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Racial disparities in presentation and outcomes of paediatric autoimmune hepatitis

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Abstract

Background & Aims: Most studies on autoimmune hepatitis (AIH) in children are in predominantly Caucasian cohorts. Paediatric AIH in African Americans (AA) is understudied, with a dearth of clinical predictors of outcome, often leading to serious complications and even mortality. The aim of the study was to define disease presentation, progression, response to therapy and outcomes in paediatric AIH in a well-defined, large, single centre, demographically diverse population.

Methods: We conducted a review of patients with AIH who were followed at this tertiary liver transplant centre. Clinical and laboratory covariates were assessed with regard to disease presentation, progression and outcomes in AA vs Non-AA children.

Results: African Americans patients constituted 42% of this cohort. At 1-year follow-up, AA children were receiving significantly higher doses of steroids compared to non-AA. More AA presented with end-stage liver disease (ESLD) with high immunoglobulin G and GGT:platelet ratio. After adjusting for other risk factor variables like gender, age at presentation and ESLD, AA children were at 4.5 times higher risk for significant outcome liver transplant/death within the first 12 months of presentation. Post-transplant, recurrent AIH was seen in 50% of AA vs 8% in non-AA.

Conclusions: African American patients with AIH are more likely to present with ESLD and have an increased early risk for transplantation with high likelihood of disease recurrence post-transplantation. Studies are needed to delineate factors such as inherent biology, genetics and access to care. Early referral and tailored immunosuppressive regimens are required for AA patients with AIH.

KEYWORDS

African American, autoimmune disease, immunosuppressive therapy, paediatrics

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver condition of unknown aetiology. Diagnosis of AIH is widely based on codified diagnostic criteria of the International Autoimmune Hepatitis Group (IAIHG), like abnormal serum biochemistry, high serum immunoglobulin G (IgG) concentrations, circulating serum autoantibodies and inflammatory liver histology with exclusion of other causes of

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; ANA, antinuclear antibody; APRI, AST-to-platelet ratio index; CI, confidence intervals; ESLD, end-stage liver disease; HLA, human leucocyte antigen; HR, hazard ratios; IAIHG, International Autoimmune Hepatitis Group; IBD, inflammatory bowel disease; IgG, immunoglobulin; INR, international normalized ratio (INR); IQR, interquartile range (IQR); LKM, liver kidney microsomal; LT, liver transplantation; PSC, primary sclerosing cholangitis.

liver disease.[1,2] Although AIH presents both in adults and children, several studies have shown that the disease process may actually start early in life, making it imperative to understand epidemiological factors, pathophysiology and natural history of disease progression in children.[3-5]

Unlike other autoimmune conditions in children, there are very few epidemiological studies on the incidence and prevalence of AIH. Based on the data available, the prevalence of AIH among Caucasians in Europe and North America ranges from 0.1 to 1.9 per 100 000 per year.[3,5,6] Most of these studies are predominantly from Caucasian cohorts; and although there are some adult studies reporting that clinical phenotype and outcome may vary by race, the focus of those studies has been the study of Hispanic and Asians cohorts, with exclusion of African American (AA) patients due to inadequate data.[7-9] A single adult retrospective study of AIH patients did show that AIH was more aggressive in AA male patients, but this study excluded children under the age of 18.[10] Current knowledge about clinical presentation, outcomes and management of paediatric AIH are also based on studies from small non-transplant centres and from centres that have a predominantly Caucasian population.[3,11-14] Till date, there are no studies from large referral centres that focus on AA patients especially children.

According to the 2015 US census bureau report, 42 million people in the United States identified themselves as 'Black' and the majority of the Black population (57%) lives in the south, with more than 106 counties showing 50% or more of their total population being Blacks.[15] This centre being a large tertiary referral liver and liver transplant centre in south-east US, provides care to a large proportion of AA children and there is complete lack of outcome data in paediatric AA children with AIH to help guide treatment protocols. To further address this important clinical question, we conducted a detailed analysis of children with AIH who were followed for over a decade at our centre. We analysed the various potential determinants of long-term outcomes in AA vs non-AA children with a focus on severity of liver disease presentation, immunosuppressive medication usage and outcomes of death and/or transplantation.

