Aperito Online Publishing

Gastro
Open Access

Received Date: July 10th, 2014
Accepted Date: July 28th, 2014
Published Date: July 31st, 2014

http://dx.doi.org/10.14437/GOA-2-106 Research Elleuch Nour, Gastro 2014, 2:1

Diagnostic Value of the New Simplified Criteria for Diagnosis of Autoimmune Hepatitis in Tunisian Patients

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Abstract

Background and Aims: In 1999, the diagnostic criteria of Autoimmune Hepatitis (AIH) have been revised by an international panel. This revised scoring system had a high diagnostic accuracy but was limited by its complexity. Subsequently, a simplified score has been proposed recently to enhance clinical practicability. The goal of this study was to compare the performance parameters of the revised and the simplified scores in Tunisian patients satisfying conventional pretreatment criteria for the diagnosis of AIH and other chronic liver diseases.

Methods: Diagnostic scores were calculated using the revised and simplified criteria in patients with AIH, viral, cholestatic and metabolic chronic liver disease. The sensitivity, specificity, and predictability of each scoring system for the pretreatment diagnosis of AIH were determined.

Results: Sixty-three patients were included. Of these, 19 held a diagnosis of AIH, and 3 were identified with AIH-primary biliary cirrhosis overlap syndrome. The remaining 41 patients had diagnoses of primary biliary cirrhosis (n=7), chronic hepatitis B (n=17), chronic hepatitis C (n=9), non alcoholic steatohepatitis (n=5) or primary sclerosing cholangitis (n=3). The revised score had greater sensitivity for the diagnosis of AIH than the simplified score (100% versus 72.7%) as 5 patients diagnosed as AIH with the revised score were nondiagnostic by the simplified score. The simplified score had a higher specificity than the revised score (100% versus 94.8%) as 2 patients with non alcoholic steatohepatitis were ascribed a false diagnostic of AIH with the revised score.

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Introduction

Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology that can affect all ethnic groups of all ages and sexes [1]. Clinical manifestations of AIH are varied, ranging from asymptomatic presentation to an acute severe disease [1,2]. The diagnosis is based on histological abnormalities, characteristic clinical and laboratory findings, abnormal level of serum globulins, and the presence of one or more characteristic autoantibodies [3]. Despite these bases, however, the diagnostic remains a challenge for hepatologists [4]. In 1993, the International Autoimmune Hepatitis Group (IAIHG) developed criteria to help the diagnosis of AIH that would be useful in clinical practice and to allow comparison between patients in trials of AIH [5]. These original criteria were revised in 1999 in order to increase the diagnostic accuracy and improve ability to exclude other forms liver disease [6]. This revised score, although useful adjunct to the diagnosis of AIH in atypical cases, remained cumbersome due to the sheer number of variables analyzed (n=13), making it difficult to apply in clinical practice [7]. To resolve these difficulties, the IAIHG developed in 2008 the simplified criteria for routine clinical use, based on four components [8]. This new simplified score was tested in many countries and validated in diverse control populations including other causes of chronic liver disease, with a high sensitivity (88%) and specificity (97%) [8,9].

Nevertheless, the simplified score has rarely been compared with the revised score and not tested in Tunisian patients. The aim of this study was to compare the performance parameters of the revised and simplified scoring systems of the IAIHG in patients satisfying conventional pretreatment criteria for the diagnosis of AIH, viral, cholestatic and metabolic chronic liver diseases.

Patients and Methods

Diagnostic criteria and patients

Patients with chronic liver diseases who had complete clinical, laboratory and histological data were enrolled in this retrospective study. They were seen in our department over a 3 year period (2010-2012). Only patients that satisfied conventional criteria for their particular diagnosis at presentation, and that have been assessed for the features common to both scoring systems, including serum immunoglobulin G (IgG) levels, conventional autoantibodies by indirect immunofluorescence, serological markers for hepatitis B and C viruses, and histological examination were selected.

