Autoimmune Hepatitis: Predictors of Native Liver Survival in Children and Adolescents

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Objective To determine predictors of native liver survival (NLS) in children and adolescents with autoimmune hepatitis (AIH).

Study design The medical records of children and adolescents with AIH were reviewed. A questionnaire was used to collect data on clinical presentation, biochemical and histologic findings, and treatment.

Results A total of 819 patients were included, 89.6% with AIH-1 and 10.4% with AIH-2. The median age (months) at onset was 108 (min 6; max 210; IQR 59). The female sex was predominant (75.8%). The overall survival was 93.0%, with an NLS of 89.9%; 4.6% underwent liver transplantation. The risk of death or liver transplantation during follow-up was 3.2 times greater in patients with AIH-1 (P = .024). Greater levels of aspartate aminotransferase, alanine aminotransferase, serum albumin, platelet, and normal international normalized ratio at the initial presentation were associated with longer NLS (P = .046, P = .006, P < .001, P = .001, and P = .019, respectively). Normal C3 levels was associated with longer NLS (P = .017), with a chance of death or liver transplantation during follow-up being 3.4 times greater in patients with C3 below normal. Death or liver transplantation during follow-up was 2.8 times greater in patients with associated sclerosing cholangitis (P = .046). Complete remission favored NLS (P < .001), with a risk of death or liver transplantation 11.7 times greater for patients not achieving remission.

Conclusions The best predictors of NLS in children and adolescents with AIH were the AIH-2 subtype, a normal C3 at diagnosis, remission during treatment, and normal a cholangiogram during the disease course. *(J Pediatr 2021;229:95-101)*.

Autoimmune hepatitis (AIH) is an immune-mediated, inflammatory liver disease. It is generally progressive and associated with significant morbidity. The most typical features of AIH are female preponderance, increased levels of immunoglobulin G (IgG), presence of serologic autoimmune markers (autoantibodies), and interface hepatitis on histology.[1]

In the absence of a single diagnostic test, the diagnosis of AIH is established by using the diagnostic score system reported by the International Autoimmune Hepatitis Group.[2,3] AIH can be further classified based on the presence of nonspecific autoantibodies, with AIH type 1 (AIH-1) being associated with the presence of anti-smooth muscle cell antibodies with or without anti-nuclear antibodies, and AIH type 2 (AIH-2) is associated with anti-liver–kidney microsome-1 antibodies and, less commonly, with anti-liver cytosol antibody-1.[4]

In children, treatment of AIH is based on induction and maintenance phases using prednisone with or without azathioprine.[5] If untreated, AIH usually progresses to liver failure requiring liver transplantation and is responsible for 2%-5% of all pediatric liver transplantation in Europe and the US.[6-8] Despite the responsiveness to medical treatment, the long-term exposure to steroids and other immunosuppressants can have substantial side effects; further, liver cirrhosis is present in 44%-80% of patients at the time of diagnosis.[7,9-12] Based on the variability of clinical presentation and stage of disease at diagnosis, it is important to establish the factors that influence prognosis and patient survival. Therefore, we conducted this study to determine the clinical and laboratory factors that predict native liver survival (NLS) in children and adolescents with AIH.

AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
ASC	Autoimmune sclerosing cholangitis
AST	Aspartate aminotransferase
FLF	Fulminant liver failure
IgG	Immunoglobulin
IgM	Immunoglobulin M
INR	International normalized ratio
NLS	Native liver survival

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Methods

This research was organized by the Pediatric Hepatology Study Group of Brazil. A questionnaire was sent to Brazilian Pediatric Hepatologists, all members of Pediatric Hepatology Study Group of Brazil, from the 17 centers of Pediatric Hepatology in Brazil. The data included patient's age, sex, type of AIH, age at onset, duration of follow-up, clinical and laboratory presentations, medications used, response to treatment, disease remission, need for liver transplantation, and mortality. All data were placed on a single platform for statistical evaluation, which ensured that there was no duplication of the same patient. This study was approved by the ethical committees of the participating institutions (CAAE No. 53562116.5.1001.0068).

Diagnosis of AIH

The diagnosis of AIH was established according to the modified International Autoimmune Hepatitis Group criteria.[2,3] All patients were screened at presentation for anti-nuclear, anti-smooth muscle cell antibodies and anti-liver–kidney microsome-1 antibodies. In addition, the patients had negative findings for hepatitis A, B, and C virus; cytomegalovirus; and Epstein–Barr virus infection. They had no history of drug or alcohol use or exposure to hepatotoxic drugs. Patients with alpha-1 antitrypsin deficiency, Wilson disease, and other liver diseases were excluded.