Key points

- African American children with autoimmune liver disease are more likely to present with end-stage liver disease, have an increased risk of liver transplantation and a high disease recurrence in the graft.
- Hence, these children require early referral, tailored immunosuppression and close follow-up.

2 | PATIENTS AND METHODS

Children's Healthcare of Atlanta (CHOA) is a major referral transplant centre in the south-east USA. After obtaining Emory University Institutional Review Board (IRB) approval, we conducted a review of our clinical, liver transplant and pathology databases for cases related to AIH of all paediatric patients (21 years of age and younger) between 1998 and 2014. One hundred and forty-eight patients with AIH and PSC were being followed up at our centre. Based on magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and liver biopsy, 39 patients who had features of primary sclerosing cholangitis (PSC) and AIH overlapping with PSC were excluded from this analysis. The remaining 109 patients were included in the present study. All patients underwent liver biopsy at diagnosis and as per IAIHG criteria, other causes of chronic liver diseases were excluded. Children who presented with acute liver failure and were transplanted emergently, had their explants reviewed along with serology for the diagnosis of AIH. All liver biopsies and explants were reviewed by two experienced pathologists who were blinded to patients' clinical and biochemical information.

2.1 | Treatment and definitions

After diagnosis, all children except those who presented in acute failure received corticosteroids and azathioprine, with close clinical and biochemical monitoring.[16] Acute liver failure (ALF) in children was defined as biochemical evidence of acute liver injury with the absence of previously known history of chronic liver disease, coagulopathy not corrected by vitamin K and international normalized ratio (INR) >1.5 in patients with encephalopathy or >2 in those without.[17] End-stage liver disease (ESLD) was defined by the presence of jaundice, coagulopathy and portal hypertension in the setting of cirrhosis from underlying AIH. Slow weaning of steroids until achievement of low dose prednisolone (5 mg/d) was considered standard of care. Biochemical remission was defined as a sustained decrease in serum alanine aminotransferase (ALT) to within the normal range (≤30 IU). Biochemical relapse was defined as ALT that was elevated two times above the upper limit of normal, based on the local laboratory reference range. Biochemical loss of remission was defined as rising ALT that necessitated the reinstitution of steroids or increasing the dose of steroids. Patients with no response to standard therapy with steroids and azathioprine for 12 months were identified as non-responders and they were then treated with either mycophenolate mofetil or tacrolimus and if that failed, they were considered for liver transplantation.

2.2 | Methodological details

To identify differences between presentation and outcomes of AIH in AA vs non-AA children with AIH, several covariates were assessed. Age at diagnosis, gender, race, AIH type, modes of presentation, laboratory values at presentation and at all subsequent visits, date of latest clinic visit, medications started at diagnosis and subsequent visits, medication dosage, dates of remission, relapse, recurrence, transplant or death were analysed. Predictive laboratory ratios like AST-to-platelet ratio index, GGT-to-platelet ratio, ALT:

aspartate transaminase (AST) ratio, etc., were calculated. Patients were divided into two groups based on their race that is AA were compared with non-AA.

2.3 | Statistical analyses

Basic descriptive statistics were conducted for an exploratory analysis of the data. Univariate statistical techniques, parametric and non-parametric, bivariate regression methods, multivariable regression model and survival methods were used. Survival in the AA group was compared to that in the non-AA group using Kaplan-Meier methods accompanied by the log-rank and Wilcoxon tests. Means are reported with SD and medians with interquartile range (IQR). Hazard ratios (HR) are reported with their 95% confidence intervals (CI) and respective *P*-values. Because race violated the proportional hazard assumption in our multivariable Cox PH models, a Heaviside function was used to estimate the hazard of death/transplant in the first 12 months of follow-up and after the first 12 months. Statistical significance was defined at a *P*-value of 0.05. All statistical analyses were performed using Microsoft Excel and SAS® Software Version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