Patients with AIH were diagnosed by descriptive criteria revised by the IAIHG in 1999 [6]. The diagnosis of Primary Biliary Cirrhosis (PBC) was established when 2 of the following 3 criteria were met: biochemical cholestasis; presence of anti-mitochondrial antibodies; non superlative destructive cholangitis and destruction of interlobular bile ducts at histology [10]. AIH-PBC overlap was considered when 2 of the 3 criteria of PBC met with 2 of the 3 AIH criteria: serum ALAT>5 times Upper Limit of Normal value (ULN); serum IgG levels twice ULN or a positive test for smooth muscle antibodies; moderate or severe periportal or periseptal lymphocytic piecemeal necrosis [11]. Primary Sclerosing Cholangitis (PSC) was defined by at least 2 criteria: biochemical cholestasis; specific cholangiographic features on cholangiography; histological changes characteristic of PSC [12]. Diagnosis of Chronic Hepatitis B (CHB) and Chronic Hepatitis C (CHC) was considered according to EASL International Consensus Conferences [13,14]. Non Alcoholic Steatohepatitis (NASH) was established on the following criteria: persistent abnormal liver tests, liver biopsy compatible with NASH, exclusion of other liver disease and alcohol consumption [15].

Scoring systems

The revised (1999) and simplified (2008) scores of the IAIHG were calculated in all patients with diverse chronic liver diseases and before treatment.

The 12 components of the revised score were applied only for one patient who had undergone HLA testing, the remaining patients not tested for HLA were graded for the 11 other components. A pretreatment score of 10 to 15 points supported a probable diagnosis of AIH and a score >15 points supported a definite diagnosis [6]. The 4 components of the simplified score were graded in all patients (Table 1). A score of 6 points constituted a probable diagnosis of AIH and a score ≥7 constituted a definite diagnosis [8].

Table 1: Simplified diagnostic criteria for the diagnosis of autoimmune hepatitis (8)

Component	Result	Points
Autoantibodies		
-ANA or SMA	≥1/40	+1
-ANA or SMA	≥1/80 or	+2
-Anti LKM1	≥1/40 or	+2
-Anti SLA	≥Positive	+2
Immunoglobulin G level	≥UNL	+1
	≥1.1UNL	+2
Liver histology	Compatible	+1
	Typical	+2
Viral disease	No viral markers	+2
	Viral markers present	0
Pretreatement aggregate score	Definite diagnosis	≥7
	Probable diagnosis	6

(ANA: Anti Nuclear Antibody; SMA: Smooth Muscle Antibody; Anti LKM1: Antibodies to Liver/Kidney Microsome type 1; Anti SLA: Antibody to Soluble Liver Antigen; UNL: Upper Normal Limit)

Statistical analysis

Sensitivity, specificity, and predictability were the performance parameters assessed for each scoring system. The gold standards of diagnosis were descriptive the IAIHG criteria of 1999 for AIH and conventional criteria described above for other chronic liver disease [6].

Sensitivity reflected the number of patients with definite or probable AIH by the descriptive criteria who were diagnosed similarly by the scoring systems under study (true positives) divided by the sum of true positives plus the number of patients with the disease by the descriptive criteria who were undiagnosed by the scoring systems under the study (false negatives).

Specificity reflected the number of patients without AIH by the descriptive criteria who were also discounted by the scoring system under the study (true negatives) divided by the sum of true negatives plus the number of patients without AIH by descriptive criteria who were diagnosed with the disease by the scoring system under the study (false positives).

Positive predictability: Number of true positives divided by the sum of the true positives and false positives.

Negative predictability: Number of true negatives divided by the sum of true negatives and false negatives.

Results

Study population

A total of 63 patients comprising 45 females (71.5%) with complete clinical, laboratory and histological data available in order to calculate both the revised and simplified IAIHG score were enrolled. Of these, 19 held a diagnosis of AIH, and 3 were identified with AIH-PBC syndrome. The remaining 41 patients had diagnoses of PBC (n=7), CHB (n=17), CHC (n=9), NASH (n=5) or PSC (n=3).