Clinical Presentation

Clinical presentation was classified as acute (nonspecific symptoms of malaise, nausea/vomiting, anorexia, abdominal pain, jaundice, dark urine, pale stools) or insidious (fatigue, nausea, abdominal pain, headache, amenorrhea, joint pain). Patients presenting with evidence of long-standing disease as shown by portal hypertension (with or without signs of encephalopathy) were classified into the insidious group. Fulminant liver failure (FLF) was defined by an abrupt onset of a liver-based coagulopathy [acute presentation, with no known evidence of chronic liver disease, with international normalized ratio (INR) ≥1.5 after parenteral administration of vitamin K and clinical hepatic encephalopathy or INR ≥2.0 with or without hepatic encephalopathy.[13,14]

Association with Sclerosing Cholangitis (Overlap Syndrome)

To investigate the coexistence of possible overlap syndrome, the biliary system was examined either via magnetic resonance cholangiopancreatography or via endoscopic retrograde cholangiopancreatography in patients who had high levels of gamma glutamyl transpeptidase on admission, those with persistent elevation despite immunosuppressive treatment, and those who developed high gamma glutamyl transpeptidase during the course of immunosuppression. Cholangiograms were reviewed by a specialized radiologist at individual clinical centers.

Liver Biopsy (Histologic Findings)

Liver biopsy was performed during the diagnostic evaluation, before starting treatment, except for patients who were admitted with liver failure or other contraindications to the procedure. Histologic measures studied included architectural changes, portal and periportal inflammatory infiltrates, liver cell damage and necrosis, interface hepatitis (piecemeal necrosis), confluent necrosis, bridging necrosis, submassive necrosis, and bile duct injury.

Treatment

Immunosuppressive therapy included a combination of prednisone (1.5 mg/kg/d, to a maximum of 60 mg/d) and azathioprine (1-1.5 mg/kg/d). Prednisone monotherapy was performed whenever severe thrombocytopenia was present. Prednisone was gradually tapered to a maintenance dose of 2.5-5 mg/d. In patients with overlap syndrome, ursodeoxycholic acid (15-20 mg/kg/d) was added to the therapy. Treatment of patients who did not respond or had contraindication for the use of azathioprine consisted of mycophenolate and cyclosporine, which occurred in 3.7% and 6.3% patients, respectively.

Remission and Relapse

Disease remission was defined as normal serum aminotransferase levels and normal serum IgG levels. Relapse was defined as an increase in serum aminotransferase levels ≥2-fold the upper limit of normal.[14]

Native Liver Survival

The variables analyzed for potential influence on NLS, defined as transplant-free survival, included type of AIH; age at disease onset; follow-up time; sex; clinical presentation (acute, insidious, and fulminant failure); extrahepatic manifestations; familial history of autoimmune diseases; AIH score; levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamyl transpeptidase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, platelets, immunoglobulin A, IgG, immunoglobulin M (IgM), C3, and C4; hepatic histologic changes (portal inflammation, interface hepatitis, rosette formation, plasma cells, fibrosis/cirrhosis, and biliary aggression); association with sclerosing cholangitis; time to remission; number of relapses; and discontinuation of treatment.

Statistical Analyses

Data are expressed as median and range, with minimum and maximum values. SPSS, version 24 (IBM Corp) was used for the statistical analyses. To determine the possible associations between the variables selected and the study outcomes, Cox regression analyses were used. Hazard ratios throughout the follow-up period were estimated and are presented with their respective 95% CIs. The level of significance was set at $P \leq .05$. Analyses were performed with Cox proportional hazards regression and logistic binary regression.

Table I. Results of the cholangiography (n = 268 patients)

Results of the cholangiography			Transplant-free survival	Death or liver transplant	Total
Cholangiography with bile duct lesions (sclerosing cholangitis)	AIH	1	50 (86.2%)	8 (13.8%)	58 (100%)
	AIH	2	2 (100%)	0 (0%)	2 (100%)
	Total		52 (86.7%)	8 (13.3%)	60 (100%)
Normal cholangiography	AIH	1	190 (96.4%)	7 (3.6%)	197 (100%)
	AIH	2	11 (100%)	0 (0%)	11 (100%)
	Total		201 (96.6%)	7 (3.4%)	208 (100%)
Total	AIH	1	240 (94.1%)	15 (5.9%)	255 (100%)
	AIH	2	13 (100%)	0 (0%)	13 (100%)
	Total		253 (94.4%)	15 (5.6%)	268 (100%)

Results

Demographic Data, Clinical Presentation, and Outcome

A total of 819 patients were included in this study, of whom 734 (89.6%) had AIH-1 and 85 (10.4%) had AIH-2. The median age (months) at onset was 108 months (min 6; max 210; IQR 59); 111.5 (6; 210) and 53.5 (8; 165) for the patients with AIH-1 and AIH-2, respectively ($P < .001$). The female sex was predominant among the patients (n = 621; 75.8%); 74.9% and 84.9% for AIH-1 and AIH-2, respectively.