Between 1998 and 2014, 109 children fulfilled criteria for AIH established by IAIHG at our centre and were eligible for the study. Tables 1 and 2 shows demographics and clinical characteristics at entry. The included patients were predominantly female (72.48%; 79/109), had a median age of 12.6 years (IQR: 8.9-15.4) at diagnosis, and had a median follow-up of 44.8 months (IQR: 18.5-82.3). AA constituted 42% of this cohort and rest were non-AA (58%). Of the 63 non-AA, there were 47 Caucasians, 10 non-Caucasians (predominantly Hispanics and Asians) and 6 were unknown (who identified themselves as mixed race). The AA group had a relatively larger proportion of females (80.4% vs 66.7%) as compared to the non-AA group. Data on absolute autoantibodies at presentation was not available in 15 patients (13.7%), and of the remaining 94 patients, 83 (76%) had ANA and/or antismooth muscle antibody (SMA) positivity suggesting type 1 AIH, 11 (10%) patients were positive for liver kidney microsomal (LKM) antibodies suggesting type 2 AIH. All of the 15 patients on whom antibody data was not available at presentation, met other clinical criteria for IAIHG. A higher proportion of non-AA children presented with acute hepatitis mode of presentation compared to AA (79.4% vs 63%) in contrast, a higher proportion of AA children presented with ESLD compared to non-AA (28.3% vs 17.5%), though these did not achieve statistical significance. AA had a significantly higher Immunoglobulin G (IgG) ($P = 0.03$) at presentation compared to non-AA. They also had a significantly higher gamma glutamyl transpeptidase (GGT):platelet ratio at entry ($P = 0.02$), consistent with their mode of ESLD presentation. Interestingly, although a small proportion (11%), coexistent autoimmune diseases were more common in the non-AA group (14.2%) vs the AA group (6.5%).

TABLE 1 Demographics, clinical characteristics and outcomes of African American (AA) patients with paediatric autoimmune hepatitis compared to those of non-AA patients (N = 109)

Characteristic	AA (*n* = 46)	Non-AA (n = 63)	*P*-value
Age (years), median (IQR)	12.6 (9.8-16.2)	12.5 (7.4-15.2)	0.24
Gender, N (%)			0.12
Female	37 (80.4%)	42 (66.7%)	
Male	9 (19.6%)	21 (33.3%)	
Race			
AA	46 (41.8%)		
Non-AA			
Caucasian	47 (42.7%)		
Others	10 (9.1%)		
Unknown	6 (6.4%)		
AIH type, N (%)			0.38
2	3 (6.5%)	8 (12.7%)	
1	38 (82.6%)	45 (71.4%)	
Unknown	5 (10.9%)	10 (15.9%)	
Presentation, N (%)			0.12
End-stage disease	13 (28.3%)	11 (17.5%)	
Acute hepatitis	28 (63.0%)	50 (79.4%)	
Acute liver failure	3 (6.5%)	1 (1.5%)	
Drug induced liver failure	1 (2.2%)	0 (0%)	
Unknown	0 (0%)	1 (1.6%)	
Coexistent autoimmune diseases			
Coeliac	0 (0%)	4 (6.3%)	
Lupus	1 (2.1%)	0 (0%)	
Vasculitis	0 (0%)	1 (1.5%)	
Inflammatory bowel disease	1 (2.1%)	2 (3.1%)	
Type 1 diabetes mellitus	1 (2.1%)	1 (1.5%)	
APECED gene positive	0 (0%)	1 (1.5%)	

3.1 | Medication usage

Table 3 shows the medication usage and patient outcomes comparing both cohorts (AA vs non-AA). Standard therapy with steroids and azathioprine was started on all patients except in children who had fulminant presentation. Total duration of follow-up was comparable in AA vs non-AA (46.9 vs 35.5 months).

TABLE 2 Laboratory characteristics at presentation of African American (AA) patients with paediatric autoimmune hepatitis compared to those of non-AA patients (N = 109)

