Comparing the Simplified and International Autoimmune Hepatitis Group Criteria in Primary Sclerosing Cholangitis

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Abstract: ***Background and aims:*** Although highly sensitive and specific, the revised International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria for autoimmune hepatitis (AIH) are cumbersome to use in clinical practice and rely upon a number of autoantibodies that are costly and are not widely available. The simplified scoring system for AIH attempts to rectify the complexity of the IAIHG criteria. To date, there have been few studies assessing the specificity of the simplified score for AIH when applied to patients with cholestatic liver diseases. The purpose of this study was to examine the specificity of the simplified scoring system for AIH as compared to the revised IAIHG criteria in a large cohort of patients with primary sclerosing cholangitis (PSC). ***Methods:*** The patient population consisted of 147 patients enrolled in two prospective trials at the Mayo Clinic examining the use of ursodeoxycholic acid in PSC. All of the patients underwent baseline blood work (including standard serologic testing to exclude other liver diseases), liver biopsy, and cholangiogram to confirm PSC. Demographic, laboratory, and histologic data were extracted for each subject. Simplified and revised IAIHG scores were calculated for each subject and compared. ***Results:*** The simplified scoring system identified 2 patients with probable AIH and no patients with definite AIH. Comparatively, the revised IAIHG scoring system identified no patients with probable or definite AIH. ***Conclusion:*** As with the revised IAIHG criteria, the simplified scoring system for AIH has excellent specificity when applied to a PSC population.

Keywords
Autoimmune hepatitis scoring system, overlap syndrome, primary biliary cirrhosis

First described in 1950, autoimmune hepatitis (AIH) is a chronic and progressive liver disease of unknown etiology. Most patients with AIH respond to immunosuppressive therapy, and medical management can prolong survival, improve quality of life, and avert the need for liver transplantation in many patients.[1-4]

Not uncommonly, AIH may coexist with other autoimmune liver diseases, namely primary biliary cirrhosis (PBC) and primary

sclerosing cholangitis (PSC); the concomitant occurrence of autoimmune liver diseases is known as overlap syndromes.[5] Although overlap syndromes have been reported extensively in the literature, the overall experience with these conditions is relatively small and anecdotal.[6] Although certainly underdiagnosed, overlap syndromes are not uncommon.[7-9] For instance, among patients with AIH, an estimated 8% and 6% have overlap with PBC and PSC, respectively.[9,10] Although standardized diagnostic criteria for overlap syndromes are nonexistent, the scoring system proposed by the International Autoimmune Hepatitis Group (IAIHG) has been useful in providing a template for the diagnosis of AIH.[6]

Diagnostic criteria for PSC include cholestatic biochemistry and characteristic histopathology featuring fibrous obliterative cholangitis. PSC must be distinguished from secondary cholangitis, as seen in immunoglobulin (Ig)G4 disease, and a variety of vascular, infectious, and neoplastic conditions.

Established in 1992, the IAIHG has been instrumental in providing an accurate method to also assess the strength of a diagnosis for AIH.[11] The original and revised diagnostic criteria for AIH require the exclusion of viral, metabolic, genetic, and toxic causes of liver disease. Although the revised criteria are accurate, they have been criticized because they are cumbersome to use (as they consist of 13 components) and rely upon serologic tests that are costly and are not widely available.[12]

Due to these concerns, a simplified scoring system based upon only 4 components was established in 2008.[13] This simplified scoring system was validated in patients on 4 continents with diverse control populations that included viral, metabolic, toxic, hereditary, and cholestatic hepatic conditions.[13] This analysis yielded a sensitivity of 88% and a specificity of 97% for the simplified scoring system.[12] In a further assessment, Czaja conducted an analysis of 24 PSC patients at the Mayo Clinic and found that the performance parameters of each scoring system were the same.[12] Although this study was insightful, the criteria by which these patients were selected were not explicitly stated, and a larger sample size is needed to provide more robust data. The aim of this study was to examine the specificity of the simplified scoring system of AIH as compared to the revised IAIHG criteria in a large, well-characterized cohort of patients with PSC.