The most common clinical presentation was acute (n = 455; 56.3%), followed by insidious features (n = 353; 43.7%). Fulminant hepatitis was observed in 35 patients (4.3%). Extrahepatic autoimmune manifestations were present in 195 patients (23.9%) and included systemic lupus erythematosus, Weber panniculitis, type 1 diabetes, thyroid disease, celiac disease, inflammatory bowel disease, glomerulopathies, and arthritis.

A family history of autoimmune disease, including diabetes, thyroid disease, Behçet disease, psoriasis, and vitiligo, was observed in 22.0% (n = 179). Increased INR (>1.5) and the presence of cirrhosis (metavir = F4) were observed in 259 (31.9 %) and 147 (22.4 %), respectively.

Cholangiography via magnetic resonance cholangiopancreatography or via endoscopy was performed in 268 patients (32.7%) and was consistent with sclerosing cholangitis in 22.4% of patients (n = 60). Bile ducts lesions on cholangiogram were more frequent in AIH-1 (n = 58), **Table I**. Of the total patients, 659 underwent liver biopsy before starting treatment (**Table II** and **Table III** [available at www.jpeds.com]). Overall, 160 patients did not undergo a liver biopsy because of contraindications to the procedures, but they met the AIH diagnostic criteria. Bile duct lesions were evaluated in liver histology (**Tables II** and **III**), with no significant influence on free-transplant survival.

Immunosuppressive treatment produced biochemical remission in 76.3% (n = 616). The overall survival was 93.0% (n = 762 of 819 patients), with an NLS of 89.9% (n = 736); 4.6% (n = 38) underwent liver transplantation (**Figure 1**). In consideration of patients with biliary lesions on cholangiogram, all deaths occurred in patients with AHI-1 (**Table I**).

Table II. Clinical and laboratory factors with potential association with the outcome of NLS

Variables	Hazard ratio (95% CI)	*P* value*
AIH type	3.22 (1.17-8.87)	.024
Age at onset, mo	1.00 (0.99-1.00)	.533
Sex	1.08 (0.64-1.83)	.774
Clinical presentation	1.34 (0.86-2.09)	.197
Fulminant hepatitis	1.96 (0.94-4.08)	.073
Extrahepatic manifestations	0.77 (0.46-1.30)	.329
Family history of autoimmune disease	0.94 (0.55-1.59)	.806
Score AIH (2008)	0.88 (0.73-1.07)	.206
AST, ×ULN	0.99 (0.97-1.00)	.046
ALT, ×ULN	0.97 (0.95-0.99)	.006
GGTP, ×ULN	1.00 (0.92-1.08)	.907
ALP, ×ULN	1.03 (0.97-1.10)	.280
TB, mg/dL	1.01 (0.98-1.04)	.419
DB, mg/dL	1.03 (0.99; 1.07)	.208
Albumin, g/dL	0.57 (0.43-0.77)	<.001
INR	1.73 (1.09-2.74)	.019
Gamma globulin, g/dL	0.98 (0.90-1.08)	.681
Leukocytes†	0.74 (0.57-0.95)	.017
Platelets†	0.77 (0.66-0.90)	.001
IgA	1.26 (0.29-5.50)	.761
IgM	2.37 (1.13-4.96)	.022
IgG	1.05 (0.45-2.42)	.918
C3	3.39 (1.24-9.27)	.017
C4	2.29 (0.82-6.44)	.115
Portal inflammation	0.44 (0.18-1.12)	.084
Interface hepatitis	0.83 (0.42-1.66)	.600
Rosettes	1.15 (0.67-1.98)	.620
Plasma cells	0.82 (0.48-1.40)	.473
Fibrosis/cirrhosis	1.30 (0.73-2.30)	.377
Bile duct injury	0.78 (0.28-2.15)	.625
Cholangiogram	2.84 (1.02-7.90)	.046
Remission	11.66 (7.06-19.24)	<.001
Time to remission, mo	0.99 (0.97-1.02)	.552
Relapse numbers	1.06 (0.91-1.25)	.442

ALP, alkaline phosphatase; *DB*, direct bilirubin; *GGTP*, glutamyl transpeptidase; *IgA*, immunoglobulin A; *TB*, total bilirubin; *ULN*, upper limit of normal.
*Wald test (for Cox regression).
†Previous natural-log data transformation.

