)	49.3
Compatible AIH	28 (3-25)	18.4
Typical AIH	49 (2-47)	32.2
Viral hepatitis		
Affected	10 (1-9)	6.6
Not affected	142 (68-74)	93.4
Drug-related hepatitis		
Affected	2 (1-1)	1.3
Not affected	150 (68-82)	98.7
NASH		
Affected	3 (2-1)	2
Not affected	149 (67-82)	98
Extra-hepatic autoimmune disease		
Not affected	146 (69-77)	96.1
Ulcerative colitis	2 (0-2)	1.3
Hypoparathyroidism	1 (0-1)	0.7
Celiac	3 (0-3)	2
Family history of autoimmune disease		
Affected	4 (1-3)	2.6
Not affected	148 (68-80)	97.4
Family history of hepatic condition		
Affected	27 (23-4)	17.8
Not affected	125 (46-79)	82.2
Cholangiography		
Normal	149 (69-80)	98
Abnormal	3 (0-3)	2

ANA, anti-nuclear antibody; SMA, smooth muscle antibody; LKM, liver kidney muscle antibody; SLA, soluble liver antigen; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; IgG, immunoglobolin G; NASH, non-alcoholic steatohepatitis.

maximum frequency in the WD group belonged to non-compatible (92.7%).

Applying the Mann–Whitney test to compare mean IgG variables, the simplified and new scoring systems showed a significant difference between mean values in AIH and WD groups, whereas mean values of each variable in AIH were significantly greater than in WD group ($P < .001$ for all variables). The relationship between LKM, ANA, and SMA autoantibody titers and autoimmune hepatitis showed

a significant relationship between LKM (P = .023), ANA (P = .002), and SMA (P = .023) antibodies and AIH.

After drawing the ROC curve and determining cut-off values for each variable (IgG, the simplified, and new scoring systems) separately in the present study, the surface area under each curve (AUC) was calculated using SPSSv.21 software. According to AUC, IgG function was found poor in diagnosis while the new score and the simplified score were evaluated as desirable. Examination of the differences in areas under the ROC curve shows that IgG in proportion to the new score method and IgG in proportion to simplified score method are significantly different (P < .01), so the new score and simplified score methods perform significantly better than IgG level. In contrast, the differences in the areas of new score and simplified score methods do not differ significantly and statistically display similar efficacy in diagnosis. The results of the ROC curve analysis for each of the 3 variables are summarized in Figure 1. As shown in Figure 1, the new score method has higher sensitivity, specificity, and predictive value than the other 2 methods at cut-off value.

DISCUSSION

To this day, the diagnosis of AIH in children remains challenging and burdened by several unmet clinical needs. First, a highly specific single diagnostic test for the diagnosis of AIH is lacking. Furthermore, diagnosis may be complicated or potentially delayed by the fact that a very heterogeneous clinical presentation characterizes AIH, and its diagnosis requires the exclusion of all other causes of liver disease.[9] Considering the epidemiology of AIH and lack of specific clinical symptoms and exclusive diagnostic criteria,[10,11] this study aims to investigate the application of a new and simplified scoring system for children diagnosed with AIH and other acute liver diseases to determine their efficacy in children.

Analysis of data in the present study indicate that of 152 children under the age of 18 (83 patients (54.6%) with AIH as case group and 69 patients (45.4%) with WD as control group), 53.3% were male and 46.7% were female, showing that, unlike age, there is a significant correlation between sex in the AIH and WD groups (P = .007). Greater distribution of girls with AIH (55.4-44.6%) in our study was in line with other studies.[5,12]

The results showed a significant relationship between ANA, SMA, and LKM autoantibodies and AIH. Similarly, Kanzler et al.[13] reviewed the ANA/SMA and anti-SLA autoantibodies in 97 patients with AIH over a long follow-up. Patients with positive ANA/SMA and anti-SLA showed the greatest clinical, biochemical, histological, and prognostic characteristics, while testing the anti-SLA antibodies is useful in AIH diagnosis in many patients that may be misdiagnosed otherwise. In a study by Mileti,[5] 100% of AIH patients were found to have positive autoantibodies, while this was 19% in the non-AIH group. Although