Methods

Study Population

PSC patients in two prospective ursodeoxycholic acid trials at the Mayo Clinic in Rochester, Minnesota were identified.[14,15] To be included in the studies, subjects had to be between 18 and 70 years of age and have a history of liver biopsy and a history of cholangiogram confirming the diagnosis of PSC. Cholestatic liver biochemistries, characteristic histopathology with typical cholangiographic findings of bile duct stenoses, and dilatations without prior bile duct surgery or secondary sclerosing cholangitis were required for the diagnosis of PSC. Other causes of liver disease were excluded.

Data Collection

Demographic information, liver enzymes, bilirubin, prothrombin time, creatinine, hepatitis B and C serologies, ceruloplasmin, alpha-1 antitrypsin quantification and phenotype, ferritin, transferrin saturation, antinuclear antibody (ANA), smooth muscle antibody (SMA), liver kidney microsomal antibody (LKM1), soluble liver antigen antibody, gamma globulins, and liver histopathology results were all recorded. SMA, ANA, LKM1, and antimitochondrial antibody were assessed via indirect immunofluorescence. All patients underwent a sufficient evaluation to definitively derive a score categorized as definite, probable, or negative for AIH according to the revised IAIHG and simplified scoring criteria. Two hepatologists (MGS, NC) independently calculated scores using both criteria (Tables 1 and 2).

Statistical Analysis

The specificity of the simplified scoring system was calculated. A definite or probable score based upon the revised IAIHG criteria was considered the gold standard diagnostic criteria for AIH.

The specificity of the simplified score was derived by the number of patients with no AIH according to the simplified score divided by the number of patients with no AIH according to the revised IAIHG criteria.

Results

Baseline characteristics for the 147 subjects are shown in Table 3. Seventy-four subjects were male (55.2%). A comprehensive work-up to exclude viral, hereditary, and toxic causes of chronic liver disease was negative in all subjects. The average age at enrollment was 43 years (19–70 years).

The simplified score for AIH suggested that 2 patients, a 45-year-old woman and a 39-year-old man at study enrollment, had probable AIH and that no patients had definite AIH (Table 4). Both patients with probable AIH according to the simplified score had histopathology compatible with AIH, ANA counts of at least 1:40, IgG counts of at least 1.1 times the upper limit of normal, and negative viral serology. Cholangiography showed a dominant stricture in the middle of the common bile duct and the right hepatic duct in the female patient and diffuse intrahepatic disease in the male patient. The male

Table 1. Revised International Autoimmune Hepatitis Group Scoring System for the Diagnosis of Autoimmune Hepatitis (AIH)

Clinical feature	Score
Female gender	+2
ALP:AST ratio	
• <1.5	+2
• 1.5–3.0	0
• >3.0	–2
Serum globulin or IgG above normal	
• >2.0	+3
• 1.5–2.0	+2
• 1.0–1.5	+1
• <1.0	0
ANA, SMA, LKM1	
• >1:80	+3
• 1:80	+2
• 1:40	+1
• <1:40	0
Illicit drug use history	
• Positive	–4
• Negative	+1
Average alcohol intake daily	
• <25 g/day	+2
• >60 g/day	–2
Histologic findings	
• Interface hepatitis	+3
• Lymphoplasmacytic infiltrate	+1
• Rosette formation	+1
• None of the above	–5
• Biliary changes	–3
• Other changes	+2
Other autoimmune disease	+2
AMA positivity	–4
Hepatitis viral markers	
• Positive	–3
• Negative	+3
Aggregate score without treatment	
• Definite AIH	>15
• Probable AIH	10–15

ALP=alkaline phosphatase; AST=aspartate aminotransferase; IG=immunoglobulin; ANA=antinuclear antibody; SMA=smooth muscle antibody; LKM1=liver kidney microsomal antibody; AMA=antimitochondrial antibody.

Reproduced from Alvarez F, et al.[11]

Table 2. Simplified Score for the Diagnosis of Autoimmune Hepatitis (AIH)

Clinical feature	Points
ANA or SMA	
• ≥1:40	+1
• ANA or SMA ≥1:80 or LKM1 ≥1:40 or SLA-positive	+2
Serum IgG	
• >upper limit of normal	+1
• >1.1 times upper limit of normal	+2
Histologic findings	
• Compatible with AIH	+1
• Typical of AIH	+2
Hepatitis viral markers	
• Negative	+2
Aggregate score without treatment	
• Definite AIH	≥7
• Probable AIH	≥6

ANA=antinuclear antibody; SMA=smooth muscle antibody; LKM1=liver kidney microsomal antibody; SLA=soluble liver antigen antibody; IG=immunoglobulin.