Characteristic	AA (n = 46)	Non-AA (n = 63)	*P*-value
Labs at diagnosis, med. (25th-75th)			
Albumin	3.1 (2.75-3.55)	3.3 (2.5-3.9)	0.63
Alk. phos.	294 (184-494)	258 (173-398)	0.50
ALT	233 (156-759)	433 (219-1447)	0.26
AST	350 (144.5-785.5)	557 (224-1391)	0.42
INR	1.2 (1.1-1.65)	1.1 (1-1.25)	0.19
PT	15.9 (14.8-21.1)	15.5 (14.4-17.8)	0.51
GGT	141 (99.5-194)	100 (71-147)	0.06
IGG	2855 (2150-4567)	1682 (1270-2198)	**0.03**
Platelet	173 (126.5-285)	202 (106-271)	0.75
Bilirubin direct	1.05 (0.30-2.40)	0.50 (0.0-4.3)	0.85
Bilirubin total	3.60 (2.10-5.30)	2.85 (1.50-7.60)	0.95
Lab ratios, med. (25th-75th)			
ALT:AST ratio	0.96 (0.62-1.34)	1.04 (0.62-1.43)	0.62
AST:platelet ratio	2.20 (0.77-3.65)	2.29 (0.84-7.37)	0.45
ALT:platelet ratio	1.82 (0.90-2.91)	2.80 (0.79-6.79)	0.25
ALT:GGT ratio	3.34 (1.25-7.56)	3.51 (2.29-18.24)	0.08
AST:GGT ratio	3.67 (0.94-7.00)	3.89 (2.30-11.38)	0.25
Platelet:GGT ratio	1.41 (0.88-2.06)	2.56 (1.37-3.84)	**0.02**
GGT:platelet ratio	0.71 (0.50-1.14)	0.39 (0.26-0.73)	**0.02**

ALT, alanine aminotransferase; AST, Aspartate Transaminase; GGT: gamma glutamyl transpeptidase; IGG, Immunoglobulin G; INR, international normalized ratio; PT, Prothrombin Time. Bold signifies that those *P* values are significant i.e. <0.05.

Table 3 also looks at outcomes between the two cohorts. As shown, there was no difference between AA and non-AA in relation to overall liver transplantation or death (30% vs 19% and 4.4% vs 3.2%). AA children were at significantly elevated risk of recurrence of same AIH in graft compared to non-AA children ($P = 0.01$). This is consistent with the high IgG levels, high GGT to platelet ratio, higher mean steroid dosing at 1 year of diagnosis and higher proportion of ESLD in AA children at presentation, suggesting aggressive disease.

Initial steroid dose and steroid wean practice was standard across all physicians. As shown in Figure 1, at 1-year follow-up, a higher proportion of AA children were on high-dose steroids compared to non-AA children (97% vs 85%) but this was not statistically significant. On further analysis of steroid dose, significantly high number of AA children were on high dose of steroids (more than 5 mg) compared to non-AA children ($P = 0.001$). At 5 years of follow-up, there was no difference in proportion or dosing difference in both cohorts. It is interesting to note that initial mean steroid dose (mg) was same in both groups but it was statistically significant at 1-year follow-up ($P = 0.001$) and after that there was a steady decrease over a 5 years follow-up. There was no significant difference in relapse rates and use of second-line agents, such as mycophenolate mofetil and tacrolimus, between the two cohorts (32.6% vs 28.6% and 13% vs 12.7%). The majority of the relapses occurred during the attempted weaning of immunosuppression.

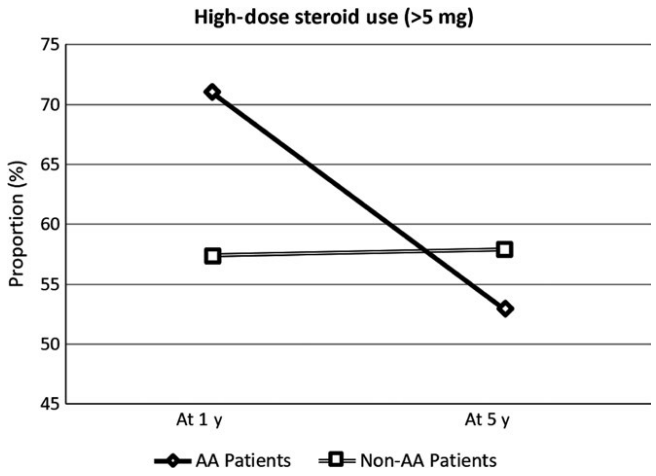

FIGURE 1 Graphs comparing the use of high-dose steroids among African American (AA) patients to non-AA patients. There is a higher proportion of AA patients receiving high-dose steroids at 1-y ($P = 0.001$). Graphs comparing the use of high-dose steroids among AA patients to non-AA patients. There is a decrease in number of AA patients receiving high-dose steroids at 5 y

3.2 | Outcomes

Table 4 shows the assessment of poor outcomes by two survival regression analyses, one assessing the outcome transplant or death

TABLE 3 Medication usage and disease outcomes of African American (AA) patients with paediatric autoimmune hepatitis compared to those of Non-AA patients (N = 109)

