# Validation and Modification of Simplified Diagnostic Criteria for Autoimmune Hepatitis in Children

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**BACKGROUND & AIMS:** Criteria for the diagnosis of autoimmune hepatitis (AIH) were formalized in 1993 and revised in 1999. Simplified criteria were developed in 2008 for adults only. We aimed to establish clinically useful diagnostic criteria for AIH in children by validating the 2008 criteria in a pediatric cohort. **METHODS:** Baseline data were available in 37 and 31 AIH and 40 and 26 non-AIH subjects to calculate 1999 and 2008 criteria, respectively. Sensitivity and specificity of the simplified criteria were calculated using 1999 criteria as the standard for subjects with available data for both criteria. **RESULTS:** The 1999 standard designated 29 of 31 subjects (94%) as definite AIH and 2 of 31 subjects (6%) as probable AIH. The simplified criteria identified 25 of 31 subjects (81%) as definite AIH, 2 of 31 subjects (6%) as probable AIH. Only 1 of 5 patients with AIH who presented with fulminant hepatic failure (FHF) was identified by the simplified criteria as having AIH. The 2008 diagnostic criteria had a sensitivity of 87% and a specificity of 89% (area under the receiver operating characteristic curve, 0.98). After removing data from patients with FHF from the analysis, the sensitivity increased to 100%. Modifying the 2008 diagnostic criteria to include either level of globulin or immunoglobulin G resulted in a similar sensitivity (92%) and specificity (95%) values (area under the receiver operating characteristic curve, 0.99). **CONCLUSIONS: The 2008 criteria diagnose AIH in children with high levels of sensitivity and specificity, and are easier to use in the clinic. Diagnosis of AIH in patients who present in FHF requires the 1999 criteria. Levels of globulin and immunoglobulin G can be used interchangeably in the simplified diagnostic criteria.**

*Keywords:* Pediatric Liver Disease; Scoring System; Diagnostic; Autoimmunity.

In 1993, the International Autoimmune Hepatitis Group (IAIHG) developed a method for diagnosing autoimmune hepatitis (AIH) and differentiate it from chronic active hepatitis. The original criteria classified patients as having "definite" or "probable" AIH[1] with revisions made in 1999 to improve specificity and simplify the scoring system.[2] The 1999 revised original criteria reported a specificity of 90%, improving the ability to distinguish AIH from other autoimmune liver diseases. The criteria remained complex, including 13 categories and 29 possible grades (Supplementary Table 1). This complexity made the 1999 revised original criteria challenging for clinical use.

In 2008, the IAIHG developed simplified diagnostic criteria, including only 4 categories: autoimmune markers, immunoglobulin G (IgG) levels, histology, and absence of viral hepatitis (Supplementary Table 2). This scoring system, unlike the previous 2, was developed using an international cohort from 10 countries. Based on receiver operating characteristic (ROC) curves, scores of 6 or greater had a sensitivity of 88% and a specificity of 97% for diagnosing probable AIH.[3] A score of 7 or greater had a sensitivity of 81% and a specificity of 99% for definite AIH.[3] The 2008 criteria have been validated in other adult cohorts over the past 3 years, with similar results reported.[4–8]

Based on consensus from the IAIHG in 1993, the diagnosis of AIH in the pediatric population was not considered to require separate diagnostic criteria. However, distinguishing AIH from primary sclerosing cholangitis (PSC) and overlap syndromes in children was a recognized problem. Two studies in the literature highlight the use of the scoring systems in the pediatric population, validating the 1999 and 2008 criteria. The first showed that the earlier scoring systems could be applied in the pediatric population but noted the importance of validation in children because of differences between the pediatric and adult populations.[9] The second study, evaluating the 2008 simplified criteria, showed high specificity but low sensitivity, calling into question the usefulness of this criteria for use in the pediatric population.[10] Prompt diagnosis of AIH is crucial for the initiation of immunosuppressive medications and substantially improves prognosis.[11,12] Thus, using the simplified criteria would be ideal for diagnosis in children. In this study we applied the IAIHG simplified criteria to a larger pediatric cohort with AIH and other chronic liver diseases to validate its usefulness in children. In addition, we modified the simplified criteria to include the use of globulin as a surrogate for IgG.

## Methods

### *Study Population*

All children (age at presentation, <21 y) included in this study were from a single pediatric hepatology center at a tertiary care hospital. Children with AIH were identified through International Classification of Diseases, 9th revision codes, pathology reports, and cross-referencing with pediatric hepatology patient lists from 1991 to 2010. AIH subjects had to have all baseline laboratory, histology, demographic, and clini-

*Abbreviations used in this paper:* AIH, autoimmune hepatitis; AUROC, area under receiver operating characteristic curve; CI, confidence interval; FHF, fulminant hepatic failure; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; PSC, primary sclerosing cholangitis; ROC, receiver operating characteristic.


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cal information necessary to calculate and confirm the diagnosis of autoimmune hepatitis using the 1999 revised original scoring system. These patients also met the diagnosis of AIH using the codified descriptive criteria from 1993, and all subjects diagnosed with AIH responded to immunosuppressive therapy. Only laboratory data from the time of initial diagnosis were used for analysis. All AIH patients were classified as type I AIH except for one female with type II AIH. One patient had AIH-PSC overlap. Five patients with AIH presented in fulminant hepatic failure (FHF).

