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# Fibrosis and Inflammation Histology Scores Predict Disease Remission in Pediatric Autoimmune Hepatitis

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**Abstract**

**Objectives:** To evaluate histological evolution and identify predictive factors for remission in pediatric autoimmune hepatitis (AIH).

**Methods:** Retrospective study of 40 children under immunosuppressive treatment (10 AIH type I, 7 AIH type II, 20 autoimmune sclerosing cholangitis (ASC) and 3 seronegative AIH) was performed. Histological fibrosis and inflammation scores were assessed on baseline (n=40) and follow up (n=19) biopsies. Clinical, biochemical and histological characteristics were analyzed to identify predictive factors for disease remission.

**Results:** Duration of follow up was median 4 years (3 months-19 years) and interval between paired biopsies was 4 years (3 months-18 years). In the paired biopsies group (n=19), histological evolution showed significant ($p \leq 0.01$) regression of fibrosis score (baseline: 3 to follow up: 1) and inflammation score (baseline: 3 to follow up: 2). In ASC subgroup (n=8), fibrosis score showed insignificant change between paired biopsies (baseline: 4 to follow up: 5) ($p=0.88$). Predictive factors for remission were (1) follow up fibrosis and inflammation scores (OR 1.71 and 5.42; $p \leq 0.05$) and (2) the evolution of fibrosis and inflammation between paired biopsies (OR 2.82 and 3.14; $p \leq 0.05$).

**Conclusions:** Treatment induces regression of histological fibrosis and inflammation in AIH, except for ASC subtype. Histological evolution predicts disease remission and highlights the importance of performing follow up biopsies in children unresponsive to treatment.

## ABBREVIATIONS

AASLD: American Association for the Study of Liver Diseases; AIH: Autoimmune Hepatitis; ASC: Autoimmune Sclerosing Cholangitis; UNL: Times the Upper Limit of Normal

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder, leading to progressive fibrosis and cirrhosis [1]. A scarce number of conflicting reports have been published to date concerning fibrosis evolution in children with AIH and receiving standard immunosuppressive therapy. Maia et al. reported no significant regression in fibrosis scores after 24 ± 18 months of therapy in eight children with AIH Type 1 [2]. On the contrary, Ferreira et al., showed either stabilization or decrease in fibrosis scores in 20 children treated for AIH Type 1 (in remission for at least 2 years prior to follow up biopsy) [3]. Autoimmune sclerosing cholangitis (ASC) patients seem to display a poorer outcome compared to other AIH types due to the progression of biliary lesions despite standard immunosuppressive therapy [4]. To date, no previous study specifically compared the histological fibrosis evolution for ASC versus other AIH types. Given that the course of fibrosis evolution remains unknown in pediatric AIH, our aim was to investigate fibrosis evolution in pediatric AIH and ASC under therapy. Additionally, we investigated predictive factors of disease remission.

## MATERIALS AND METHODS

Forty patients aged 0-18 years and diagnosed with AIH from 1987 to 2014 were retrospectively identified in the Pediatric Hepatology database of *Cliniques Universitaires Saint-Luc*. The inclusion criteria were: (1) pre-transplant state and (2) probable or definite AIH according to the International Autoimmune Hepatitis Group revised scoring system that has proven its utility in children, including those affected by the ASC subtype [1,4,5]. Nineteen of the 40 initial patients had paired baseline and follow up biopsies, while for the remaining 21 no follow up biopsy was performed. Clinical, demographical, biochemical, immunological, histological and treatment data for the research population (n=40) was collected retrospectively based on electronic medical charts and stored biopsy samples. This research project was assessed and approved by the Biomedical Ethics Committee of the *Université Catholique de Louvain* (Brussels)

### AIH subtypes

AIH subtypes were diagnosed based on established criteria: (1) positive antinuclear antibodies and/or anti-smooth muscle antibodies for AIH Type 1, (2) positive anti-liver-kidney microsome-1 antibodies and/or anti-liver cytosol-1 antibodies for AIH Type 2, (3) biliary impairment in histology/percutaneous cholangiography ± elevated gamma glutamyl transferase and positive perinuclear anti-neutrophil cytosol antibodies for ASC, and (4) no autoantibodies in the event of an established AIH diagnosis for seronegative AIH [6]. Biliary impairment evidenced in magnetic resonance cholangiograpy or in hepatobiliary ultrasound with high frequency transducer was also considered as ASC diagnosis factors due to the sensitivity of those methods in children [7].

