



Association Between Black Race and Presentation and Liver-Related Outcomes of Patients With Autoimmune Hepatitis

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INTRODUCTION & AIMS:

Small studies have found that black patients with autoimmune hepatitis (AIH) present with more aggressive disease. We aimed to characterize the presentation and outcome in black and white patients with AIH.

METHODS:

We performed a retrospective study, collecting information from databases of patients with AIH attending the Institute of Liver studies at King's College Hospital, London (1971–October 2015, the Royal Free Hospital, London (1982 through December 2016) and the multicenter Dutch Autoimmune Hepatitis Study Group cohort (2006–August 2016). We identified 88 black patients with AIH and we compared their clinical characteristics and outcomes to 897 white patients with AIH.

RESULTS:

Black patients presented at a younger age (median 38 years vs 45 years) ($P = .007$), had higher IgG levels (mean 31.0 mg/dL vs 27.5 mg/dL) ($P = .04$), but there were no significant differences between groups in auto-antibody profiles, International AIH Group scores, or sex distribution of disease. A higher proportion of black patients had systemic lupus erythematosus (10%) than white patients (2%) ($P \leq .001$). There was no significant difference in proportions of patients with a response to standard therapy (86% for black patients vs 91% for white patients; $P = .20$) or in rate of relapse (57% vs 50%; $P = .3$). Despite this, black patients had an increased risk of liver transplantation and liver-related death (hazard ratio 2.4, 95% confidence interval, 1.4–4.0; $P < .001$). Overall mortality was similar between the two groups.

CONCLUSION:

In a comparison of black and white patients with AIH in Europe, we found that black patients present at a younger age, have higher levels of IgG levels, and a greater proportion have SLE. We also found black patients to have a greater risk of liver transplantation and liver-related mortality, indicating more aggressive disease.

Keywords: IAIHG; SLE; Survival; Disease Progression.

Autoimmune hepatitis (AIH) is a rare, chronic progressive immune-mediated inflammatory disorder of the liver that affects children and adults.^{1,2} It is characterized by female predominance, hypergammaglobulinemia, circulating autoantibodies and interface hepatitis on liver biopsy.¹ Clinical presentation ranges from asymptomatic biochemical liver abnormalities to acute liver failure or cirrhosis.^{1,3,4} Genetic factors play a role in the natural history of AIH; white

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Abbreviations used in this paper: AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; IAIHG, International Autoimmune Hepatitis Group; INR, international normalized ratio; IQR, interquartile range; SLE, systemic lupus erythematosus.

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*HLA-DRB1*0301* positive AIH type 1 patients are more likely to be male and to deteriorate despite steroids and *HLA-DRB1*0401* positive patients tend to be older and respond better to corticosteroid therapy.⁵⁻⁷ A few studies reported differences in disease presentation and outcome between different ethnic groups.⁸⁻¹² In 2 studies from the United States and the United Kingdom, it was found that non-Caucasian patients with AIH have more aggressive disease at initial presentation, a higher likelihood of cirrhosis being present at diagnosis.^{9,10} A recent population based analysis found that black AIH patients have a higher rate of hospitalization and death during hospitalization than white patients.¹³ The difference in presentation and outcome between black and patients of other ethnic or racial background may in part be genetically driven,^{14,15} but confounding structural and social factors such as socioeconomic status and access to health care have not convincingly been excluded. The studies to date have been single-center experiences reporting outcomes with relatively small numbers of patients. We aimed to compare the clinical presentation and outcome of black AIH patients from African or Caribbean descent in reference to a Caucasian population in a retrospective multi-center study.

Materials and Methods

Three well-established and updated databases of patients with AIH attending the Institute of Liver studies at King's College Hospital in London between 1971 and October 2015, the Royal Free Hospital in London between 1982 and December 2016, and the multicenter DAIHG (Dutch Autoimmune Hepatitis Study Group) study cohort between 2006 and August 2016 were reviewed. The King's College Hospital and the Royal Free Hospital are 2 of 7 liver transplant centers in the United Kingdom. These liver units treat local patients, but both have large national and international referral practices.¹⁶ The DAIHG study cohort data were updated in 6 academic centers, including all 3 Dutch transplant centers, and 10 general referral hospitals.¹⁷ Patient records were systematically reviewed and examined with regards to self-reported racial background as well as clinical characteristics, excluding patients with features of primary sclerosing cholangitis and primary biliary cholangitis variant syndromes. Black background was based on self-reported sub-Saharan Africa, Afro-American or Afro-Caribbean origin, whereas white background was based on self-reported Caucasian or European origin. In the cohort of 985 patients, black race was identified in 88 patients and white race in 897 (Figure 1). All patients had a clinical diagnosis of probable or definite AIH according to the 1999 International Autoimmune Hepatitis Group (IAIHG) scoring system (564 UK and 421 Dutch AIH patients). We compared the black and white patient groups in relation to clinical, laboratory,

What You Need to Know

Background

Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver that can manifest in all ethnic and racial groups. Genetics, ethnicity, and race have an impact on the development of immune mediated conditions. Socioeconomic status may affect health care outcomes.