All non-AIH subjects had other confirmed liver diseases and were identified from pediatric hepatology databases from 1991 to 2010. They were included in the study only if they had sufficient data available to calculate both the 1999 and 2008 scores. Diagnoses included primary sclerosing cholangitis (n = 10), viral hepatitis (n = 5), nonalcoholic steatohepatitis (n = 12), and metabolic/genetic liver diseases (n = 13: cystic fibrosis, α-1-antitrypsin disease, glycogen storage disease, biliary atresia, progressive familial intrahepatic cholestasis types 2 and 3, ornithine transcarbamylase deficiency, bile acid conjugation defect, methylmalonic acidemia, and congenital hepatic fibrosis). Viral hepatitis was excluded using serologies for hepatitis A, B, and C. Four AIH subjects were excluded because they initially were diagnosed at other institutions, and baseline data were not available for them to be included in the analysis (Figure 1). The study was approved by the University of California San Francisco Committee on Human Research.

### *Scoring Systems*

Because the 2008 simplified criteria did not include response to therapy in the diagnostic score, we opted to use only pretreatment criteria scores from the 1999 original revised scoring system when establishing the diagnosis of AIH. For the 1999 original revised criteria, a score of 10 to 15 equaled a probable AIH diagnosis and scores greater than 15 indicated a diagnosis of definite AIH (Supplementary Table 1). For the 2008 simplified criteria, a score of 6 was used for probable AIH and a score of 7 or greater constituted definite AIH (Supplementary Table 2).

The 2008 criteria were calculated using 4 predefined parameters: auto-antibodies, IgG level, liver histology, and absence of viral hepatitis. To evaluate IgG compared with globulin level, the 2008 criteria subsequently were calculated using serum globulins instead of IgG. Those who had serum globulin levels in the normal range received 0 points, if the level was above normal the subject received 1 point, and those who had 1.1 times the upper limit of normal received 2 points.

### *Statistical Analyses*

Sensitivity and specificity of the 2008 criteria were calculated using 1999 criteria as the gold standard. In addition, sensitivity and specificity were calculated, modifying the 2008 criteria by using either IgG or globulin levels. The $\kappa$ statistic was used to evaluate agreement between scores using IgG versus IgG or globulin levels. ROC curves were plotted to illustrate the specificity and sensitivity of the 2008 simplified diagnostic criteria compared with the 1999 revised original criteria. Results were reported as percentages, or in the case of continuous variables, as medians and interquartile ranges. The Mann–Whitney *U* test was used to evaluate differences between 2 groups with continuous variables and the chi-square test for dichotomous variables. The Fisher exact test was used where appropriate. A *P* value of less than .05 was considered statistically significant. Statistical analyses were performed on STATA version 11.1 software (College Station, TX).

## Results

An initial 238 subjects with various liver diseases were evaluated. We identified 77 patients (37 AIH, 40 non-AIH) who had complete data available to calculate the 1999 score (Figure 1). Within the AIH group, 31 of 37 subjects had IgG levels to calculate the 2008 score but all 37 subjects had either IgG or globulin levels, or both, available at diagnosis. Of these patients, 36 had AIH and 1 had overlap AIH-PSC at the time of diagnosis. From the non-AIH group, 26 of 40 subjects had IgG levels to calculate the 2008 score but all 40 subjects had either IgG or globulin levels, or both, available at initial diagnosis. There were more females (70%), and family history of other autoimmune diseases was more common in the AIH group. AIH patients had higher median serum aspartate aminotransferase, alanine aminotransferase, IgG, total globulin, total protein, and autoantibody marker positivity (Table 1). The median serum alkaline phosphatase levels were similar between groups (Table 1).

Within the AIH group, the 1999 original revised criteria categorized 29 of 31 (94%) patients as definite AIH and 2 of 31 (6%) patients as probable AIH. The 2008 criteria defined 25 of 31 (81%) patients as definite AIH, 2 of 31 (6%) patients as

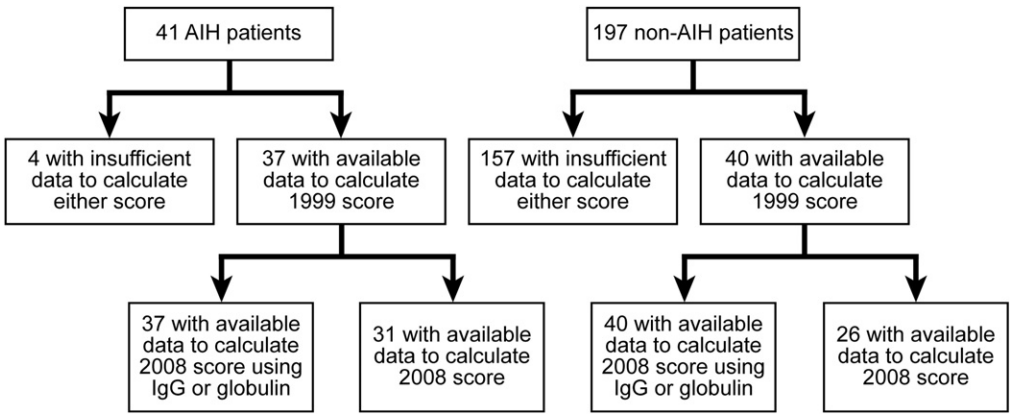


**Figure 1.** Flow diagram of the initial 238 patients evaluated for inclusion in this study. Seventy-seven patients (37 AIH, 40 non-AIH) had complete laboratory, histologic, demographic, and clinical data available to calculate the 1999 AIH score.