Reproduced from Hennes EM, et al.[13]

Table 3. Baseline Characteristics

Variable	Mean	Range
AST (U/mL) (8–48)	88	19–340
ALP (U/L) (45–142)	765	158–5,376
Bilirubin (mg/dL) (0.1–1.0)	1.0	0.2–9.8
Prothrombin time (sec) (8.3–10.8)	11.1	8.6–13.8

ALP=alkaline phosphatase; AST=aspartate aminotransferase.

Table 4. Autoimmune Hepatitis (AIH) Diagnosis Using Simplified Score and Revised International Autoimmune Hepatitis Group (IAIHG) Criteria

AIH Score	No	Probable	Definite
Simplified	145 (98.6%)	2 (1.4%)	0
Revised IAIHG	147 (100%)	0	0

patient also had ulcerative colitis. The revised IAIHG criteria determined that no patients had probable or definite AIH.

The specificity of the simplified scoring system for AIH, when evaluated in a well-established PSC population, was 98.6%.

Discussion

This study demonstrates that the simplified score for AIH has a similar specificity when compared to the revised IAIHG criteria in a large cohort of well-characterized patients with PSC.

AIH is a difficult clinical diagnosis, as there are no pathognomonic features and the condition can mimic almost any form of acute or chronic liver disease. The revised IAIHG and simplified scoring systems are useful tools that facilitate diagnosis. However, it is debatable as to whether there is a true gold standard by which to diagnose AIH. The challenge for an AIH scoring system is to include the minority of AIH patients who present with a cholestatic picture, while not misdiagnosing patients with PSC or PBC who do not have an overlap with AIH. Variant syndromes create an added component of complexity to the diagnostic considerations of a patient with an autoimmune liver disease.[8,16]

The PSC-AIH overlap syndrome is not uncommon. This hybrid disease has been well described, particularly in the pediatric population. Prior studies have estimated that 41% of patients with cholangiographic features of PSC have either probable or definite AIH based upon IAIHG criteria; however, only 2% of these patients have definite AIH.[17] Autoimmune liver diseases in patients can also evolve from one disease to another, suggesting that underlying AIH may need to be considered more than once. Befuddling matters further, in PSC, the alkaline phosphatase level is often raised only moderately and elevated aminotransferase levels are common.[11] Clearly, any patient with AIH who has cholestatic features, bile duct abnormalities on liver biopsy, inflammatory bowel disease, or loss of response to immunosuppressive therapy requires exclusion of concomitant PSC.

Distinction between PSC and PSC-AIH overlap is clinically important. Although there are no large therapeutic trials for patients with PSC-AIH overlap, immunosuppressant treatment is warranted for active AIH. Although less is known regarding the PSC-AIH overlap syndrome than the PBC-AIH overlap syndrome, PSC-AIH overlap may be associated with a better prognosis than PSC alone.[18] However, this hybrid syndrome portends a worse prognosis than AIH alone.[18] Further studies are needed to better define the long-term clinical outcomes and optimal treatment strategies of patients with PSC-AIH overlap.

This study has a number of strengths and several limitations. The main strength of the analysis is that a comparison between both scoring systems has never been made in such a large cohort of patients with PSC. Another strength of the study is that the patient population was homogeneous, which allows for a comparison of both scoring systems without confounding variables that might diminish the accuracy of one score over another. The main limitation of the study is that, as the patient population was comprised of carefully selected subjects eligible for two PSC studies, the pretest probability of the patients having overlap with AIH was exceedingly low, and, hence, both scoring systems would be expected to have high specificities. Although it is conceivable that in an unselected PSC population the scoring systems may not be equivalent, the scoring systems could not be adequately compared unless a homogeneous population devoid of confounding variables was used.

The main advantage of the simplified score is that it is straightforward and feasible to use, as it is based upon only 4 components and there is no reliance on less common autoantibodies. The revised IAIHG score may continue to play an important role in the work-up of patients with autoimmune liver diseases, however, as it allows for comparison between varied patient populations and enables adequate assessment in patients with atypical manifestations of AIH.[12] However, this study suggests that among patients with well-established PSC, the simplified score for AIH may be used in lieu of the revised IAIHG score to exclude AIH. Further studies in other carefully defined PSC patients would be useful in validating the findings of this analysis.

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