Findings

AIH patients of black background present at an earlier age than white patients. Black AIH patients have a more severe disease course, with a higher chance of liver transplantation or death due to liver failure.

Implications for patient care

Black AIH patients may need a more stringent therapeutic approach to prevent worse liver-related outcomes.

and histological features as well as treatment outcome, liver transplantation, and overall and liver-related mortality.

As described in previous studies, standard diagnostic criteria for the presence of AIH were fulfilled.^{17,18} All patients were treated according to standardized protocols published previously.^{19,20} Response to treatment and relapse were defined in accordance with the revised IAIHG criteria.²¹ Second-line therapy was defined as ever being treated with medications other than azathioprine or corticosteroids (including mycophenolate mofetil, tacrolimus, cyclosporine A, or sirolimus). The presence of concomitant extra-hepatic autoimmune disease including celiac disease, autoimmune thyroiditis as well as systemic lupus erythematosus (SLE) was retrieved from the patient records. Data on mortality and causes of death were retrieved from medical records or by contacting the attending physicians or general practitioners or family doctors. In the Dutch cohort, liver transplantation rates were assessed by cross-checking the clinical record data with the transplantation list from all 3 transplantation centers. Follow-up ended at the date of death or liver transplantation, or at the end of the study. This study was approved by the Research Ethics Committee of King's College Hospital (04/Q0703/23), the Royal Free Hospital (London, United Kingdom), and the ethics committee at the VU University Medical Center (Amsterdam, the Netherlands) and all the participating centers. In all participating transplant centers, no donor organs were obtained from executed prisoners or other institutionalized persons.

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 (IBM, Armonk, NY) and GraphPad Prism 7.02 (GraphPad