Predictors of NLS

Cox regression analysis showed that the type of AIH, levels of AST, ALT, and albumin, INR >1.5, number of leukocytes and

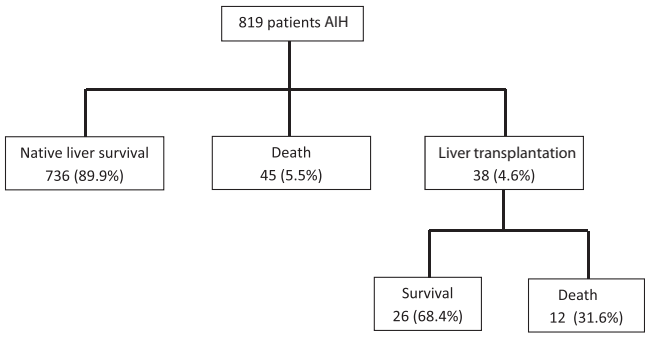

Figure 1. Flowchart of the patients' clinical course (n = 819).

platelets, levels of IgM and C3, altered cholangiogram, and disease remission were significant factors for NLS (Table II).

Cox regression models (proportional hazards regression) showed that the risk of death or liver transplantation during follow-up was 3.2 times greater in patients with AIH-1 than in patients with AIH-2 ($P = .024$). Among the laboratory examinations, greater levels of AST and ALT at the initial presentation were associated with longer NLS, with the probability of death or liver transplantation decreasing by 3% and 1% with the increase of 1 unit (× upper limit of normal) of ALT ($P = .006$) and AST ($P = .046$), respectively. Greater serum albumin levels were associated with a longer NLS ($P < .001$), with the probability of death or liver transplantation during follow up decreasing by 43% with an increase of 1 g/dL of albumin. The chance of death or liver transplantation decreased by 26% with an increase of 1 unit of leukocyte count (natural-log scale) ($P = .017$). Greater platelet counts were associated with longer NLS ($P = .001$), with a chance of death or liver transplantation, during follow-up, decreasing by 23% with an increase of one unit of platelet count on the natural-log scale. Patients with greater IgM had lower NLS ($P = .022$), with a chance of death or liver transplantation being 2.4 times greater in patients with IgM above normal during follow-up. Normal C3 levels was associated with longer NLS ($P = .017$), with a chance of death or liver transplantation during follow-up being 3.4 times greater in patients with C3 below normal (Tables II and III).

Death or liver transplantation during follow-up occurred 1.7 times more in patients with liver failure ($P = .019$) and patients with AIH and abnormal cholangiogram having lower NLS during follow-up ($P = .046$), with death or liver transplantation during follow-up being 2.8 times greater in patients with associated sclerosing cholangitis. An analysis of the data during progression of the disease showed that complete remission favored NLS ($P < .001$), with a risk of death or liver transplantation 11.7 times greater for those patients not achieving remission (Tables II and III).

The variables associated with NLS, with statistical significance should be highlighted by the CI: type of AIH, C3 level, association with sclerosing cholangitis (cholangiography abnormal), and disease remission (Table II and Figure 2).

To assess whether the overlap of AIH with sclerosing cholangitis, proposed as autoimmune sclerosing cholangitis (ASC), may have influenced the outcome of this study, we evaluated the transplant-free survival excluding the 60 patients with biliary lesions on cholangiography (n = 759). Cox regression analysis of these patients showed that the type of AIH influenced NLS significantly (hazard ratio 2.978; 95% CI 1.075-8.251; $P = .036$), with worse free-transplant survival for AIH-1 (Figure 2).

Discussion

Analyzing clinical and laboratory predictors of NLS in this large cohort of children and adolescents with a known diagnosis of AIH, we found an overall survival of 93% (n = 762), with an NLS of 89.9% (n = 736). Among the factors linked to survival with the native liver, the greatest associations were present for the type of AIH, ability to induce remission, co-existence of sclerosing cholangitis, and low C3.

The precise phenotyping of patients at presentation may give insight into pathogenic mechanisms of disease and potential drivers of long-term survival. Consistent with this paradigm, AIH-1 was the most common phenotype in our cohort and had a greater risk of undergoing liver transplantation or death. This finding differs from previous publications that the presence of anti-LKM is a risk factor for mortality[15] and that patients with AIH-2 have tend to present as acute liver failure and be more refractory to eventual withdrawal of immunosuppressive tretments.[4]

In this context, it is important to determine whether the small number of patients with AIH-2, expected by the known epidemiology of this diseases in the Americas,[16] and whether the diagnosis of ASC or overlap syndrome, more common in patients with AIH-1, influenced the results.

This study is a large cohort with a long follow-up, meaning that when many patients were diagnosed and treated, the diagnosis of AIH was established according to the AIH International Study Group criteria.[2,3] In 2018, Mieli-Vergani et al[4] proposed that in children and adolescents there are 3 autoimmune liver disorders (AIH, ASC, and de novo AIH after liver transplant) and proposed a new scoring system for testing and validation. The authors also state that juvenile sclerosing cholangitis often has autoimmune features identical to AIH type 1, diagnosis being possible only with cholangiography and that the term ASC is becoming increasingly more used but is not universally accepted.