Characteristic	AA (n = 46)	Non-AA (n = 63)	*P*-value
Medication use, % (N)			
Steroids started	80.4%	81.0%	0.95
Steroids at 1 y visit	96.8%	85.1%	0.10
Steroids At 5 y visit	64.7%	63.2%	0.92
Steroids at most recent visit	55.6%	43.8%	0.29
Second-line agent	13.0%	12.7%	0.96
Tacrolimus	4/14 (29%)		
Mycophenolate mofetil	3/14 (21%)		
Tacrolimus and mycophenolate	3/14 (21%)		
High-dose steroid use, % (N)			
At 1 y visit[a]	71.0%	57.4%	**0.001**
At 5 y visit[b]	52.9%	57.9%	0.77
Relapse, % (N)	32.6%	28.6%	0.37
Remission, % (N)	39.1%	47.6%	0.38
Transplanted, % (N)	30.4%	19.0%	0.17
Died, % (N)	4.4%	3.2%	0.75
Recurrent disease, % (N)	15.2%	1.6%	**0.01**
Transplant-free survival, % (N)	65.2%	81.0%	0.09
Follow-up (mo), med. (IQR)	46.9 (28.4-79.2)	35.5 (15.8-82.8)	0.36

and the other evaluating relapse as an outcome. It shows that those with worse outcomes related to liver transplant and/or death had ESLD at presentation ($P < 0.001$), low albumin ($P = 0.02$), high prothrombin time (PT) ($P = 0.001$) and low platelet count at presentation ($P = 0.03$). Risk of adverse outcome (liver transplantation or death) was eight-fold higher with ESLD presentation ($P < 0.001$), three-fold higher with decrease in platelet count by 50,000 ($P = 0.01$) and 1.5-fold higher per unit increase in PT ($P < 0.001$). Variables related to paediatric AIH which were noted to be significant for predicting the poor outcome like transplantation/death were then entered into multivariate risk factor analysis as shown in Table 5. The following variables were entered into the model: gender, race, age at presentation, steroids initiated, AIH type and ESLD at presentation. Variables independently associated with a poor outcome especially liver transplant/death were steroids initiated at presentation factor (HR: 16.49; 95% CI: 3.61-75.38; $P < 0.001$), ESLD (HR 3.81; 95% CI: 1.23-11.80; $P = 0.02$) and race within first 12 months of presentation (HR 4.52; 95% CI: 1.04-19.61; $P = 0.04$). It is important to note that after adjusting other risk factor variables like gender, age at presentation, steroids initiation at diagnosis, type of AIH and ESLD, AA children were at 4.5 times more risk for significant outcome liver transplant/death within first 12 months of presentation.

The probability of having a poor outcome over the follow-up period among AA and non-AA children is shown in Figure 2. Overall transplant-free survival was reduced in AA patients compared to non-AA patients (65% vs 80%) but this was not statistically significant ($P = 0.09$). Upon 1-year follow–up, AA children had lower transplant-free survival compared to non-AA children (79.4% vs 94.6%, *P*-value = 0.05) as supported by the Kaplan-Meier analysis. However, there was no significant difference at 60 months of follow-up (76.6% vs 86.7% *P*-value = 0.2). Lack of clear significance in this Kaplan-Meier survival analysis may be due to the relatively small number of patients.

4 | DISCUSSION

This current retrospective review of a large cohort of children with AIH from a single centre provides novel information about the mode of presentation, natural history, response to therapy, predictors and clinical outcomes of paediatric AIH, with a special impact of ethnicity on the natural history of paediatric AIH. To our knowledge, this is the first major study in North America on childhood AIH focusing on ethnicity, especially on the AA population. AA children with AIH tend to have more severe disease at presentation clinically, biochemically and histologically in the form of ESLD and ALF compared to non-AA. They have significantly higher IgG levels, high GGT to platelet ratio, higher mean steroid dosing at 1 year of diagnosis putting them at risk for initial decreased transplant-free survival and recurrent disease post-transplant. In contrast to data in adults, there was no difference in overall mortality in AA compared to non-AA.[10] This might be explained by the fact that AA children received liver transplant within the first 12 months of presentation.