### Outcomes and treatment

Outcome definitions were based on the American Association for the Study of Liver Diseases (AASLD) guidelines [6]. Remission was defined as normalization of AST, ALT, gammaglobulin levels, with low or negative autoantibodies titles, in the absence of clinical symptoms after at least 6 months of immunosuppressive therapy. Incomplete response was considered to have occurred when clinical and biochemical parameters stabilized or improved, but without achieving remission. Treatment failure was defined as worsening of clinical and biochemical parameters, leading to liver transplantation or death. When liver transplantation was performed, data collection ended after the time point of transplantation. Conventional immunosuppressive therapy was employed as induction treatment, with prednisolone 1-2mg/Kg/d (maximum 60mg/d) gradually tapered off once patients demonstrated clinical and biochemical improvement [6]. In addition, azathioprine was administered as a steroid-sparing agent at a dosage of 1-2mg/Kg/d, with the ultimate aim of maintaining remission under azathioprine monotherapy. Treatment alternatives such as mycophenolate mofetil, cyclosporine, or tacrolimus were administered in the event of (1) intolerable adverse effects, (2) persistent incomplete response, or (3) treatment failure. For ASC patients, ursodeoxycholic acid was added at the dose of 20-30 mg/kg per day. Treatment withdrawal was considered after at least 2 years of clinical and biochemical remission, in accordance with the AASLD guidelines [6]. Indication for follow up biopsies included (1) absence of or partial biochemical response to treatment, (2) relapse after remission during follow up, (3) abnormal liver echography with increasing echogenicity or nodule formation, and (4) suspicion of suboptimal compliance.

### Histological analysis

Histological analysis was performed blinded to the clinical information. Baseline and latest follow up liver biopsies were included in the study and analyzed only when containing at least five portal tracts, given that the study cohort was pediatric [8-10]. Biopsies were evaluated for fibrosis using the Ishak staging scale (0-6) [11], which were proven reproducible and valid in chronic hepatopathy [12,13]. Inflammation was assessed using the Batts & Ludwig scale (0-4) in order to differentiate portal and lobular inflammation [14,15]. For portal and lobular inflammation, only the higher score of the two was taken into account, in order to reduce interobserver variability [16-18]. Inflammation and fibrosis analyses were performed on hematoxylin-eosin- and Masson's-trichrome-stained slides, respectively. Fibrosis and inflammation evolution scores were defined as the difference between follow up and baseline fibrosis and inflammation scores, respectively.

### Statistical analysis

Statistical analysis was conducted using SPSS 21.0 (IBM SPSS Statistics software for Windows version 21.0 Armonk, NY: IBM Corp) and Graphpad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). Continuous variables were presented as mean ± standard deviations or medians [range], and categorical variables as numbers and percentages. Student's t-test was used to compare continuous variables between subgroups. The Mann-Whitney U test was employed when appropriate. Categorical variables were compared using Pearson's Chi-squared test or Fisher's exact test. Univariate logistic regression analysis was conducted to determine long-term prognostic indicators for remission. Results were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). In the logistic regression analysis, outcome was defined as remission versus non-remission (incomplete response or treatment failure). The Receiving Operator Characteristics method was used to assess diagnostic performance of influential variables. Backward of forward elimination techniques using the maximum likelihood method were applied with a selected p-value <0.25 in univariate analysis to enter the model, and ≤ 0.05 to remain in the model. Correlations between variables had been previously tested using Pearson's rank-correlation coefficient (r <0.5 was defined as satisfying). A two-tailed p-value ≤ 0.05 was considered to indicate statistical significance for all analyses.