The limitations of our study include the retrospective nature of its design and analytical strategy, which may include the lack of individual data elements, as well as the reading of cholangiograms and assessment of the liver histology at individual clinical sites (instead of a centralized reading). Another point to be considered is the possibility that the overlap of AIH and SC may modify influence the outcome/prognosis of patients with AIH-1. To control for this variable, we excluded patients with biliary lesions on cholangiography from the analysis of transplant-free survival.

A genetic predisposition and/or an imbalance between effector and regulatory immunity in a particular autoimmune ecosystem are key pathologic factors for disease development.[17] In pediatric AIH, several genetic predispositions have been reported to confer susceptibility to AIH. The strongest association is within the HLA-DRB1 locus, a class II MHC locus. In Europe, pediatric AIH-1 is associated with HLA-DRB1*0301.[18] AIH-2 is associated with HLA DRB1*0701.[19] In Brazil, the primary susceptibility allele for AIH-1 is DRB1*1301, but a secondary association with DRB1*0301 has also been reported.[20] In South America, particularly in Argentina, HLA-DRB1*1301 predisposes to childhood AIH-1.[21] Czaja et al[22] evaluated the clinical manifestations and genetic risk factors of 161 patients from the US and compared with 115 patients from Brazil. The patients

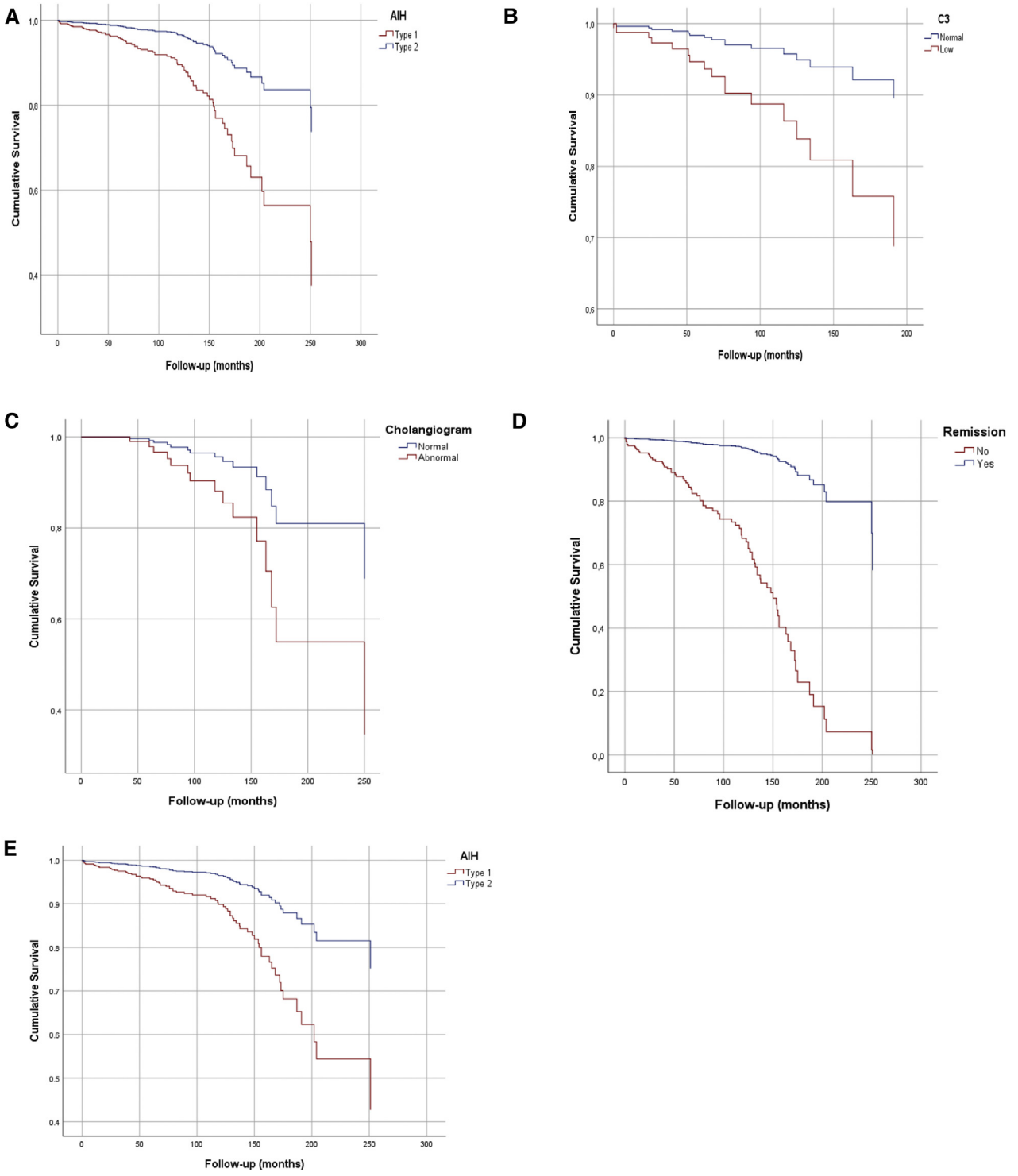

Figure 2. Cox regression for NLS of patients with AIH. **A,** Patients with AIH 1 and 2 types (n = 819; *P* = .024). **B,** With normal or low C3 (n = 311; *P* = .017). **C,** With autoimmune sclerosing cholangitis (overlap) vs those without (n = 268; *P* = .046). **D,** Patients with and without remission of the disease (n = 807; *P* < .001). **E,** Patients with AIH (1 and 2) without biliary lesions (n = 759; *P* = .036).

from Brazil had earlier disease onset, lower frequency of concurrent immune diseases, greater serum levels of AST and gamma globulin, greater occurrence of smooth muscle antibodies, and lower frequency of antinuclear antibodies than the patients from the US. HLA DR13 and DRB1*1301 occurred more commonly in the Brazilian patients and HLA DR4 less often. Normal subjects from each country had similar frequencies of HLA DR13 and DR3. Thus, we propose that genetic variation could be the basis for the worse outcome in Brazilian population with AIH-1.

The coexistence of biliary injury suggests the potential extension of the immunologic target to include biliary cells and/or a more complex pathogenic mechanisms of disease that may change the responsiveness to immunosuppression. In our cohort, of the 268 patients who underwent cholangiography, 22.4% had abnormal cholangiogram with features of sclerosing cholangitis, an association that has been reported by other investigators.[23]

In this cohort, the risk of death or liver transplantation during follow-up was 2.8 times more for patients with abnormal cholangiograms. Rodrigues et al[24] studied 134 children and adolescents with AIH and reported that the presence of overlap syndrome did not influence the survival rate or need for liver transplantation. Studying different patient cohorts, Deneau et al[9] reported that patients had a 5-year NLS of 78% in primary sclerosing cholangitis, 90% in ASC, and 87% in AIH. Notably, the survival was significantly reduced in patients with AIH with concomitant features of concurrent primary sclerosing cholangitis in a Dutch cohort of adult patients.[25]