Previous studies of children with AIH showed that in Caucasians, acute hepatitis is the most common mode of presentation (80%), where as in Asians, cirrhosis is the predominant mode (56%).[3,5-7] Our study showed that the acute mode of presentation (acute hepatitis)

TABLE 4 Risk factors for adverse clinical outcomes among patients with paediatric autoimmune hepatitis (N = 109)

Characteristic	Transplant or death		Relapse	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age (per 1 y)	0.99 (0.90-1.09)	0.805	0.99 (0.92-1.06)	0.69
Gender, N (%)				
Female	1.65 (0.46-5.87)	0.440	1.18 (0.50-2.78)	0.71
Male	—		—	
Race				
AA	1.79 (0.67-4.81)	0.248	1.03 (0.49-2.19)	0.94
Non-AA	—		—	
AIH type, N (%)				
2	0.97 (0.21-4.39)	0.969	0.61 (0.18-2.08)	0.43
1	—		—	
Presentation, N (%)				
End-stage disease	8.1 (2.9-22.5)	**0.001**	0.79 (0.30-2.09)	0.62
Acute hepatitis	—		—	
Acute liver failure	—		—	
Drug-induced liver failure	—		—	
Labs at diagnosis (within 30 d)				
Albumin (per 1 unit)	0.17 (0.04-0.78)	**0.02**	1.23 (0.67-2.24)	0.51
Alk. phos. (per 100 units)	0.99 (0.64-1.54)	0.96	0.78 (0.57-1.07)	0.12
ALT (per 100 units)	0.92 (0.77-1.10)	0.37	1.00 (0.94-1.08)	0.91
AST (per 100 units)	0.92 (0.76-1.12)	0.41	0.99 (0.93-1.05)	0.69
INR (per 0.1 s)	1.31 (0.90-1.91)	0.17	0.85 (0.56-1.29)	0.44
PT (per 1)	1.46 (1.16-1.85)	**0.001**	0.92 (0.79-1.06)	0.23
GGT (per 10)	1.07 (0.94-1.22)	0.32	0.99 (0.91-1.07)	0.78
IGG (per 500)	1.03 (0.75-1.40)	0.86	0.98 (0.79-1.22)	0.84
Platelet (per 50)	0.31 (0.11-0.89)	**0.03**	1.18 (1.03-1.35)	0.02
Lab ratios (per 1 unit increase)				
ALT:AST ratio	1.55 (0.49-4.79)	0.46	1.20 (0.62-2.31)	0.59
AST:platelet ratio	1.00 (0.88-1.14)	0.96	0.90 (0.77-1.05)	0.16
ALT:platelet ratio	1.03 (0.87-1.22)	0.74	0.89 (0.74-1.06)	0.20
ALT:GGT ratio	0.95 (0.82-1.10)	0.45	1.00 (0.94-1.07)	0.94
AST:GGT ratio	0.96 (0.84-1.09)	0.50	0.99 (0.93-1.05)	0.65
Platelet:GGT ratio	0.16 (0.03-0.93)	**0.04**	1.15 (0.91-1.45)	0.25
GGT:platelet ratio	2.84 (1.35-5.70)	**0.006**	0.38 (0.12-1.18)	0.09

ALT, alanine aminotransferase; AST, Aspartate Transaminase; GGT: gamma glutamyl transpeptidase; IGG, Immunoglobulin G; INR, international normalized ratio; PT, Prothrombin Time. Bold signifies that those *P* values are significant i.e. <0.05.

was more common in non-AA than AA; but severe and aggressive form of liver disease (ALF and ESLD) were more common in AA than non-AA. This is unlikely to be an impact of socioeconomic factors like insurance as majority of our AA children had Medicaid, which gives unrestricted access to free health care. Finally, recurrence of the same disease in allografts of AA children post-transplant while they were followed closely including immunosuppression levels, suggests that AA indeed have more aggressive disease rather than this being an issue of inadequate access or delay in seeking medical care.

TABLE 5 Multivariable risk factor model for death or transplant among patients with paediatric autoimmune hepatitis

Risk Factor	Hazard Ratio	95% CI	*P*-value
Gender: female vs male	2.59	0.28-23.55	0.40
Race: AA vs Non-AA	3.24	0.93-11.35	0.07
<12 mo	4.52	1.04-19.61	**0.04**
≥12 mo	1.15	0.09-14.03	0.91
Age at presentation (per 1 y)	0.92	0.81-1.05	0.19
Steroids initiated (no vs yes)	16.49	3.61-75.38	**0.001**
AIH type 2 vs type 1	0.74	0.07-7.43	0.74
End-stage disease at presentation	3.81	1.23-11.80	**0.02**

AIH, autoimmune hepatitis. Bold signifies that those *P* values are significant i.e. <0.05.