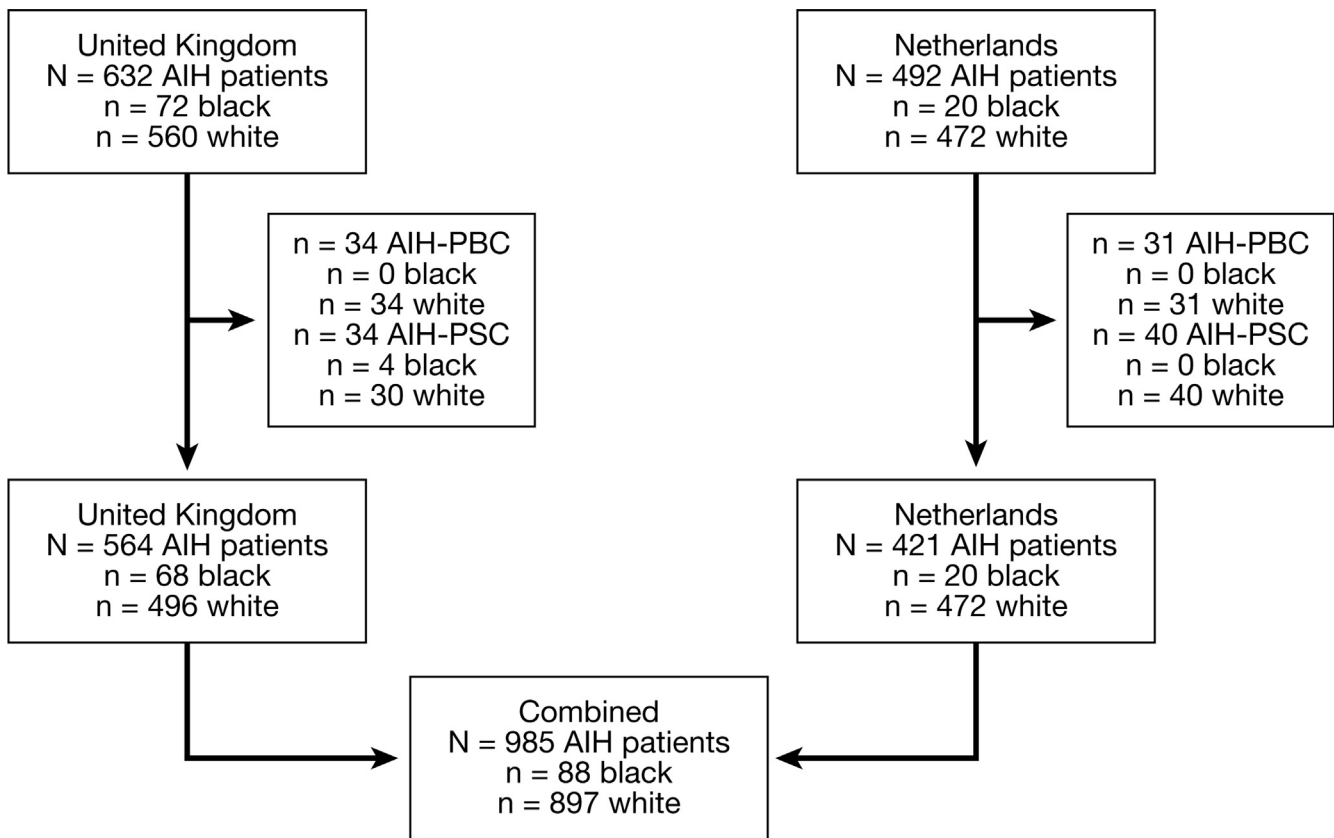


Figure 1. Flowchart of selection of autoimmune hepatitis (AIH) patients in the UK and Dutch cohorts. PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Software, La Jolla, CA). Demographic and therapy-specific data are given descriptively as mean \pm SD and median (interquartile range [IQR]) when appropriate. Statistical testing of continuous variables between groups was performed with Student's *t* test, Mann-Whitney *U* test or Wilcoxon signed rank test. Proportional differences were tested with the chi-square test or Fisher's exact test. A *P* value of $<.05$ was considered statistically significant. The primary outcome measure was a composite endpoint of liver transplantation and liver-related death. Overall survival curves were obtained via Kaplan-Meier's estimate. For differences in survival between groups the log-rank test and Cox regression analysis was performed, only using time-independent variables.

Results

UK Cohort

The UK cohort consisted of 68 (12%) black patients and 496 (88%) white patients. Black patients presented at a younger age (median 38 years of age vs 44 years of age, $P = .05$), but the proportion of female sex (77% vs 79%, $P = .7$), IAIHG score (20 vs 20, $P = .15$), and transaminase level (median 551 IU/L vs 586 IU/L, $P = .9$) were similar between both groups. There were no

differences in antinuclear antibodies, anti-smooth muscle antibodies, and liver kidney microsome-1 positivity (Supplementary Table 1). Median international normalized ratios (INR) for prothrombin time levels were higher (1.3 vs 1.2, $P = .051$) and albumin levels were lower (32.1 g/L vs 34.4 g/L, $P = .017$) in black patients. Black patients more often had concomitant SLE (10% vs 2%, $P = .003$) than white patients, but mean IgG levels were similar (29.3 vs 27.4 g/L, $P = .3$). The median follow-up and associated treatment exposure was shorter in the black patients than white patients (103 [IQR, 41–149] months vs 126 [IQR, 58–202] months, $P = .01$). The response to standard therapy was significantly lower in black patients than white patients (81% vs 93%, $P = .005$). Twenty (34%) black patients and 144 (32%) white patients had cirrhosis at diagnosis ($P = .8$). Twelve (18%) black patients and 38 (8%) white patients underwent liver transplantation ($P = .007$). Sixteen (24%) black patients and 67 (14%) white patients reached the combined endpoint of liver-transplantation and liver-related death ($P = .029$).

Dutch Cohort

The Dutch cohort consisted of 20 (5%) black patients and 401 (95%) white patients. Black patients presented at a younger age (median 38 years of age vs 46 years of age, $P = .05$), but the proportion of female sex (75% vs

77%, $P = .8$), IAIHG score (20 vs 18, $P = .3$), and transaminase level (median 378 IU/L vs 492 IU/L, $P = .2$) were similar between both groups. There were no differences in antinuclear antibodies, anti-smooth muscle antibodies, and liver kidney microsome-1 positivity (Supplementary Table 2). Median INR (1.1 vs 1.1, $P = .7$) and mean albumin (35.8 g/L vs 36.2 g/L, $P = .7$) levels were similar in black and white patients respectively. Black patients more often had concomitant SLE (10% vs 2%, $P = .08$) and had higher mean IgG levels (40.4 vs 27.6 g/L, $P = .001$). Two (13%) black patients and 56 (19%) white patients had cirrhosis at diagnosis ($P = .7$). The median follow-up and associated treatment exposure were similar in both groups (181 [IQR, 133–212] months vs 178 [IQR, 139–239] months, $P = .7$). The response to standard therapy were similar in both groups (100% vs 89%, $P = .1$). A total of 185 (38%) patients were managed at a transplant center, whereas the majority of patients was treated at general (37%) or nontransplant academic referral (25%) hospitals. Black patients were less often managed at transplant (3 [15%] vs 155 [39%], $P = .03$) or academic referral centers (9 [45%] vs 256 [64%], $P = .09$). The rate of biopsy-proven cirrhosis was 19%, which was not related to transplant (21%) or academic referral center (21%). The rates of liver-related death and liver transplantation for all patients were significantly higher in the transplant centers than in the general and academic centers ($n = 24$ [15%

vs $n = 12$ [5%], $P < .001$). No black patients and 11 white patients (3%) underwent liver transplantation ($P = 1.0$). Three (15%) black patients and 33 (8%) white patients reached the combined endpoint of liver-transplantation and liver-related death ($P = .2$).