It is expected that cirrhosis at presentation is associated with a worse outcome, but this was not the case in this study, as reported by other studies.[14] Radhakrishnan et al[15] showed that cirrhosis at presentation did not seem to influence outcome on natural history and long-term outcome in children with AIH. There are studies showing a decrease in fibrosis with a favorable therapeutic response.[26] Thus, in this study, cirrhosis at presentation was not associated with a worse transplant-free survival, probably because treatment promoted remission of disease and suppressed the progression of cirrhosis.

Of the 35 patients who presented FLF, 24 (68.6%) were alive without liver transplant, which means that the NLS in this group of patients was lower in relation to the total sample studied (89.9%), although it was not statistically significant. In a pediatric cohort, prednisone treatment has led to the recovery of 4 of 9 children with FLF due to AIH referred to a transplant center, the other 5 requiring liver transplant despite steroids.[27] Similarly good results with steroid therapy are reported from India, where 10 of 13 patients with severe acute presentation of AIH, including encephalopathy in 6, were rescued by prednisone treatment.[28]

The ability to induce remission with immunosuppressive drugs in children with AIH has been reported to occur in 60%-90% of children.[4] In our large cohort, biochemical remission was achieved in 76.3% of children and adolescents and was associated with an improvement in NLS. As would be expected, an incomplete normalization of ALT at 6 months of immunosuppression represented a significant independent predictor of liver-related death or the need for liver transplantation, as reported previously.[29] This finding also has been reported in adult patients, in whom the complete biochemical remission within 1 year of treatment initiation had the lowest risk of liver-related adverse outcomes.[30]

One of the main predictors of NLS in our large cohort was the serum C3 level at diagnosis. C3 is a key effector of pathobiological processes involving the complement system and low expression levels are associated with many infectious or immunological diseases. The specific decrease in C3 and increase in immunoglobulins in our studies may be biologically interrelated and indicate more active inflammatory circuits driving hepatocellular injury. Complement components play important roles in several autoimmune diseases including rheumatoid arthritis and ANCA-associated vasculitis.[31] In AIH, the presence of plasma cells, autoantibodies, and IgG are recognized hallmarks of disease. In the analysis reported herein, the newly identified link between C3 and NLS points to a potential direct or indirect role of complement factors in pathogenesis of liver injury. The biological mechanisms underlying this association are not yet known, but are likely to be the focus of future studies to validate our findings in separate cohorts and detailed tissue analysis to quantify C3 and related factors. Doherty et al[32] and Vergani et al[33] demonstrated that lower C4 levels were a predisposing factor of AIH, a finding that was not reproduced in our cohort. The complement system, an essential part of the innate immune system, is involved in various autoimmune diseases. Activation of the complement system by autoantibodies results in immune activation and tissue damage. Little is known about the role of the complement system in autoimmune liver disease. Genetically determined, isolated, partial deficiency of the HLA class III complement component C4 has been reported in pediatric patients with type-1 and -2 AIH.[33] Because inhibition of the complement system is currently being tested in several autoimmune diseases as a therapeutic option, its role in autoimmune liver disease requires further clarification.