Comparison of scoring systems for AIH

The revised scoring system graded all patients who satisfied the descriptive criteria for AIH as having either definite (n=9) or probable (n=10) AIH. In contrast, the simplified scoring system made the diagnosis of definite (n=4) or probable (n=10) less frequently: 73.5% versus 100%. Five patients with HAI according to the descriptive criteria had non diagnostic scores using the simplified scoring system (Table 2).

Table 2: Comparison of each scoring system for the diagnosis of autoimmune hepatitis (n=19).

Diagnosis of AIH by scoring system n (%)					
Definite AIH		Probable AIH		Nondiagnostic	
Revised	Simplified	Revised	Simplified	Revised	Simplified
9 (47.5 %)	4 (21%)	10 (52.5 %)	10 (52.5%)	0	5 (26.5%)

(AIH: Autoimmune Hepatitis)

Comparison of scoring systems for overlap AIH/PBC

The revised scoring system graded all patients who satisfied overlap AIH/PBC criteria as having probable AIH (n=3). In contrast, 1 patient with overlap AIH/PBC was not diagnosed as AIH with the simplified scoring system.

Scoring discrepancies for AIH

Five patients with AIH were not ascribed a diagnosis of AIH on the simplified criteria, whereas the revised criteria identified all these as having either probable or definite AIH. We analyzed differences between patients ascribed a false negative and a true positive diagnosis of AIH: these differences related to the points awarded for features graded in the revised score but not in the simplified score. Points awarded by the revised score for female gender (n=4), abnormal serum ɤ globuline level despite normal serum IgG level (n=5), ratio of serum alkaline phosphatase to aspartate aminotransferase levels less than 1.5 (n=5), concurrent immune diseases (n=4), presence of HLDR4 (n=1), no alcohol and drugs consumption (n=6) were the bases for ascribing a diagnosis of AIH to the 5 patients not diagnosed by the simplified criteria (Table 3).

Table 3: Features associated with diagnostic discrepancies between the 2 scoring systems.

Features unrecognized or scored less via the simplified score	Number of patients (n =6)
Female gender	4
Concurrent immune diseases	6
AP/ASAT (ALAT) ratio <1.5	6
Elevated serum ɤ globulin and normal Ig G levels	6
HLA DR3 or DR4	1
Alcohol consumption <25g/day	6

(AP: Alkaline Phosphatase level; ASAT (ALAT): Aspartate or Alanine Aminotransferase level)

Comparison of scoring systems for excluding other diagnoses

Neither the revised nor the simplified scoring system graded patients with CHB, CHC, PBC and PSC as having definite or probable AIH. The revised score graded 2 of 5 patients with NASH as having probable AIH, whereas the simplified score excluded the diagnosis of AIH in all cases. The patients with NASH ascribed a false negative diagnosis of AIH were all female and had positive auto-antibodies and increased serum ɤ globuline level despite normal serum IgG level (Table 4).

Performance parameters for diagnosis of AIH

The sensitivity and specificity for the revised score were 100% and 94.8% for diagnosis of AIH. The positive and negative predictive values of the revised score were 91.7% and 100%.

The sensitivity and specificity for the simplified score were 72.7% and 100% for diagnosis of AIH. The positive and negative predictive values of the simplified score were 100% and 86.7% (Table 5).

Table 4: Comparison of clinical diagnosis and scoring diagnosis in each system.

Diagnosis by scoring system n (%)				
Clinical diagnosis	**Probable or definite AIH**		**Nondiagnostic**	
	Revised	**Simplified**	**Revised**	**Simplified**
AIH (n=19)	19 (100%)	14 (73.7%)	0	5(26.3%)
Overlap AIH/PBC (n=3)	3 (100%)	2 (67%)	0	1 (33%)
CHB (n=17)	0	0	17 (100%)	17(100%)
CHC (n=9)	0	0	9 (100%)	9 (100%)
NASH (n=5)	2 (40%)	0	3 (60%)	5 (100%)
PBC (n=7)	0	0	7 (100%)	7 (100%)
PSC (n=3)	0	0	3 (100%)	3 (100%)

Table 5: Performance parameters of the revised and simplified score for diagnosis of autoimmune hepatitis.