Combined Cohort

The combined study population comprised of 985 patients (736 definite AIH and 259 probable AIH; 88 black patients, 897 white patients). Black patients presented at a younger age than white patients (median 38 years of age vs 45 years of age, $P = .007$), but had similar sex distribution and IAIHG post-treatment scores as well as autoantibody positivity (Table 1). Black patients had higher IgG levels (mean 31.0 g/L vs 27.5 g/L, $P = .04$) and a higher rate of SLE (10% vs 2%, $P < .001$). There were no differences in age or severity of presentation between black patients with and without concomitant SLE. The difference in IgG levels between black and white patients persisted after exclusion of patients with SLE (30.4 g/L vs 27.4 g/L, $P = .055$). The prevalence of cirrhosis at baseline was similar in both groups (29% vs 27%, $P = .5$) in the 822 (84%) AIH patients who underwent liver biopsy at diagnosis. There was a clear difference in rates of biopsy proven cirrhosis between the UK and Dutch patients (32% vs 19%, $P < .001$). The INRs were similar in black and white patients, whereas

Table 1. Baseline Characteristics

	Black (n = 88)	White (n = 897)	P	n
Age at diagnosis, y	38 (23–49)	45 (24–58)	.007	981
Female	67 (76)	700 (78)	.7	985
Post-treatment IAIHG score	20 (17–22)	19 (17–22)	.9	941
Definite post-treatment IAIHG score	61 (69)	665 (74)	.3	985
ALT or AST, IU/L	483 (192–932)	539 (197–1080)	.8	850
ALP, IU/L	191 (145–269)	174 (129–252)	.1	823
Bilirubin, mmol/L	57 (30–165)	55 (19–180)	.7	810
Creatinine, μ mol/L	72 (62–89)	73 (63–85)	.9	597
INR	1.2 (1.1–1.6)	1.2 (1.0–1.4)	.082	634
Mean albumin, g/L (range)	32.8 (16–46)	35.1 (15–55)	.005	762
Mean peak IgG, g/L (range)	31.0 (4.6–91.1)	27.5 (4.8–89.5)	.043	748
ANA positivity \geq 1:40	58 (68)	572 (69)	.8	909
SMA positivity \geq 1:40	47 (55)	478 (60)	.4	890
LKM-1 positivity \geq 1:40	4 (5)	44 (6)	.8	807
AMA positivity \geq 1:80	2 (2)	30 (4)	.8	924
SLE	9 (10)	19 (2)	<.001	985
Thyroid disease	8 (9)	127 (14)	.2	983
Hypothyroidism	7 (10)	93 (11)		
Hyperthyroidism	1 (2)	28 (3)		
Celiac disease	0 (0)	8 (1)	1.0	983
Acute presentation (<6 months)	54 (68)	375 (61)	.3	693
Cirrhosis at diagnosis	22 (29)	200 (27)	.6	822
Managed at transplant center	71 (81)	651 (73)	.1	985

NOTE. Values are median (interquartile range) or n (%), unless otherwise indicated.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibodies; AST, aspartate aminotransferase; IAIHG, International Autoimmune Hepatitis Group; LKM-1, liver kidney microsome-1 antibody; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibody.

Table 2. Therapy and Outcome

	Black (n = 88)	White (n = 897)	P	n
Therapy				
Steroids for induction	84 (99)	841 (95)	.2	971
Azathioprine for maintenance	59 (75)	703 (81)	.2	949
Ever on second-line therapy	13 (17)	96 (11)	.1	953
Response to standard therapy	67 (86)	773 (91)	.1	928
Relapse	39 (57)	405 (50)	.3	875
Number of relapses	1 (0-3)	1 (0-2)	.018	815
Outcome				
HCC	2 (2)	23 (3)	1.0	973
Liver transplantation	12 (14)	49 (6)	.002	984
Liver transplantation + liver-related death	19 (22)	100 (11)	.004	985
Overall death	10 (11)	138 (15)	.3	985

NOTE. Values are n (%) or median (interquartile range).
HCC, hepatocellular carcinoma.

the albumin levels were significantly lower (mean 32.8 g/L vs 35.1 g/L, $P = .005$) in black patients. Both black and white patients were treated with steroids as standard induction therapy (99% vs 95%, $P = .2$) and had a

similar exposure to azathioprine as maintenance therapy (75% vs 81 %, $P = .2$) (Table 2). Black patients had a similar clinical response rates to standard therapy compared with white patients (86% vs 91%, $P = .2$) and also comparable occurrence of at least 1 relapse (57% vs 50%, $P = .3$). However, during follow-up there was a higher proportion total number of recorded relapses in black AIH patients in both the King's College Hospital and the Dutch cohorts ($P = .018$). Overall, there was no significant difference in the rate of use of second-line therapies (17% vs 11%, $P = .1$).