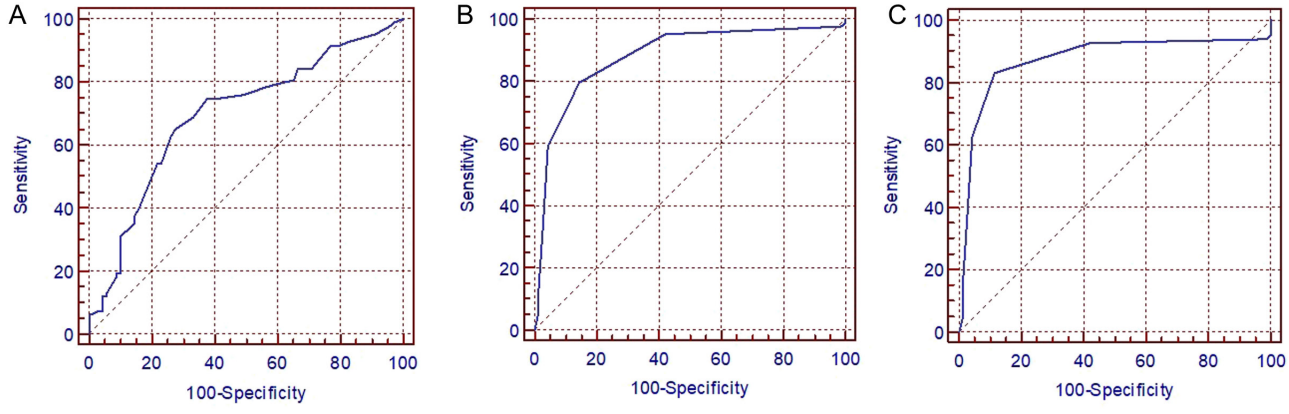

Figure 1. (A)-(C) ROC curve and its indicators for measuring IgG titer (A), simplified scoring system (B), and new scoring system (C).

the autoantibody titers are important diagnostic factors, they are not enough on their own, and comprehensive diagnostic criteria are needed. In Gregorio et al.,[14] autoantibody analysis was used to differentiate between AIH and Autoimmune Sclerosing Cholangitis (ASC) and showed that ANA, SMA, or a combination of them share the same frequency and their titers are similar in ASC and AIH. Floreani et al.[15] also showed that pediatric ASC was often associated with high titers of autoantibodies, especially ANA and SMA, increased IgG and interface hepatitis. Almost all ASC patients were diagnosed with positive ANA or SMA.

In the present study, the highest IgG frequency was observed in levels higher than normal level in the AIH group (73.4%) while the levels higher than normal level were significantly less in patients with WD (28.9%, $P < .001$). In other words, 26.5% of AIH patients and 70.6% of WD patients were found to have normal IgG levels. Fallatah and Akbar[16] argue that a high level of IgG serum is the best indicator in differentiating autoimmune hepatitis diagnosis from other hepatic conditions: they report that serum IgG levels in AIH patients were significantly higher than in patients with non-autoimmune hepatitis and cirrhosis of the liver (81.4%). Gregorio et al.[17] also reported the correlation between IgG levels and the ANA, SMA, LKM-1, and anti-LSP titers.

In the present study, an analysis of the mean values of IgG, the simplified and new scoring system shows a significant difference between the mean values of each variable in AIH and WD groups, and the frequency of patients with AIH was greater than that of WD in terms of each variable. Also, comparing the areas under the ROC curve in both IgG and the new score method and IgG and simplified score method showed a significant difference ($P < .01$). Therefore, new score and simplified score methods are considerably better than IgG levels for diagnostic purposes. However, the areas under of ROC curve did not show a significant difference ($P = .5$) between new score and simplified score methods, so these 2 methods are statistically the same in the diagnostic efficiency.

The analysis of the surface area under the ROC curve showed that the best and most balanced casein terms of sensitivity and specificity in determining the cut-off value, sensitivity, and specificity percentage in measuring IgG, simplified score, and new score were cut-off = 3.6, 65.1% and 72.5% for IgG with PPV = 51.9% and NPV = 39.6%; cut-off = 3, 79.5% and 85.5% for the simplified score with PPV = 52.8% and NPV = 37%; and cut-off = 5, 83.1% and 88.4% for the new score with PPV= 53% and NPV= 36.3%. As such, the new score method has the highest predictive value at its cut-off value, indicating a greater degree of accuracy in the differential diagnosis. While the proposed cut-offs for diagnostic criteria are generally lower than our calculated cut-offs, so that with cut-off = 6 for the simplifies scoring system,[5] specificity 98.6% and sensitivity 13.3%, PPV and NPV were 91.6% and 48.5%, respectively, and with cut-off = 7 for the new scoring system,[6] specifity 97.1% and sensitivity 38.6%, PPV and NPV, were calculated to be 94.1% and 56.7%, respectively, which is significantly lower than the values obtained and indicates the accuracy of the study and the importance and necessity of the territorial alignment.