## RESULTS

### Description of population and liver biopsy samples

In total, 59 biopsies were analyzed (40 diagnostic and 19 follow up biopsies), containing a median of 10 portal tracts [5-25]. Median time interval between paired baseline and follow up biopsies was 4 years (3m-18y). The main characteristics of the study population (n=40) were summarized in Table 1. Half of ASC patients (10/20) had co-existing inflammatory bowel disease. At the time of diagnosis, ASC patients presented a median serum gamma glutamyl transferase level of 3.6 times the upper limit of normal (ULN) (0.6-8.9) (n=20), versus 0.9 ULN (0.4-4) (n=20) for other AIH types (p=0.003). Nineteen over 20 ASC patients (95%) presented elevated (≥ 1/160) perinuclear anti-neutrophil cytosol antibodies titles during the course of disease, versus 4/20 (20%) patients for other AIH types (p<0.001).

### Clinico-biochemical outcome and treatment regimen

At last study visit, 24/40 (60%) patients were in remission, 10/40 (25%) patients displayed an incomplete response to treatment, 5/40 (12,5%) showed treatment failure, and one patient (2,5%) had insufficient follow up. Among those five children with treatment failure, three underwent liver transplantation (3 with ASC) and two patients died (1 AIH Type 1 and 1 ASC). Those latter patients were affected by fulminant liver failure and succumbed to infectious treatment-related complications approximately 3 months after treatment initiation (prednisolone 2mg/Kg/d with

**Table 1**: Description of overall population (n=40).

| | FU Biopsy group (n = 19) | No FU biopsy group (n=21) | *p-value* | Total (n=40) |
|---|---|---|---|---|
| **Gender (M/F)** | 3 (19%)/16 | 12(57%)/9 | *0.01* | 15 (37.5%)/25 |
| **Total follow up** *(median [range])* | 8y [3m-19y] | 2y [3m-15y] | *<0.01* | 4y [3 months – 19y] |
| **Age at diagnosis** *(median [range])* | 11y [2y-15y] | 11y [2y-14y] | *0.61* | 11y [2y – 15y] |
| **AIH Type** | | | | |
| Type 1 | 6 (32%) | 4 (19%) | *0.47* | 10 (25%) |
| Type 2 | 4 (21%) | 3 (14%) | *0.69* | 7 (17.5%) |
| ASC (overlap syndrome) | 8 (42%) | 12 (57%) | *0.53* | 20 (50%) |
| Seronegative AIH | 1 (5%) | 2 (10%) | *1* | 3 (7.5%) |
| **Presentation mode** | | | | |
| Acute | 11 (58%) | 10 (47.5%) | 0.55 | 21 (52.5%) |
| Liver failure | 4 (21%) | 5 (24%) | 1 | 9 (22.5%) |
| Incidental | 4 (21%) | 6 (28.5%) | 0.72 | 10 (25%) |
| **ALT at diagnosis (ULN)** (median [range]) | 6.4 [1.6-57.1] | 15.4 [0.7-97.1] | 0.45 | 6.3 [0.7 – 97.1] |
| **Gammaglobulin at diagnosis (ULN)** (median [range]) | 1.5 [0.3-4.4] | 1.2 [0.4-3] | 0.26 | 1.3 [0.3 – 4.4] |
| **Total bilirubin at diagnosis (mg/dL)** (median [range]) | 1.27 [0.3-43] | 1.15 [0.2-28.5] | 0.2 | 1.2 [0.2 – 43] |
| **INR at diagnosis** (median [range]) | 1.3 [0.9-3.8] | 1.2 (1.1-2.2) | 0.45 | 1.2 [0.9 – 3.8] |
| **Ishak's score at diagnosis** (median [range]) | 3[1-6] | 3 [0-5] | 0.04 | 3 [0-6] |
| **Batts & Ludwig's score at diagnosis** (median [range]) | 3 [2-4] | 3 [1-4] | 0.06 | 3 [1-4] |
| **Average azathioprine dose (mg/Kg/d)** (mean ± SD) | 1.6 ± 0.3 | 1.7 ± 0.4 | 0.36 | 1.6 ± 0.4 |