Outcome

The median duration of follow-up in the combined cohort was shorter in the black than in the white patients (127 [IQRm 48-173] months vs 152 [IQR, 91-223] months, $P < .001$). The rate of hepatocellular carcinoma (HCC) development was similar in both groups (2% vs 2%, $P = 1.0$), but the incidence per 10 patient years was lower in the white patient group (0.018 per 10 patient-years vs 0.022 per 10 patient-years). The rate of transplantation and liver-related death was significantly

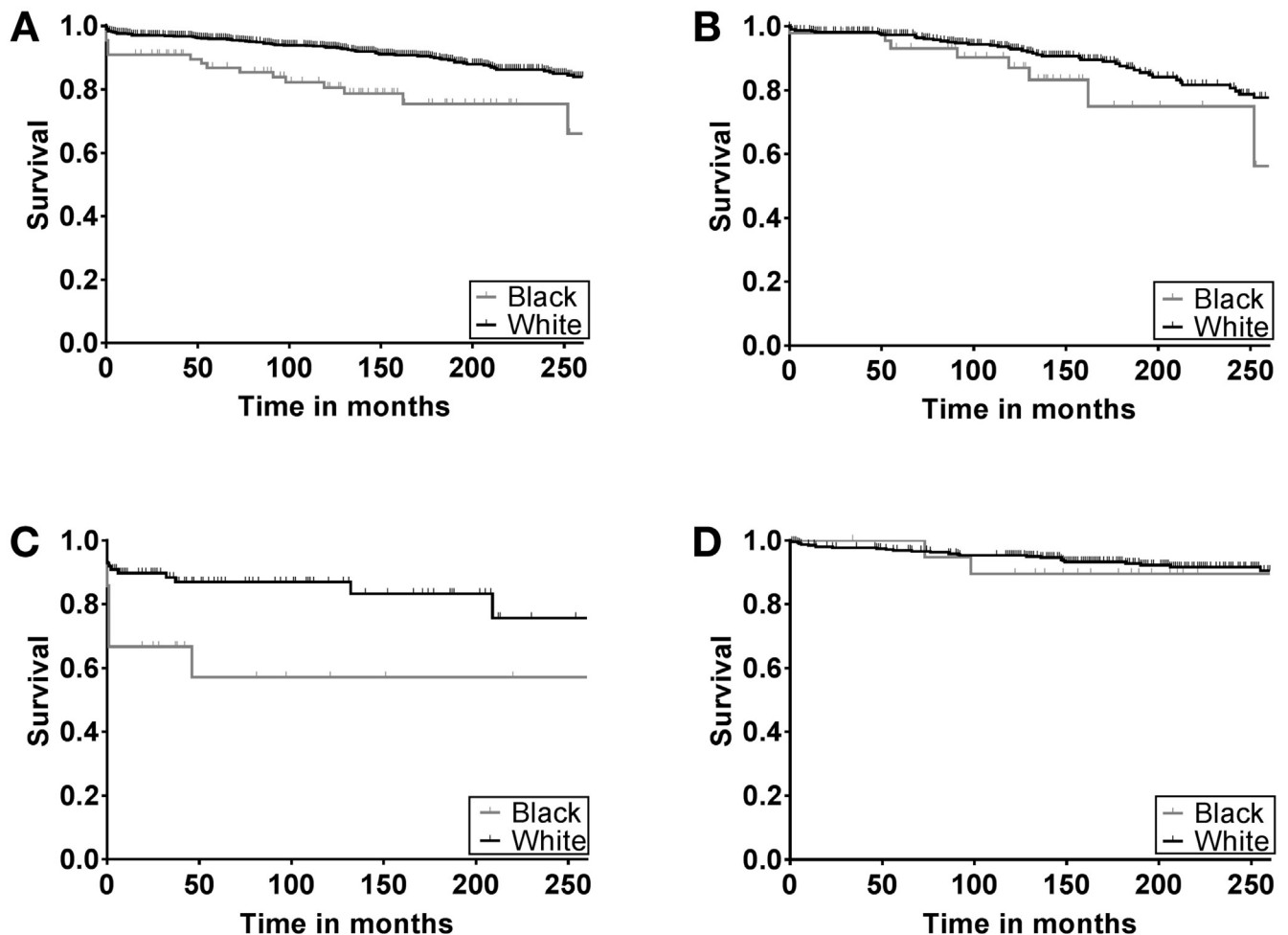


Figure 2. Transplant free and liver related death survival analysis in the (A) combined, (B) Kings College Hospital (United Kingdom), (C) Royal Free Hospital (United Kingdom), and (D) Dutch cohorts.

higher in the black patients in the UK cohort ($P = .029$), whereas the rates of transplantation, liver-related mortality, and overall mortality did not differ significantly between black and white patients in the Dutch cohort. In the combined cohort, the black AIH patients underwent liver transplantation more often than white patients (14% vs 6%, $P = .002$), but overall mortality was similar between the 2 groups (11% vs 15%, $P = .3$). Log-rank survival analysis showed an impaired combined transplant-free and liver-related mortality for black patients in the combined UK and Dutch cohorts ($P < .001$) (Figure 2A). This was primarily driven by the UK cohort ($P < .001$, Figure 2B and C), as the Dutch cohort did not reveal a significant association ($P = .4$) (Figure 2D). This suggests that the difference in rates of cirrhosis between the UK and Dutch patients (32% vs 19%, $P < .001$) is in part driving this association. Cox regression analysis in the combined UK and Dutch cohorts showed an association of black race with liver transplant and liver-related death (hazard ratio, 2.4; 95% confidence interval, 1.4–4.0; $P = .001$) (Table 3), independent of age, cirrhosis at diagnosis, and SLE in the multivariate analysis. Incorporation of transplant center status and country in the model did not change these results. The presence of cirrhosis at diagnosis was associated with an increased risk of liver transplantation or liver-related death.

