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BRIEF DEFINITIVE REPORT

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Limitation of the simplified scoring system for the diagnosis of autoimmune Hepatitis with acute onset

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Abstract

Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease of unknown aetiology characterized by the presence of autoantibodies, hypergammaglobulinaemia with specific IgG increase and interface hepatitis on liver histology. The clinical course of AIH is classically characterized by fluctuating periods of decreased or increased disease activity and therefore its clinical spectrum is variable ranging from no symptoms to severe acute hepatitis and even fulminant hepatic failure. Acute presentation may not differ from acute hepatitis of other causes and diagnosis can be difficult. We describe our experience on diagnostic performance of the two AIH scoring systems in acute onset of AIH and found that revised version of the original criteria (1999) achieves the diagnosis in about 30% of patients who presented with normal IgG serum levels and lower frequency of autoantibody positivity in whom the simplified score did not allow the diagnosis.

KEYWORDS

AIH scoring system, anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), autoimmune hepatitis (AIH), IgG serum levels

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory condition of the liver that can affect patients of all ages, sexes and races.[1] The diagnosis needs to be considered in any patient with elevated aminotransferases. Prompt diagnosis and immunosuppressive therapy can control disease activity in almost all affected patients, and various case series have reported even normal life expectancy in properly diagnosed and treated patients.[2]

Early diagnosis can be quite difficult because the clinical picture is heterogeneous and there is no specific test applicable to all patients.[3] In particular, the differential diagnosis may be very challenging in patients with atypical features or mixed manifestations.[4]

A clinical scenario in which the AIH diagnosis may be highly difficult to be performed is represented by cases that onset with 'acute' presentation.[5]

In this group of patients, the lack of some disease-specific parameters such as raised serum IgG levels and seropositivity for non-organ specific autoantibodies (NOSA) make the diagnosis both less prompt and easy.

A simple and unfailing diagnostic tool for AIH has not been established. In 1993, the International Autoimmune Hepatitis Group for (IAIHG) proposed diagnostic criteria, which were revised in

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; AST, Aspartate aminotransferase; IgG, immunoglobulin G; LC1, anti-liver cytosol; LKM1, anti-liver-kidney microsomal; NOSA, non-organ specific autoantibodies; pANCA, perinuclear anti-neutrophil cytoplasm antibodies; SLA, soluble liver antigen; SMA, anti-smooth muscle antibodies; UNL, upper normal level.

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1999.[6,7] These criteria were designed primarily for the consensus of experts and introduced to allow the comparison of studies from different centres.

As these criteria are quite complex, and included a wide variety of parameters, in 2008 the IAIHG decided to develop a simplified scoring system for wider and faster applicability in clinical practice, based on the data from patients with well-established diagnosis. This system consisted of only four items: anti-nuclear autoantibodies (ANA) or smooth muscle autoantibodies (SMA), serum IgG levels, liver histology and the absence of viral hepatitis.[8]

Although retrospectively, the high specificity and specificity of the simplified scoring system in AIH diagnosis has been validated by various studies.[9-12]

However, it has been suggested that the diagnostic scoring systems are not interchangeable, and the revised version of the original criteria would have greater value in diagnosing patients with few or atypical features of AIH.[13]

In this regard, we evaluated our historical series of AIH patients with acute onset and we tested the simplified score on all patients to assess its performance in the AIH diagnosis in this clinical setting.

2 | PATIENTS AND METHODS

2.1 | Patients

This is a retrospective study involving 344 patients recruited from the 'Center for the Study and Treatment of Autoimmune Diseases of the Liver and Biliary System' of the S. Orsola-Malpighi Hospital, Bologna, Italy recruited in the last 20 years. Of these 344 patients, 70 (20%) were selected for this study because they met the criteria for a diagnosis of acute-onset AIH as defined below (Figure 1).