**Abbreviations:** AIH: Autoimmune Hepatitis; ALT: Serum Alanine Aminotransferase; ASC: Autoimmune Sclerosing Cholangitis; FU: Follow Up; INR: International Normalized Ratio; ULN: Times the Upper Limit of Normal

azathioprine 0.8-1.4mg/Kg/d). Liver failure was not controlled when infectious complications occurred. No difference in average azathioprine dosage was observed between the remission group (1.7 ± 0.3 mg/kg/d; n=24) and non-remission group (1.6 ± 0.5; n=16) (p=0.38). At last visit, treatment had been successfully stopped in 3 patients (1 ASC, 1 seronegative AIH and 1 AIH type 2). Among the 37 patients who were still receiving treatment, 16 were given corticosteroids and azathioprine, 17 azathioprine monotherapy, and 4 mycophenolate mofetil monotherapy. Seven of the 16 patients still receiving corticosteroids (44%) achieved remission by last visit, versus 14/21 patients (67%) who were receiving azathioprine or mycophenolate mofetil monotherapy (p=0.2). The use of second-line therapies when necessary during follow up (n=13) showed no clear impact on long-term clinico-biochemical outcome in our cohort. Remission at last study visit was achieved by 8/20 ASC patients (40%) versus 16/20 for other AIH types (80%) (p=0.02).

## Evolution of histological scores for fibrosis and inflammation

In the 19 children with paired biopsies, a significant regression was observed in both fibrosis and inflammation scores between baseline and follow up biopsy. The fibrosis score decreased from 3 (1-6) to 1 (0-6) (p=0.01), and inflammation score from 3 (2-4) to 2 (1-4) (p<0.01) (Figures 1,2). A positive correlation was proven between fibrosis and inflammation evolution scores ($r^2$ 0.82; p<0.001). When the ASC group (n=8) was considered individually, no fibrosis improvement was observed between diagnosis and follow up biopsy (4 (2-6) to 5 (1-6); p=0.88). On the contrary, fibrosis regression was clearly confirmed for other AIH type groups (n=11) (3 (1-5) to 1 (0-4); p<0.001). Median time before follow up biopsy was 3.5 years (1-14 years) for the ASC group versus 4 years (3 months-18 years) for the other AIH type group (p=0.34). At follow up biopsy, six of the 19 re-biopsied patients (32%) had been in remission for 3 years (1-4) (2 AIH Type 1, 2 AIH Type 2, 1 ASC and 1 seronegative AIH) while the other 13 exhibited clinical and/or biochemical disease activity. Fibrosis score at follow up biopsy for remission patients was 1 (0-5), versus 2 (1-6) for active disease patients (p=0.18). All six patients in remission showed fibrosis regression versus 7/13 (54%) active disease patients (p=0.11).

## Comparison between follow up biopsy group (n=19) and no follow up biopsy group (n=21)

When we compared the paired biopsies group (n=19) with patients who did not undergo a follow up biopsy (n=21), no significant difference was observed in long-term outcome. The