In summary, analyzing the biochemical, histologic, and radiologic factors at diagnosis and during the course of disease in a large cohort of children and adolescents with AIH, we found that the best predictors of NLS were the subtype AIH-2, a normal C3 at diagnosis, a remission with the treatment, and normal cholangiogram during the disease course. We recognize the limitations of retrospective analyses, which raise the possibility of incomplete patient data. This weakness is minimized by the large cohort size which represents the real-world experience that enabled us to perform comparative analyses of subgroups with acceptable numbers of subjects. The ability to reproduce differences in AIH subtypes, remission, cholangiogram, and other biochemical measures reported in previous reports further support the strength of our study design. In this context, the findings of decreased serum C3 levels as an important predictor of low NLS emerge as a new biomarker of disease severity. Future prospective studies can be designed to validate these findings and to explore whether C3 or other components of the complement system may be therapeutic targets in AIH. ■

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Appendix

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Table III. Clinical and laboratory factors potentially influencing the outcome of NLS

Variables	NLS		OR yes/no (95% CI); logistic regression	P*	HR yes/no (95% CI); Cox regression	P†
	Death or liver transplantation	Alive without liver transplantation				
AIH type (n) (%)						
Type 1	78 (94.0)	656 (89.1)	1.90 (0.75-4.84)	.177	3.22 (1.17-8.87)	.024
Type 2	5 (6.0)	80 (10.9)	1		1	
Age at onset, mo, median (min; max)	99 (12; 186)	109 (6; 210)	1.00 (0.99-1.00)	.162	1.00 (0.99-1.00)	.533
Follow-up, mo, median (min; max)	95 (0; 251)	77 (1; 286)	1.01 (1.00-1.01)	.078	–	–
Sex, n (%)						
Male	18 (21.7)	180 (24.5)	1		1.08 (0.64-1.83)	.774
Female	65 (78.3)	556 (75.5)	1.17 (0.68-2.02)	.577	1	
Clinical presentation						
Acute, n (%)	41 (50.6)	414 (56.9)	1		1	
Insidious, n (%)	40 (49.4)	313 (43.1)	1.29 (0.82-2.04)	.277	1.34 (0.86-2.09)	.197
Fulminant, n (%)						
Yes	11 (13.3)	24 (3.3)	4.53 (2.13-9.63)	<.001	1.96 (0.94-4.08)	.073
No	72 (86.7)	712 (96.7)	1		1	
Extrahepatic manifestations, n (%)						
Yes	19 (23.5)	176 (24.0)	0.97 (0.57-1.67)	.917	0.77 (0.46-1.30)	.329
No	62 (76.5)	558 (76.0)	1		1	
Family history of autoimmune disease, n (%)						
Yes	19 (23.5)	160 (21.8)	1.10 (0.64-1.89)	.737	0.94 (0.55-1.59)	.806
No	62 (76.5)	573 (78.2)	1		1	
Score AIH (2008), median (min; max)	7 (2; 8)	7 (3; 10)	0.89 (0.73-1.09)	.248	0.88 (0.73-1.07)	.206
Score AIH (1999), median (min; max)	17 (11; 28)	17 (5; 123)	0.99 (0.94-1.05)	.790	0.98 (0.91-1.04)	.459
AST, ×ULN, median (min; max)	11 (1; 160)	18 (0; 169)	0.99 (0.98-1.00)	.081	0.99 (0.97-1.00)	.046
ALT, ×ULN, median (min; max)	6.7 (0.3; 156)	13.7 (0; 95)	0.98 (0.96-1.00)	.016	0.97 (0.95-0.99)	.006
GGTP, ×ULN, median (min; max)	2 (0; 20)	3 (0; 37)	0.93 (0.86-1.01)	.068	1.00 (0.92-1.08)	.907
ALP, ×ULN, median (min; max)	1.6 (0.1; 10.0)	1.3 (0.0; 47.7)	1.02 (0.95-1.09)	.580	1.03 (0.97-1.10)	.280
TB, mg/dL, median (min; max)	3.6 (0.9; 32.1)	3.2 (0; 66.2)	1.04 (1.01-1.07)	.025	1.01 (0.98-1.04)	.419
DB, mg/dL, median (min; max)	2.5 (0.3; 24.0)	2.1 (0.0; 37.4)	1.06 (1.01-1.11)	.015	1.03 (0.99-1.07)	.208
Albumin, g/dL, median (min; max)	3.0 (1.3; 5.2)	3.5 (0.0; 33.0)	0.54 (0.40-0.74)	<.001	0.57 (0.43-0.77)	<.001
INR						
>1.5	33 (41.3)	226 (30.9)	1.57 (0.98-2.52)	.061	1.73 (1.09-2.74)	.019
<1.5	47 (58.8)	505 (69.1)	1		1	
Leukocytes,‡ median (min; max)	5410 (1800; 19 500)	6750 (7; 64 200)	0.73 (0.53-1.00)	.053	0.74 (0.57-0.95)	.017
Platelets,‡ median (min; max)	102 000 (24 000; 563 000)	170 000 (115; 804 000)	0.64 (0.50-0.83)	.001	0.77 (0.66-0.90)	.001
IgA, n (%)						
Normal	17 (89.5)	255 (91.7)	1		1	
Low	2 (10.5)	23 (8.3)	1.30 (0.28; 6.00)	.733	1.26 (0.29; 5.50)	.761
IgM, n (%)						
Normal	13 (44.8)	228 (63.23)	1		1	
High	16 (55.2)	132 (36.7)	2.13 (0.99-4.56)	.053	2.37 (1.13-4.96)	.022
IgG, n (%)						
Normal	7 (21.9)	76 (18.4)	1		1	
High	25 (78.1)	337 (81.6)	0.81 (0.34-1.93)	.628	1.05 (0.45-2.42)	.918
C3, n (%)						
Normal	6 (35.3)	203 (69.0)	1		1	
Low	11 (64.7)	91 (31.0)	4.09 (1.47-11.40)	.007	3.39 (1.24-9.27)	.017
C4, n (%)						
Normal	5 (27.8)	142 (47.5)	1		1	
Low	13 (72.2)	157 (52.5)	2.35 (0.82-6.76)	.113	2.29 (0.82-6.44)	.115
Portal inflammation (moderate-severe), n (%)						
Yes	51 (91.1)	565 (93.7)	0.69 (0.26-1.82)	.449	0.44 (0.18-1.12)	.084
No	5 (8.9)	38 (6.3)	1		1	
Interface hepatitis, n (%)						
Yes	46 (82.1)	488 (83.0)	0.94 (0.46-1.93)	.872	0.83 (0.42-1.66)	.600
No	10 (17.9)	100 (17.0)	1		1	
Rosettes, n (%)						
Yes	31 (56.4)	302 (50.8)	1.25 (0.72-2.18)	.434	1.15 (0.67-1.98)	.620
No	24 (43.6)	292 (49.2)	1		1	
Plasma cells, n (%)						
Yes	32 (55.2)	303 (50.8)	1.19 (0.69-2.05)	.529	0.82 (0.48-1.40)	.473
No	26 (44.8)	293 (49.2)	1		1	
Fibrosis/cirrhosis, n (%)						
Fibrosis	38 (67.9)	471 (78.5)	1			
Cirrhosis	18 (32.1)	129 (21.5)	1.73 (0.96-3.13)	.071	1.30 (0.73-2.30)	.377