Performance parameters	Revised score	Simplified score
Sensitivity	100%	72.7%
Specificity	94.8%	100%
Positive predictability	91.7%	100%
Negative predictability	100%	86.7%

Discussion

In this retrospective study, the simplified and revised scores for diagnosis of AIH were evaluated in Tunisian patients. Our results indicate that each scoring system has high sensitivity and specificity for the diagnosis of definite or probable AIH and corroborate with previous studies [9].

The highest sensitivity (100%) of the revised score may be related to the descriptive criteria used as a gold-standard to identify patients with AIH, since they have been defined by the IAIHG in 1999 [6].

On the other hand, the high specificity of the simplified criteria (100%) has been reported in previous studies, where the simplified score achieved a specificity ranging from 90 to 97% [16].

Possible explanation for this higher specificity is that the simplified score may reduce the diagnostic confusion that can be associated with the trapping of hypergammaglobulinemia and autoantibody positivity in patients with concurrent immune features not related to AIH [9]. Indeed, female gender, concurrent autoimmune diseases, serum ɤ globulin concentration, ratio of the serum alkaline phosphates level to

aspartate aminotransferase level are intrinsic to the revised score but not included in the simplified score. As seen in our study, these features may render a greater number of probable diagnose of AIH by the revised score in diseases that are etiologically distinct, compared to the simplified score.

This high specificity is important in our country, where CHC is more prevalent than AIH and has classically been implicated in many different extra-hepatic and auto-immune manifestations [17]. Therefore, CHC has to be clearly differentiated from AIH, and the high specificity of the simplified criteria may avoid false diagnoses of AIH. Moreover, NASH is associated with antinuclear antibodies and smooth muscle antibodies in up to a third of patients and is becoming a major cause of chronic hepatitis; therefore, it is important to distinguish it from AIH [2]. Especially in NASH cirrhosis in woman, hypergammaglobulinemia and autoantibodies can lead to diagnostic confusion. In these cases, the specificity of the simplified criteria can avoid false positive diagnosis of AIH. In our study, 2 patients with NASH were falsely evaluated as probable AIH by the revised criteria whereas the simplified score excluded AIH in all cases.

Alternatively, the simplified score may underestimate the diagnosis of AIH. As seen in our study, 5 patients with AIH were wrongly excluded by the simplified score. This concern patients who have few or atypical features of the disease [9].

Finally, each scoring system can contribute to the diagnosis of AIH. The revised score is most useful in the evaluation of patients with few or atypical features of AIH [9]. The simplified score can be easily applied with a high specificity, excluding patients with etiologically distinctive disease who have concurrent immune trapping.

It is therefore recommended that, in clinical practice, the simplified score be used as first option, due to their advantage in the diagnosis of AIH with a high specificity and their simplicity in everyday clinical practice [17]. The revised score should be further applied to avoid a false negative diagnosis in patients with atypical features [17].

However that may be, diagnosis of AIH remains clinical and rests on a combination of compatible clinical, biochemical, immunological and histological features together with exclusion of other liver disease [18, 19]. Scoring systems exist to support, not to suppressed, the clinical diagnosis [9].

Limitation of this study is the small number of patients. This is related to the fact that all patients, including non autoimmune chronic liver disease, must have been assessed for all the parameters of the revised and simplified scores to be included in the study. These laboratory tests are numerous and expensive and liver histology was not always mandatory and justified for the diagnosis of viral and cholestatic liver disease [10-14]. Therefore, a prospective study will be more appropriate, but to our knowledge, any prospective evaluation of these criteria has yet been published in the literature. Since most of the validation studies of the simplified criteria were performed in Western country, the strength of this is study is that it is the first one that tested the simplified criteria in Tunisian patients.

Conclusion

In this study we determined that both scoring system had a high specificity and sensibility for the diagnosis of AIH in Tunisian patients, and the simplified score has superior specificity. These results are in accordance with previous studies. The simplified score will not replace the revised score, on the contrary, they can be used in a complementary manner: simplified score as a first option and revised score in patients with atypical features if AIH.

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