All the patients had been diagnosed with AIH on the basis of the established diagnostic criteria of the International Autoimmune Hepatitis Group according to the revised version of the original criteria developed by International Autoimmune Hepatitis Group in 1999.[7]

In particular, viral and other notable causes of liver disease (HCV, HBV, HEV, cytomegalovirus and Epstein Barr viruses, abuse of alcohol, deficit of both ceruloplasmin and alpha-1 antitrypsin, high serum level of ferritin) were excluded in all patients. The pharmacological anamnesis was negative for all potential hepatotoxic drugs. This

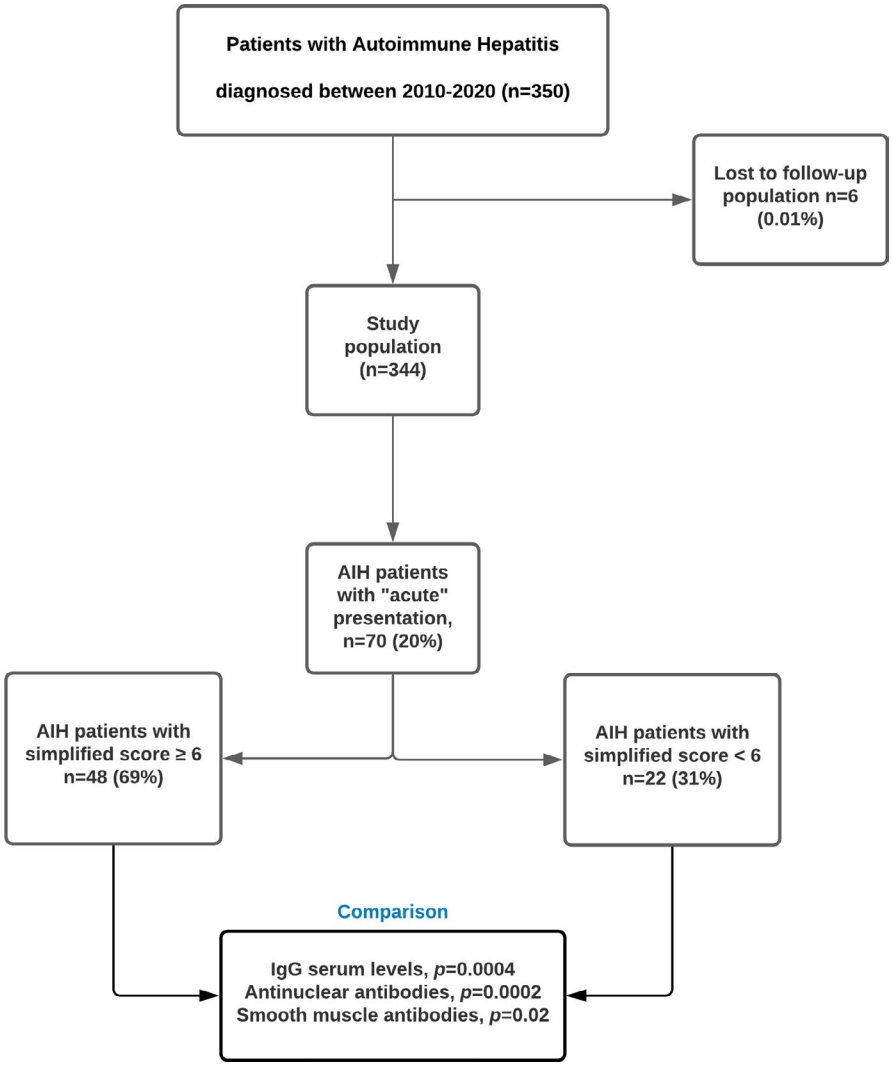

FIGURE 1 Flow chart of study population. Comparison of the two groups of patients who met the simplified score criteria for the AIH diagnosis: those with simplified score <6 had significantly lower IgG values [median 1120 mg/dl (range 800-4800) vs 2400 mg/dl (range 940-4800), $P = .0004$] and both lower ANA (50% vs 75% $P = .0004$) and SMA positivity (36% vs 66% $P = .02$)

study was approved by the local ethical committee. Oral or written consent was obtained from patients.