(*continued*)

Table III. Continued

Variables	NLS		OR yes/no (95% CI); logistic regression	P*	HR yes/no (95% CI); Cox regression	P†
	Death or liver transplantation	Alive without liver transplantation				
Bile duct injury, n (%)						
Yes	4 (6.8)	54 (9.0)	0.73 (0.26-2.10)	.565	0.78 (0.28-2.15)	.625
No	55 (93.2)	545 (91.0)	1		1	
Cholangiogram, n (%)						
Normal	7 (46.7)	201 (79.4)	1		1	
Abnormal	8 (53.3)	52 (20.6)	4.42 (1.53-12.74)	.006	2.84 (1.02-7.90)	.046
Remission						
Remission rate, n (%)						
Yes	24 (29.3)	592 (81.7)	1		1	
No	58 (70.7)	133 (18.3)	10.78 (6.45-17.94)	<.001	11.66 (7.06-19.24)	<.001
Time to remission, mo, median (min; max)	5 (0; 44)	6 (1; 250)	0.99 (0.96-1.03)	.650	0.99 (0.97-1.02)	.552
Relapse numbers, median (min; max)	3 (0; 7)	3 (0; 13)	1.08 (0.93-1.26)	.314	1.06 (0.9-1.25)	.442

ALP, alkaline phosphatase; *DB*, direct bilirubin; *GGTP*, glutamyl transpeptidase; *HR*, hazard ratio; *IgA*, immunoglobulin A; *TB*, total bilirubin; *ULN*, upper limit of normal.
*Wald test (for logistic regression).
†Wald test (for Cox regression).
‡Previous natural-log data transformation.