AA patients have high likelihood of disease recurrence post-transplantation (50% of AA patients as compared to only 8% in non-AA ($P = 0.04$). In studies done mostly in Caucasian populations, there was a large variation in rates of recurrence (12%-46% of patients).[18,19] In our bivariate and multivariate modelling, there were no factors that were significantly associated with recurrences like early weaning of steroid therapy, HLA mismatch or post-transplant immunosuppressive regimens as all our AIH patients received triple immunosuppression with tacrolimus, mycophenolate mofetil and prednisone. AA patients were more likely to present with a higher IgG ($P = 0.02$) and a higher proportion of them had ESLD at presentation, as compared to non-AA patients, and these factors might make AA patients susceptible hosts, triggering disease recurrence. Immune phenotype and inflammatory activity have been reported to be important risk factors for disease recurrence[18,20] but ethnicity as a risk factor for recurrent disease is a novel finding in our study.

Non-invasive serum biomarkers like APRI are used in adults and in children for predicting liver fibrosis.[21] APRI was not found to be significantly different in our study cohort and we postulate that it could be due to higher prevalence of ESLD in our cohort. In a meta-analysis of 40 studies, APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis and APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant fibrosis. The study authors also concluded that it was less reliable for advanced fibrosis and cirrhosis,[22] and since our AA children presented with ESLD it is possible that APRI did not give us reliable results. In this study, we observed an interesting fact that serum GGT to platelet ratio was significantly different in AA compared to non-AA. Recently, few studies have shown that GGT to platelet ratio had a higher predictive values compared to APRI especially in patients with chronic hepatitis B and non-alcoholic fatty liver disease (NAFLD).[23,24] In children, serum GGT has been shown to be an important parameter estimating the severity of liver fibrosis and ultimately portal hypertension.[25] In our study, GGT:platelet ratio was observed to be a significant predictor of liver transplantation or death. A high GGT:platelet ratio increased the chance of poor outcome. AA children had high GGT:platelet ratio indicating the presence of portal hypertension or advanced liver disease at presentation. This was corroborated by data related to portal hypertension which showed that higher proportion of AA children had signs of portal hypertension: ascites (69.2% vs 63.6%), varices (23.0% vs 18.1%) and splenomegaly (92% vs 90). Undoubtedly this ratio should be validated in a larger cohort of paediatric patients.

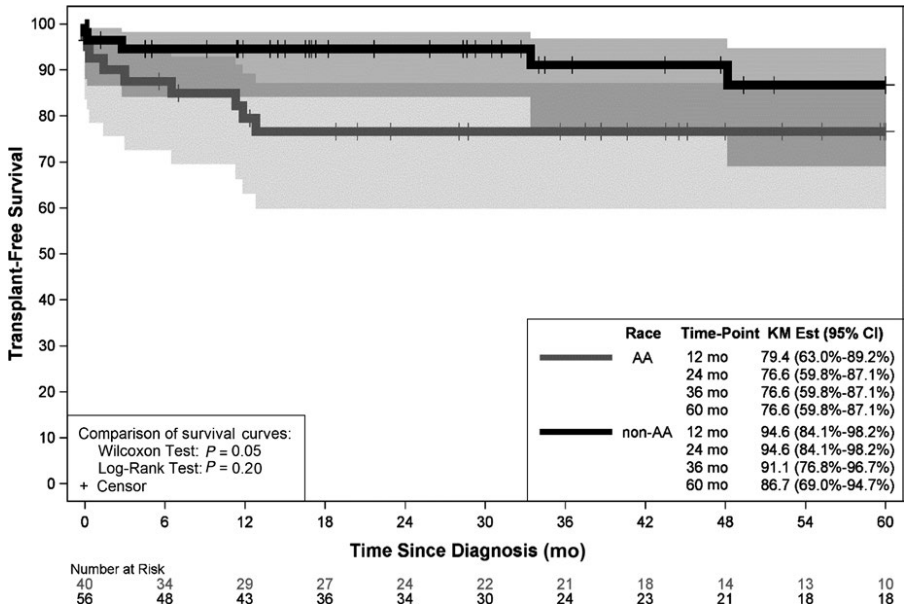

FIGURE 2 Kaplan-Meier curves comparing the transplant-free survival among African American (AA) patients to non-AA patients. Kaplan-Meier curves comparing the transplant-free survival among AA patients to non-AA patients. The upper black curve represents survival in the Non-AA population and the lower grey curve represents survival in the AA population