Discussion

In this retrospective study of black patients with AIH from selected centers in the United Kingdom and the Netherlands, we observed a lower age of onset and a greater risk of liver transplant or liver-related death, which may illustrate a more aggressive disease course compared with white patients. We also demonstrated that these outcomes occurred in health care systems with universal access to care, even without a higher likelihood of cirrhosis at diagnosis or without an initial inferior apparent treatment responses to induction therapy among black patients. Higher IgG levels at diagnosis were noted compared with a white reference

population. Although no differences in terms of autoantibody profile were noted, black patients more often had concomitant SLE. Overall, there was a low rate of HCC and we did not observe an association between HCC development and race which is consistent with the similar rates of cirrhosis in both groups.²² In both countries and health care systems, the vast majority of patients received corticosteroids for induction of remission, with azathioprine being added for maintenance therapy. Interestingly, there were no differences in terms of response of therapy between groups, and a similar proportion of patients needed escalation of therapy with second line agents. However, the number of relapses was higher in black patients compared with white patients, suggesting that these patients have a more severe disease phenotype and are in need of a better maintenance therapy. Alternatively, limited compliance to therapy could be a factor, although we could not reliably address this issue. Lim et al⁸ reported that although both black and white patients responded well to standard therapy, the dosage of steroids was significantly higher in black patients despite similar use of azathioprine (Table 4). These data suggest that current treatment regimens may be inadequate for black patients; therefore, future studies should focus on the development of different treatment protocols stratified according to race to address this issue.^{23,24} Importantly, this study also confirms that race also impacts on the natural history of the disease, as black patients were more likely to have progressive disease requiring liver transplantation. We propose 3 possible explanations for this outcome. First, and although this was a multicenter study, it was hospital based and therefore could be limited by tertiary referral bias, which might lead to an overestimation in severity. In line with this, we observed overall less severe disease with lower rates of cirrhosis and outcomes in the Dutch cohort, which comprised AIH patients managed predominantly at general and academic hospitals, and less frequently at transplant hospitals, whereas the UK cohort consisted of 2 transplant centers. Nevertheless, as advanced health care is accessible through both the National Health Service in

Table 3. Survival: Transplant and Liver-Related Death

	Univariate				Overall			
	UK Cohort		Dutch Cohort		Univariate		Multivariate	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Black	2.5 (1.5–4.4)	.001	1.6 (0.5–5.4)	.4	2.5 (1.6–4.2)	<.001	2.4 (1.4–4.0)	.001
Age	1.0 (1.0–1.0)	.6	1.0 (1.0–1.0)	.012	1.0 (1.0–1.0)	.14	1.0 (1.0–1.0)	.049
Gender	0.9 (0.5–1.5)	.7	1.2 (0.5–2.7)	.7	0.9 (0.6–1.5)	.9		
Cirrhosis at diagnosis	3.3 (2.1–5.1)	<.001	1.8 (0.9–3.9)	.12	3.2 (2.2–4.5)	<.001	3.1 (2.1–4.4)	<.001
SLE	2.7 (1.2–6.2)	.02	1.0 (0.1–7.8)	.9	2.3 (1.1–4.9)	.035	1.9 (0.9–4.3)	.12

NOTE. Cox regression analysis of combined liver transplant and/or liver related death. Patients without biopsy at diagnosis were included in this analysis as not having cirrhosis. The multivariate analysis was conducted in 969 of 985 (98%) patients with available data for included variables. CI, confidence interval; HR, hazard ratio; SLE, systemic lupus erythematosus.

Table 4. Review of Literature on Ethnic/Racial Background and Presentation and Outcome in Autoimmune Hepatitis

Study	Population	Presentation	Response	Outcome	Study setting
Lim et al (2001) ⁸	27 African American and 24 white AIH patients	Cirrhosis in 85% of African Americans and 38% of white patients	Both groups responded well to therapy	African Americans required higher prednisone doses than white patients	1 tertiary referral center
Zolfino et al (2002) ⁹	6 African and 5 Asian and 1 Arabic AIH patients	Cirrhosis in 1 of the African and 4 Asian patients	Complete response in 2 African, 2 Asian, and 1 Arab patient; partial or no response in 7 patients	Death or transplantation in 2 (33%) African, 4 (80%) Asian, and 1 (100%) Arab patient	1 tertiary referral center
Verma et al (2007) ¹⁰	37 Black and 64 non-black AIH patients	Cirrhosis and acute presentation were more common in black than non-black patients (57% vs 38% and 76% vs 50%, respectively)	Black patients were less likely to achieve remission (76%) than non-black patients (90%)	Black patients had a 4-fold higher mortality rate and were referred 2 times more often for transplantation than non-black patients	1 tertiary referral center
Wen et al (2018) ¹³	Hospitalizations for AIH in 1463 black and 4666 white AIH patients	Cirrhosis in 12.5% of black and 15.1% of white patients	Black patients were hospitalized for AIH at a rate 69% higher than whites	Black patients had higher odds of death during hospitalization for AIH than white patients	U.S. Nationwide Inpatient Sample database (2008–2012)
Webb et al (2018) ¹⁶	Transplantation list: 796 black and 3665 white AIH patients	—	—	Black patients with AIH were listed for transplantation more than 10 years younger than white patients	U.S. and UK transplantation centers (1995–2014)
Lee et al (2018) ¹²	10 Black, 29 Latino, and 19 Asian Pacific Islander AIH and 2049 control patients	Biochemistry and rates of cirrhosis were similar between the groups	No difference in time to steroid discontinuation or clinical course between the groups	Black, Latino and Asian Pacific Islander patients had almost 10 times higher odds of AIH than whites	1 tertiary referral center