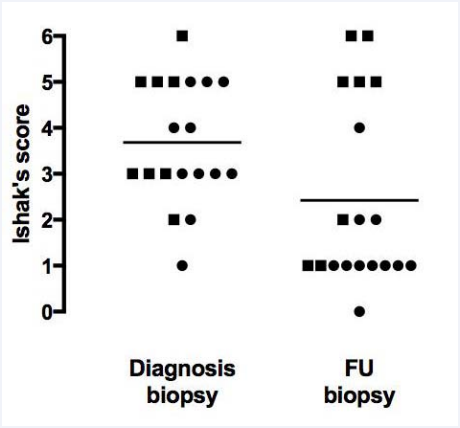


**Figure 1** Fibrosis score evolution. Squares represent ASC patients; lines represent mean fibrosis scores.

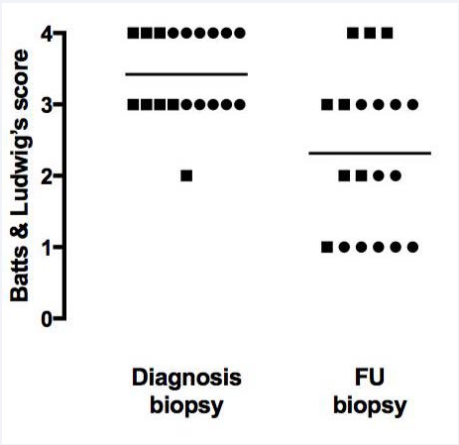


**Figure 2** Inflammation score evolution. Squares represent ASC patients; lines represent mean inflammation scores.

main characteristics of those two subgroups were summarized in Table 1. Patients who did undergo follow up biopsy had a higher median baseline histological fibrosis score (3 (1-6); n=19) compared to patients who did not undergo follow up biopsy (3 (0-5); n=21) (p=0.04). Total follow up was significantly longer in patients who underwent a follow up biopsy (Table 1).

### Histological cirrhosis and long-term clinico-biochemical outcome

Incomplete/complete cirrhosis (Ishak Stage 5 or 6) at diagnosis (n=10) displayed no impact upon long-term clinico-biochemical outcome in our cohort. We documented a significant fibrosis regression from Ishak Stage 5 to 1 in three patients after 4 years [3-13]. The only regression from complete cirrhosis that we documented was from Ishak Stage 6 to 5 after 4 years.

### Logistic regression to predict long-term clinico-biochemical outcome

In univariate analysis, the (1) fibrosis evolution, (2) inflammation evolution, (3) follow up biopsy fibrosis, and (4) follow up biopsy inflammation scores were identified as significant histological factors associated with clinico-biochemical outcome (Table 2). On the contrary, demographical, biochemical, and treatment features of our cohort did not significantly predict long-term outcome in this analysis. Receiving Operator Characteristics (ROC) curves assessed that fibrosis evolution has the best diagnosis performance, with an area under the curve of 85% ($p<0.05$) (versus 83% for inflammation evolution; $p<0.05$). In the multivariate logistic regression model, the fibrosis evolution score was still associated with long-term outcome of the disease (OR 2.7; p=0.04), whereas ALT at diagnosis (OR 0.83; p=0.2) and average azathioprine dosage (OR 0.01; p=0.07) did not prove to be significant predictors.

## DISCUSSION

Our research highlights for the first time the utility of fibrosis and inflammation histological scores on the follow up biopsy as predictors of long-term clinico-biochemical outcome in pediatric AIH. We showed that fibrosis and inflammation evolution scores between baseline and follow up biopsy, as well as fibrosis and inflammation scores on follow up biopsy, were predictors of long-term clinical and biochemical remission. In addition, we found a positive correlation between histological inflammation and fibrosis evolution scores, in line with previous published research concerning the histopathological mechanisms of fibrosis [2,19,20]. Although the usefulness of diagnostic biopsy is well established in AIH, the necessity of performing follow up biopsies remains a subject of debate [6,21,22]. In our cohort, most of the patients underwent a follow up biopsy due to persistent biochemical disease activity. A normalized follow up biopsy cannot predict relapse-free survival after treatment cessation [23-26]. Therefore, in view of our findings, the prognostic value of follow up biopsy seems to be more useful in children affected by persistent disease activity in order to support appropriate treatment adaptation. Follow up biopsy should be performed in children who do not achieve remission under standard immunosuppressive therapy, with subsequent treatment modifications in the absence of fibrosis improvement.

Histological analysis of pre-treatment and follow up biopsies showed significant regression in fibrosis and inflammation scores in patients receiving immunosuppressive therapy, which is in concordance with observations in adult AIH patients reporting possible fibrosis regression with treatment [19,20,27-30]. In children, Ferreira et al. also reported a reduction in fibrosis score in 20 children affected by AIH Type 1 [3]. These authors highlighted the potential risk of mistaking the necro-

**Table 2:** Results of univariate logistic regression to predict final outcome.

| Variables | OR | 95%CI | p-value |
|---|---|---|---|
| Fibrosis evolution score | 2.82 | 1.1-7.4 | 0.03 |
| Inflammation evolution score | 3.14 | 1.1-9 | 0.03 |
| FU biopsy fibrosis | 1.71 | 1-3 | 0.05 |
| FU biopsy inflammation | 5.42 | 1.3-23 | 0.02 |
| Time before FU biopsy | 0.91 | 0.7-1.1 | 0.33 |
| Pre-treatment biopsy fibrosis | 0.72 | 0.3-1.5 | 0.38 |
| Pre-treatment biopsy inflammation | 0.77 | 0.2-3.7 | 0.89 |
| Number of relapses | 1.08 | 0.4-3 | 0.88 |
| Gender | 1.5 | 0.1-20.8 | 0.73 |
| Age at diagnosis | 1.1 | 0.9-1.4 | 0.26 |
| AIH type | 1.37 | 0.5-3.6 | 0.52 |
| Severity of initial clinical presentation | 0.47 | 0.1-1.7 | 0.25 |
| ALT at diagnosis | 0.79 | 0.5-1.1 | 0.16 |
| AST at diagnosis | 0.85 | 0.7-1 | 0.11 |
| Gammaglobulins at diagnosis | 0.64 | 0.1-1.7 | 0.37 |
| INR at diagnosis | 1.78 | 0.4-6.5 | 0.38 |
| Albumin at diagnosis | 0.38 | 0.1-1.7 | 0.21 |
| TPMT activity | 2 | 0.1-51 | 0.57 |
| Use of second-line therapies | 0.36 | 0.1-2.9 | 0.4 |
| Average azathioprine dosage | 0.28 | 0.1-2.1 | 0.21 |
| Administration of cyclosporine | 1.6 | 0.2-11 | 0.63 |

**Abbreviations:** AIH: Autoimmune Hepatitis; ALT: Serum Alanine Aminotransferase; AST: Serum Aspartate Aminotransferase; FU: Follow Up; INR: International Normalized Ratio; TPMT: Thiopurine Methyltransferase

inflammatory distortion of pre-treatment liver structure for fibrosis. We minimized this risk by defining a minimal portal tracts number required in order to analyze biopsies [17,29,31]. A possible source of error consists of patient selection for follow up biopsy (19 patients underwent a follow up biopsy out of the 40 patients in the overall cohort). In out cohort, follow up biopsy was more frequently performed in children with longer follow up, and in children with higher histological fibrosis score at diagnosis. At follow up biopsy, 13/19 patients (68%) exhibited clinical and/or biochemical signs of disease activity, corroborating that the main criteria in our cohort to perform a follow up biopsy was an insufficient response to therapy. All six patients in biochemical remission at follow up biopsy showed fibrosis regression, corroborating previous observations in pediatric AIH [3]. Fibrosis and inflammation regression in our cohort would then probably have been even more important if systematic follow up biopsies had been realized in all patients.

In our overall cohort, 50% of patients exhibited ASC. For the first time, our series compares the histological evolution of ASC with that of other AIH subtypes. This latter group was not subdivided in the various subtypes due to the sample size. Histological fibrosis regression was not confirmed for ASC patients, while it was clearly demonstrated for other AIH types. Furthermore, the long-term clinico-biochemical remission rate was lower in this subgroup compared to other AIH types. Our data thus confirms that ASC prognosis is more uncertain than that for other AIH types [4]. However, histological fibrosis should be interpreted carefully in ASC. In this group, liver fibrosis can be related to both necro-inflammatory AIH activity and biliary disease. As an original observation in our cohort, one patient with AIH type 2 could successfully be weaned from immunosuppression up to 7 years of follow up [23].

## CONCLUSION

In conclusion, fibrosis and inflammation scores decreased significantly in AIH children under immunosuppressive treatment, except in the ASC subgroup that has a worse outcome compared to other AIH types. We also proved for the first time that long-term disease remission can be predicted using the histological fibrosis evolution score between baseline and follow up biopsy. A large-scale, prospective, controlled study with systematic post-treatment biopsies would prove useful in further validating our results.

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