Children with AIH are considered to have a good response to standard therapy with prednisolone and azathioprine; around 80-90% achieve clinical and biochemical remission.[3,26-28] However, our cohort had a clinical response rate of 80% and biochemical remission rate of only 55% at 1 year. Our low biochemical remission rate might be due to the fact that nearly 42% of our population are AA who predominantly present with ESLD and low transplant-free survival compared to non-AA. Multivariate regression analysis using AA ethnicity showed a significant result with a hazard ratio of 4.5 for AA children in multivariate analysis after adjusting for all other risk factors suggests that these children may be at increased risk for major poor outcomes like liver transplant and death within the first 12 months of presentation. In addition, AA children being at 4.5 times a higher risk for liver transplant and/or death after adjusting for other risk factors and early decreased transplant-free survival, may be due to relatively high number of ESLD in AA group.

Children's Healthcare of Atlanta is a tertiary referral centre; therefore, our paediatric AIH cohort may be sicker than has been reported in prior studies.[29] Hence, we cannot completely exclude selection bias and a potential contributor the current findings. We also did not determine the effect of non-compliance with treatment regimens. However, it was clear that, a significantly higher number of AA children were on high mean dose of steroids (more than 5 mg) at 1 year after diagnosis compared to non-AA children alluding to a certain degree of compliance with medications and clinic follow-up. These factors may contribute to the differences in clinical outcomes even though this effect was not significant in the multivariate model. Prior studies of adults with AIH showed that AA adults require higher doses and have a poor initial response to methylprednisone in transplant setting compared to non-AAs.[8,10] In contrast to our findings, a study conducted in adult patients with AIH being followed up at Emory University, Atlanta by Lim et al[30] showed that at 1 year into presentation, dose of steroid was not different among AAs and Caucasians but few years into follow-up AAs required higher doses. This study, however, did conclude that AA adult patients presented at an earlier age with more severe ESLD than non-AA. This disparity has been a focus of ongoing research considering inherent biology and genetics of autoimmune disease plus genetic variations in metabolism of immunosuppressive drugs.

We acknowledge that like all retrospective analysis our study also has limitations. Although including earlier time points provides a robust longitudinal follow-up, we were limited by data/laboratory reporting in the late 1990s. Hence, information regarding quality of life, socioeconomic status and compliance factors was not available in patient records which may contribute to ESLD and increased early risk of liver transplantation in AA patients. We were also not able to provide IAIHG score at baseline for all patients due to non-availability of absolute titre levels in patients due to various reasons like initial laboratories being done at referring centre or old records currently not available and 1990s laboratory reporting practices of positive/negative without reporting absolute titre. Selection bias is a possibility, but being the only major tertiary referral transplant centre in the south-east USA, in addition to treating acutely ill children with AIH, our centre treats children from a broad spectrum of diseases and races. Although it is a large study in paediatric patients, including 109 patients with more than a decade of follow-up at a single centre, we were not able to achieve statistical significance in few areas of analysis due to lack of power. Even though all biopsies were reviewed independently by a pathologist we did not look further into detailed histological data differences between AA and non-AA patients as many previous studies had not shown any significant differences in inflammatory parameters. Finally, we used normalization of transaminases to define biochemical remission and did not include normalization of IgG and autoantibody marker levels and only recently adopted this practice. We have now changed our clinical practice, and have started checking IgG and antibody levels as part of remission definition and this data will be available for future studies.

In conclusion, our study highlights the differences in presentation, outcomes and survival between the AA and the non-AA patients with AIH onset in the paediatric age group. Being the largest cohort of paediatric patients with AIH reported to date, our findings are generalizable, but we suggest conducting similar studies at large multicentre level to make firm conclusions. This data emphasizes the need for additional studies to delineate factors such as inherent biology, genetics and access to healthcare, with immunotherapy regimens specifically tailored to AA children.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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