AIH, autoimmune hepatitis.

the United Kingdom and mandatory insurance policy in the Netherlands, this bias likely affects both groups. Hence, it seems unlikely to account for the poorer outcome observed in black AIH patients, although the relatively small number of included black AIH patients in the Dutch cohort may explain the lack of association with outcome in the Dutch cohort due to lack of power. A recent study of the UK and U.S. national liver transplant registries reported that black patients were listed at younger age and had higher Model for End-Stage Liver Disease scores than other races (Table 4).²⁵ Second, socioeconomic status, health care access, and practice, and thus quality of care, are factors that must be considered comparing disease characteristics and outcomes among different groups.²⁶ For example, mortality differences between white and African descendent North Americans with cirrhosis disappear after adjustment for socioeconomic status.²⁷ The earlier age at diagnosis and similar cirrhosis rates argue against a systematic delay in the diagnosis of AIH in black patients, assuming that untreated disease progression rates are similar. The elevated hazard of liver transplantation or liver-related death for black patients could be attributed to a more aggressive disease phenotype, which might progress despite similar rates of initial treatment response, which is supported by a recent population study in the United States (Table 4).¹³ Unfortunately, Wen et al¹³ did not report on the clinical characteristics, but rather relied on international classification of disease 9 codes. Conversely, the differences in liver-related mortality and liver transplantation could reflect variations in the quality and experience of care depending upon race. Last, it is possible that genetic variations may have been responsible for the worse outcome observed in black patients with AIH. There are well established differences between black and white patient groups regarding the incidence of SLE and other immunoinflammatory disorders such as sarcoidosis. Additionally, differences in other immune parameters such as ethnic neutropenia²⁸ and the distribution of the Duffy antigen receptor for chemokines polymorphisms²⁹ suggest that genetic influences on the immune system differ between populations. Previous studies have shown that genetic factors influence AIH occurrence, clinical expression, and response to corticosteroid therapy,^{6,14,30} but the genetic contributions to disease onset and phenotype of AIH have not been explored in patients of African or Caribbean descent. In white Northern European populations, the *HLA-DRB1*04:01* genotype was associated with a higher rate of remission and with a lower frequency of cirrhosis and need for liver transplantation.⁵ Interestingly, it has been shown that HLA-DR4 is underrepresented in African Americans compared with Caucasian individuals.³¹ The current study provides no information about HLA class II genotypes, constituting 1 key limitation in interpreting the data. Additionally, common with other retrospective studies, our results may be influenced by referral bias, missing data, skewed outcome

parameters and we cannot ascribe causality of poorer outcomes to race. As race was self-reported and categorized as black or white, we could not control for the likely genetic heterogeneity within these large groups. A further limitation is the lack of data on adherence to treatment within the studied groups. However, the strength of this study comprises the large catchment area in 2 different countries with accessible health care systems.

Future, prospective studies are required to explore the mechanism, importance, and generalizability of our findings. The impact of genetic variants among different racial groups in Europe, and globally, on clinical outcomes would help inform our understanding of disease biology, etiology, and risk prediction. Qualitative and quantitative exploration of the experiences of patients and access to health care, capturing data on, among others, socioeconomic status, race, sex, and treatment center should be performed. The proposed IAIHG retrospective and prospective registries offer a suitable starting point and further focused studies will be required.^{23,24}

In summary, the results of this study show that the presentation and clinical course of AIH is different in black patients compared with a reference cohort of white AIH patients. Black AIH patients present at a younger age, with higher IgG levels and a higher prevalence of SLE than a white reference population. Black AIH patients appear to have a higher rate of transplantation and liver-related mortality, despite a similar disease stage at presentation. It is likely that a combination of different factors may account for this observation, including time of diagnosis, treatment regimen, and genetic and environmental disparities between the different groups.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2018.11.028>

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Conflicts of interest

The authors disclose no conflicts.