Similar to this study, Mileti and Rosenthal[5] reported the 2008 simplified scoring system as an appropriate clinical method with 87% sensitivity and 89% specificity. Hennes et al.[4] studied the simplified scoring system in AIH diagnosis in 250 patients (case group) and 193 liver patients (as controls) from 11 centers over 10 countries in North America, Latin America, Europe, and Asia. They reported 2 cut-off points in validation sets: 88% sensitivity and 97% specificity (cut-off ≥ 6) and 81% sensitivity and 99% specificity (cut-off ≥ 7). Wobser et al.[18] did a retrospective single-center study and compared the accuracy of both AIH scores in 70 patients with AIH and 211 patients with chronic liver diseases. The sensitivity and specificity of detecting a probable AIH (scores ≥ 6) were 96% and 97% with a positive and NPV of 92% and 99%, respectively. For diagnosis of definite AIH (scores ≥ 7), the sensitivity and specificity were 43% and 100% with a positive and NPV of 97% and 84%, respectively. The concordance with the revised original criteria was 63%. They reported that the specificity for excluding AIH was excellent in both scoring system.

Also, ROC analysis conducted by Czaja et al.[19] who compared the revised evaluation system (1999) and the Simplified Evaluation System (2008), showed that the simplified system for AIH was more specific (90% vs. 73%) and more predictive (92% vs. 82%) than the revised evaluation system. As no validation study exists for the new scoring system, ROC analysis parameters are promising and noteworthy for purpose of examining this system.

CONCLUSION

To conclude, the results of this study, like other studies, show that female gender, autoantibody titers, and

increased IgG levels can significantly affect the AIH susceptibility. Moreover, the results from the statistical comparison of 3 methods (IgG and simplified and new scoring systems) showed that scoring systems methods have good performance in identifying and differentiating patients with AIH and have statistically inconsiderable difference; nonetheless, the new score method was characterized by higher sensitivity and specificity that indicate its higher accuracy and predictive power. Therefore, the present study, showed the new scoring system in diagnosis of AIH is more efficient than the simple one, but it takes further studies to validate and confirm the new score method.

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Informed consent: Informed consent was obtained from all patients.

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REFERENCES

1. Pathak S, Kamat D. Autoimmune hepatitis in children. Pediatr Ann. 2018;47(2):e81-e86. [CrossRef]
2. Mieli-Vergani G, Vergani D. Autoimmune hepatitis. Nat Rev Gastroenterol Hepatol. 2011;8(6):320-329. [CrossRef]
3. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929-938. [CrossRef]
4. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169-176. [CrossRef]
5. Mileti E, Rosenthal P, Peters MG. Validation and modification of simplified diagnostic criteria for autoimmune hepatitis in children. Clin Gastroenterol Hepatol. 2012;10(4):417-21.e1-e2. [CrossRef]
6. Mieli-Vergani G, Vergani D, Baumann U, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN hepatology committee position statement. J Pediatr Gastroenterol Nutr. 2018;66(2):345-360. [CrossRef]
7. Seo JK. Diagnosis of Wilson disease in young children: Molecular genetic testing and a paradigm shift from the laboratory diagnosis. Pediatr Gastroenterol Hepatol Nutr. 2012;15(4):197-209. [CrossRef]
8. Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. Gastroenterology. 2010;139(1):58-72.e4. [CrossRef]
9. Sciveres M, Nastasio S, Maggiore G. Novel diagnostic and therapeutic strategies in juvenile autoimmune hepatitis. Front Pediatr. 2019;7:382. [CrossRef]
10. Abe M, Mashiba T, Zeniya M, et al. Present status of autoimmune hepatitis in Japan: A nationwide survey. J Gastroenterol. 2011;46(9):1136-1141. [CrossRef]
11. Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. Clin Liver Dis. 2002;6(3):635-647. [CrossRef]
12. Corrigan M, Hirschfield GM, Oo YH, Adams DH. Autoimmune hepatitis: An approach to disease understanding and management. Br Med Bull. 2015;114(1):181-191. [CrossRef]
13. Kanzler S, Weidemann C, Gerken G, et al. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. J Hepatol. 1999;31(4):635-640. [CrossRef]
14. Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: A 16-year prospective study. Hepatology. 2001;33(3):544-553. [CrossRef]
15. Floreani A, De Martin S, Secchi MF, Cazzagon N. Extrahepatic autoimmunity in autoimmune liver disease. Eur J Intern Med. 2019;59:1-7. [CrossRef]
16. Fallatah HI, Akbar HO. Elevated serum immunoglobulin G levels in patients with chronic liver disease in comparison to patients with autoimmune hepatitis. Libyan J Med. 2010;5(1):4857. [CrossRef]
17. Gregorio GV, McFarlane B, Bracken P, Vergani D, Mieli-Vergani G. Organ and non-organ specific autoantibody titres and IgG levels as markers of disease activity: A longitudinal study in childhood autoimmune liver disease. Autoimmunity. 2002;35(8):515-519. [CrossRef]
18. Wobser H, Paur T, Schnoy E, Hartl J, Kirchner G.I. Suitability of the simplified autoimmune hepatitis score for the diagnosis of autoimmune hepatitis in a German cohort. U Eur Gastroenterol J. 2018;6(2):247-254. [CrossRef]
19. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatology. 2008;48(5):1540-1548. [CrossRef]