2.2 | Serology

Sera were tested using indirect immunofluorescence (IIF) on rat tissue, as previously described, to search for the following reactivities: anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), anti-liver-kidney microsomal type 1 antibodies, anti-liver cytosol type 1 (LC1) antibodies and anti-mitochondrial antibodies (AMA). A titre ≥1:40 was considered positive.[14-17]

Patients who tested negative by IIF but with clinical suspicion of AIH were tested with second-level technique by immunoblot (Liver Profile, Euroimmune) providing a qualitative in vitro assay for human autoantibodies of the immunoglobulin class IgG to the following antigens: LKM-1 (liver-kidney microsomes; cytochrome P450 II D6), LC-1 (cytosolic liver antigen type 1; formiminotransferase-cyclodeaminase) and SLA/LP (soluble liver antigen/liver-pancreas antigen), and AMA-M2 (pyruvate-dehydrogenase-complex).[18]

2.3 | Liver histology

Liver biopsy was available at presentation in 55 patients of the selected 70 patients (78%), since 15 patients refused to undergo the procedure. Even if no morphological features are pathognomonic of AIH, all patients had the characteristic histological picture of interface (periportal or periseptal) hepatitis with a predominantly lymphoplasmacytic necroinflammatory infiltrate, with or without lobular (intra-acinar) involvement and portal–portal or central–portal bridging necrosis.

Presence of liver cell rosettes and nodular regeneration was considered indicative of severe inflammatory activity.[7]

A histological diagnosis of cirrhosis required the presence of F5–F6 fibrosis according to the Ishak's score.[19]

2.4 | Definition of 'Acute Onset'

The clinical presentation of AIH was defined as described previously.[20] The 'acute' presentation was defined as evidence of acute hepatitis with jaundice and, under the laboratory profile, transaminases serum levels values ≥10 times the upper normal level (10× UNL) and/or a value of total serum bilirubin >5 mg/dl, as reported previously.[21]

The presentation was defined as 'chronic' when non-specific symptoms were present, and were not directly and primarily attributable to chronic liver disease (asthenia, weight loss, amenorrhea, fever, nausea, loss of appetite) and as 'asymptomatic' when, during screening examinations, an increase in transaminase or bilirubin serum levels were found in the absence of other symptoms.[20,21]

In both these categories of patients (chronic and asymptomatic) the transaminases were under 10× UNL and the bilirubin was <5 mg/dl. The patients were monitored with three/six months or annual control visits or hospital admittance according to clinical necessity.

2.5 | Treatment

All AIH patients received conventional treatment with corticosteroids and azathioprine.[5,22] In particular, after the diagnosis was established, the therapeutic regimen with prednisolone or prednisone started at the dosage of 0.5-1 mg/kg/day for the first 4 weeks with a subsequent slow progressive reduction of the steroid (reduction of 4-6 mg after every 4-6 weeks of therapy in according with transaminases serum levels); after the first four weeks of therapy, azathioprine was added.

According to the IAIHG guidelines patients who normalized transaminases and IgG levels within the six months from the start of therapy were considered 'responders', whereas patients who still maintained transaminase levels higher than the upper normal limit, but <2× were considered to have an 'incomplete response' and those having levels higher than 2× were considered to have 'non response'. [22,23]

2.6 | Statistical analysis

Comparative analysis of the categorical values was carried out using the Fisher's exact test. The Mann-Whitney test was used for evaluating the continuous variables. A $p \leq 0.05$ was considered significant. Graph Pad InStat 3.0 for Macintosh was used for the statistical analysis.

3 | RESULTS

Seventy (20%) of the 344 AIH patients satisfied the criteria for acute presentation of AIH.

All these 70 cases received a diagnosis of AIH by the application of the revised version of the original criteria; in particular 38 (54%) received a diagnosis of 'probable' AIH, and 32 (46%) of 'definite' AIH.

In addition, all 15 patients without a liver biopsy received a diagnosis of "probable" AIH when both scores were applied; clearly in all these cases the score for histology was zero. Twenty-two (31%) out of the 70 patients did not reach a score (<6) using the simplified score, so this group did not even reach the diagnosis of 'probable' AIH.

Compared to the group of patients who met the simplified score criteria for the AIH diagnosis, those with simplified score <6 had significantly lower IgG values [median 1120 mg/dl (range 800-4800) vs 2400 mg/dl (range 940-4800), $P = .0004$] and both lower ANA (50% vs 75% $P = .0004$) and SMA positivity (36% vs 66% $P = .02$).

Otherwise, there were no significant differences between the two groups for all the other parameters considered (age at diagnosis, gender, transaminases, bilirubin, alkaline phosphatase, γGT, albumin, histological activity and staging, relapse rate, disease progression, LKM1, LC1, SLA, pANCA, AMA, HLA, and associated autoimmune extrahepatic diseases).

Median follow-up was 60 months (range 3-240). No statistically significant differences were found between AIH patients with simplified score <6 and those with simplified score ≥6 on the treatment response. The results are reported in the Table 1.

4 | DISCUSSION

From the clinical point of view, the presentation at diagnosis of AIH is very heterogeneous with a wide spectrum of manifestations that can be virtually absent (asymptomatic presentation with incidental finding of the disease), or those of acute icteric hepatitis, even extremely severe and rapidly evolving into acute liver failure (fulminant course), passing through the manifestations of compensated or decompensated cirrhosis (jaundice, ascites, encephalopathy).[5,24,25]

In this study, we focused on patients with AIH with acute clinical onset. The clinical criteria used by us and others [21,26-28] to define acute onset are necessarily arbitrary as there is a lack of defined and agreed criteria for making this diagnosis, unlike in patients with severe acute AIH,[22] but we do not have in our series of patients any case of severe acute onset. The diagnosis of autoimmune hepatitis can be very difficult when the disease presents with acute onset for several reasons and our study shows that in this setting the use of the simplified score can have a limitation of sensitivity.

Our study demonstrates that acute onset AIH patients not captured by the simplified score have significantly lower IgG serum levels and ANA and SMA positivity rate.

AIH with normal IgG level is not surprising, since in a recent multi-center study Hart et al described the absence of hyper-IgG in up to 10% of cases, without affecting the clinical and

TABLE 1 Comparison of AIH patients according to the simplified score (<6 vs ≥6)

Clinical biochemical histological and serological parameters of the study population (n = 70)	AIH patients with simplified score <6 (22 patients, 31%)	AIH patients with simplified score ≥6 (48 patients, 69%)	*P*
Male gender (%)	5 (23%)	11 (23%)	NS
Age at diagnosis median (range) [y]	43 (14-78)	42 (10-74)	NS
AST median (range) [×UNL]	17 (2-43)	22 (2-76)	NS
ALT median (range) [×UNL]	25 (2-91)	31 (4-70)	NS
Alk Phosph. median (range) [×UNL]	1.3 (0.5-8)	3.4 (0.5-10)	.01
γGT median (range) [×UNL]	3 (0.2-21)	3.4 (0.5-10)	NS
Total Bilirubin median (range) mg/dl	13 (0.3-49)	7 (0.7-44)	NS
IgG median (range) mg/dl	1120 (800-4800)	2400 (940-4800)	.0004
Albumin median (range) g/l	37.4 (18-62)	37.9 (21-53)	NS
Histological activity[a] (2-18)	9 (3-14)	9 (2-18)	NS
Histological staging[a] (1-6)	2 (1-5)	2 (1-6)	NS
Relapse (%)	17 (77%)	30 (62.5%)	NS
Disease progression (%)	2 (10%)	5 (10%)	NS
Follow up median (range) months	36 (3-240)	48 (6-180)	NS
Complete response (%)	17 (77%)	32 (66%)	NS
ANA +ve (%)	11 (50%)	36 (75%)	.0002
SMA +ve (%)	8 (36.3%)	32 (66%)	.02
LKM type 1 +ve (%)	4 (18%)	5 (20.8)	NS
LC1 +ve (%)	1 (4%)	2 (4%)	NS
SLA +ve (%)	3 (14%)	10 (21%)	NS
pANCA +ve (%)	3 (14%)	19 (39%)	NS
AMA +ve (%)	2 (9%)	4 (8%)	NS
DRB1*03 or DRB1*04 (%)	10 (45%)	32 (67%)	NS
Autoimmune extrahepatic diseases (%)	5 (23%)	16 (33%)	NS

Abbreviations: ALP, Alkaline Phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; LC1, liver cytosol antibodies type 1; LKM1, liver kidney microsome antibodies type 1; NS, not significant; pANCA, anti neutrophil cytoplasmic antibodies with perinuclear pattern; SLA, anti-soluble liver antigen; SMA, smooth muscle antibodies; UNL, upper normal level; γGT, gamma-glutamyl transferas.

[a]Ishak's score[(19)].

histological activity of the disease and without any difference in the outcome.[29]

Furthermore, our observations are in agreement with Joshita et al where the acute presentation of AIH was characterized by a high number of patients with low IgG levels and absence of NOSA.[30] In particular, more than half AIH patients with acute presentation were characterized by a normal IgG level, while the frequency of seropositivity for ANA and SMA was 73% and 28% respectively. It is therefore evident that the simplified score in this particular setting of patients is unreliable and the risk, that the diagnosis can be delayed, and the disease can progress before starting immunosuppressive therapy, is significantly high. Similarly, there are a number of studies on paediatric cases that come to the same conclusions as we do regarding the low sensitivity of the simplified score in this specific group of patients.[31,32] In this respect, it should be noted that the simplified criteria are not applicable to the paediatric AIH population whether the patients present acutely or not.[33]

Why there are AIH patients without both hyper-IgG and autoantibodies is not clear [34,35]; It has been suggested that they are in a complexed form (immune complexes) and thus not detectable in this particular subgroup of patients or that this particular subgroup of patients could have a too short exposure to the immunologic trigger of AIH.[29]

In conclusion, from our results the following considerations arise: (a) acute onset AIH often can lack its main characteristics such as hyper-IgG and autoantibodies, thus making the diagnosis more difficult; (b) since some of these acute cases of AIH may rarely progress to acute liver failure, this distinct aspect should be kept in mind as the identification of AIH as the aetiology of acute AIH and/or acute liver failure is very important because delay in diagnosis and initiation of therapy leads to a poorer prognosis, whereas prompt immunosuppression lowers the risk of evolution of the disease and the need for liver transplantation; (c) even though the simplified score was designed as an easy-to-use bedside aid, there is a considerable proportion of patients with AIH with acute onset (up to 30%) where the score fails in its aim. For these patients it would be appropriate to apply the revised version of the original criteria, certainly longer and more investigative, but more sensitive as it evaluates many more parameters than simplified score and this allows to make up for the absence of one of them.[13]

Therefore, as previously suggested, we confirm that AIH scoring systems are not fully interchangeable, and both scoring systems exist to support, not supersede, the clinical diagnosis. [13]

In certain clinical circumstances, one system may be more valuable than the other: the revised version of the original criteria has greater sensitivity in diagnosing patients with few or atypical AIH features.[10,13]

AIH with acute presentation thus would represent a clinical scenario in which the revised version of the original criteria performs better than the simplified one, but in conclusion no score can completely replace clinical judgement in diagnosis.[10]

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CONFLICT OF INTEREST

All the authors of this manuscript have no conflict of interest to declare.

AUTHOR DECLARATION

(a) The research was approved by local ethical committee. (b) Verbal or written informed consent was obtained by all patients.

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