Supplementary Table 1. Baseline Characteristics, Therapy, and Outcome of UK AIH Patients

	Black (n = 68)	White (n = 496)	P	n
Age at diagnosis, y	38 (22–48)	44 (22–58)	.05	560
Female	52 (77)	391 (79)	.7	564
Post-treatment IAIHG score	20 (17–22)	20 (18–23)	.15	520
ALT or AST, IU/L	551 (209–1044)	586 (199–1125)	.9	517
ALP, IU/L	194 (146–291)	183 (136–273)	.3	501
Bilirubin, mmol/L)	75 (31–184)	69 (21–225)	.9	506
Creatinine, μ mol/L	75 (65–89)	73 (63–88)	.5	313
INR	1.3 (1.1–1.6)	1.2 (1.0–1.5)	.051	428
Mean albumin, g/L (range)	32.1 (16–45)	34.4 (20–55)	.017	480
Mean peak IgG, g/L (range)	29.3 (4.6–71.7)	27.4 (4.8–89.7)	.3	525
ANA positivity \geq 1:40	42 (65)	312 (65)	.9	542
SMA positivity \geq 1:40	40 (61)	299 (63)	.7	538
LKM-1 positivity \geq 1:40	3 (5)	29 (6)	.8	545
AMA positivity \geq 1:80	2 (3)	19 (4)	1.0	545
SLE	7 (10)	11 (2)	.003	564
Thyroid disease	7 (10)	93 (19)	.092	562
Hypothyroidism	7 (10)	69 (17)		562
Hyperthyroidism	0 (0)	19 (5)		562
Celiac disease	0 (0)	6 (1)	1.0	562
Acute presentation (<6 months)	43 (67)	267 (58)	.2	521
Cirrhosis at diagnosis	20 (34)	144 (32)	.8	509
Managed at transplant center	68 (100)	496 (100)	NA	564
Therapy				
Steroids for induction	65 (100)	480 (99)	1.0	551
Azathioprine for maintenance	41 (70)	375 (80)	.064	528
Ever on second-line therapy	12 (21)	63 (13)	.13	532
Response to standard therapy	47 (81)	424 (93)	.005	514
Relapse	25 (52)	191 (46)	.4	462
Number of relapses	1 (0–3)	0 (0–1)	.09	403
Outcome				
HCC	2 (3)	21 (4)	1.0	552
Liver transplantation	12 (18)	38 (8)	.007	563
Liver transplantation + Liver related death	16 (24)	67 (14)	.029	564
Overall death	5 (7)	75 (15)	.09	564

NOTE. Values are median (interquartile range) or n (%), unless otherwise indicated.

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; IAIHG, International Autoimmune Hepatitis Group; LKM-1, liver kidney microsome-1 antibody; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibody.

Supplementary Table 2. Baseline Characteristics, Therapy, and Outcome in the Dutch Cohort

	Black (n = 20)	White (n = 401)	P	n
Age at diagnosis, y	38 (27–50)	46 (28–59)	.2	421
Female	15 (75)	309 (77)	.8	421
Post-treatment IAIHG score	20 (16–22)	18 (16–21)	.3	421
ALT or AST, IU/L	378 (166–526)	492 (185–1604)	.2	333
ALP, IU/L	170 (87–212)	158 (117–236)	.8	322
Bilirubin, mmol/L)	39 (17–131)	40 (14–128)	.9	304
Creatinine, μ mol/L	62 (55–78)	73 (63–83)	.2	292
INR	1.1 (1.1–1.2)	1.1 (1.0–1.3)	.7	206
Mean albumin, g/L (range)	35.8 (26–46)	36.2 (15–54)	.8	282
Mean peak IgG, g/L (range)	40.4 (19.6–91.1)	27.6 (7.4–75.3)	.001	223
ANA positivity \geq 1:40	16 (80)	260 (75)	.8	367
SMA positivity \geq 1:40	7 (35)	179 (54)	.1	352
LKM-1 positivity \geq 1:40	1 (6)	15 (6)	1.0	262
AMA positivity \geq 1:80	0 (0)	11 (3)	1.0	379
SLE	2 (10)	8 (2)	.08	421
Thyroid disease	1 (5)	34 (9)	1.0	421
Hypothyroidism	0 (0)	24 (6)		421
Hyperthyroidism	1 (5)	10 (3)		421
Celiac disease	0 (0)	2 (1)	1.0	412
Acute presentation (<6 months)	11 (69)	108 (69)	1.0	172
Cirrhosis at diagnosis	2 (13)	56 (19)	.7	313
Managed at transplant center	3 (15)	155 (39)	.03	421
Therapy				
Steroids for induction	19 (95)	361 (90)	.7	420
Azathioprine for maintenance	18 (90)	328 (82)	.5	421
Ever on second-line therapy	1 (5)	33 (8)	1.0	421
Response to standard therapy	20 (100)	349 (89)	.1	414
Relapse	14 (70)	214 (55)	.2	413
Number of relapses	2 (0–4)	1 (0–2)	.038	412
Outcome				
HCC	0 (0)	2 (1)	1.0	421
Liver transplantation	0 (0)	11 (3)	1.0	421
Liver transplantation + liver-related death	3 (15)	33 (8)	.2	421
Overall death	5 (25)	63 (16)	.3	421

NOTE. Values are median (interquartile range) or n (%), unless otherwise indicated.

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; IAIHG, International Autoimmune Hepatitis Group; LKM-1, liver kidney microsome-1 antibody; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibody.